

Ethical Issues Arising from Commercial Sponsorship and from Relationships with the Pharmaceutical Industry—Report and Recommendations of the Ethics Subcommittee of the International Headache Society

Preface

These recommendations, the second set developed for the International Headache Society (IHS) by its Ethics Subcommittee, evolved over 3 years. This extended period allowed time for public consultation, an important part of the formulation process, and for consequent revision.

The recommendations were presented in this final form to IHS Council in late 2005, and approved for publication in *Cephalalgia*. The delay from then until now would have been better avoided. The reasons for it, which did not lie with the Subcommittee, are not of current interest. What matters is that these recommendations remain entirely relevant to their purpose.

In one area – the registration of clinical trials – matters have moved on in the interim. As the Subcommittee anticipated, registration of trials is becoming standard practice [1]. This goal is not yet achieved, but laudable and largely voluntary initiatives by the pharmaceutical industry have brought about much recent progress. Clear international consensus has yet to emerge on what needs to be included in a clinical trials registry, and when. This does not help, since it is not entirely certain what the desired end is. But it seems likely that, with or without further regulation, this end will be both clear and in sight in not too long. Headache will benefit, along with all other fields of medicine.

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Chairman,
IHS Ethics Subcommittee
May 2008

Reference

1. Crawley FP. Clinical trials registries and results reporting. *Int J Pharm Med* 2007; 21:295–296.

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1.0 Summary of recommendations

1.1 Conflicts of interests in relationships with commercial sponsors

1. We believe that the ultimate solution to unmanageable conflicts of interest is removal of the context that gives rise to them.
2. We recommend therefore that IHS actively seek funding from other sources than the pharmaceutical industry, promoting the message that it is in the interests of society and employers to manage headache better.
3. We recommend that IHS formally adopt the *Policy on Commercial Sponsorship* set out below in section 4.1.3.
4. We recommend that IHS endeavour to extend its relationships with industry based in equal partnership rather than dependent upon sponsorship.
5. We recommend that, within the context of its strategic planning, IHS review and state unambiguously the primary objective of the International Headache Congress (IHC). Our preference is that this event should be returned uncompromisingly to its original mission of education.
6. We recommend that IHS, together with the Editor-in-Chief of *Cephalalgia*, develop and publish a policy with respect to the review and acceptance of articles likely to generate substantial income from reprint sales.
7. We recommend that IHS develop and publish a *Statement of Values* that it will hold as non-negotiable in all its dealings, to which it will adhere in the pursuit of its objectives and to which as a matter of policy it will expect its members (whether individuals or national societies) and partners, including sponsors, to subscribe.
8. We recommend that every member of IHS who has a position of leadership or influence in the Society or in the headache field more generally be required to read, understand, sign and comply with the Society's policy on conflicts of interest.

9. We recommend for adoption by the Society the *Policy on Conflicts of Interest for IHS Members* set out below in section 4.1.3.
10. We make no recommendation on the acceptance of gifts and hospitality other than that these should be reasonable, unconditional and, if appropriate, declared. Worldwide cultural variation makes any general statement difficult.

1.2 Commercially sponsored research

1.2.1 Compensation for injury to subjects of commercially sponsored research

1. We believe that compensation for harm to patients and healthy volunteers arising from sponsored research should be a requirement, regardless of fault, everywhere in the world where sponsored research is conducted.
2. We recommend therefore that sponsors voluntarily apply the highest standards everywhere, without variation and regardless of local less-demanding requirements. (The meaning of 'highest standards' is stated in section 4.2.1.3.)
3. We recommend that IHS members should not undertake sponsored research where these arrangements are not in place.
4. Investigators who undertake 'add-ons' to a sponsored study must accept and make due provision for their responsibility to provide compensation, or otherwise explain very carefully to research subjects that compensation may not be available.
5. Nevertheless, patients who suffer harm should not be involved in disputes between sponsor and investigator over whether or not harm may be attributed to activities 'outside-protocol'. In all cases where the sponsor may seek to shift responsibility for compensation to the investigator, 'highest standards' require that compensation be paid first; the sponsor may then seek to recover from the investigator.

1.2.2 Payments to participants in or parties to commercially sponsored research

1. We recommend that, in commercially sponsored research undertaken by IHS members and involving patients as subjects:
 - a) all participation should be appropriately recompensed, in a manner that reflects work done and at rates and through payments declared to and approved by the relevant ethics committee;

- b) payments *per capita* should be the basis of reimbursement to investigators for most clinical trials;
 - c) disclosure to subjects of research of payments to investigators should be a matter for local ethics committees;
 - d) payments to institutions should fully cover the overhead costs and no more.
2. We believe that payments to research subjects are matters for local regulation and local ethics committees.

1.2.3 Commercial confidentiality and constraints upon freedom of information

1. We recommend that sponsors and investigators commit at outset, in contract within the research protocol, to the principle of trial reports being made publicly available as soon as is reasonably practicable.
2. We support a universal condition, to be imposed by institutional ethics committees, that there is an intention by investigators and sponsors to publish results of research involving patients, whatever they may be.
3. We recommend that IHS, as a matter of policy, endorse moves towards compulsory registration, *before the first patient is enrolled*, of all headache trials conducted from now on throughout the world. We further recommend adoption of specified criteria for a suitable registry.
4. We do not wholly endorse the 2001 statement *Sponsorship, Authorship, and Accountability* issued by the International Committee of Medical Journal Editors, and do not recommend its adoption by *Cephalalgia*.
5. We recommend that IHS consider a system of 'name and shame' in known cases of non-publication of sponsored research. A trial may be deemed non-published 1 year after data-lock if there is not at least one published and citable abstract describing the principal efficacy analysis.
6. We recommend that IHS consider, now and perhaps again in the future, a clinical trials amnesty. This would in essence be an offer to consider for publication trials completed some time ago for which the acceptable time-window for publication had passed.

1.2.4 Exclusion of children from commercially sponsored research

1. We recommend that IHS, in its strategic planning, consider the unmet needs of children and

adolescents with headache and find ways to demonstrate to industry the size and potential commercial value of the market in remedies for childhood and adolescent headache.

2. We recommend that the Clinical Trials Subcommittee produce and publish specific recommendations on end-points for trials in these age groups.
3. We recommend that the World Headache Alliance be brought into this arena, applying pressure from the general population upon sponsors to address these needs.

1.2.5 *The developing world, and its exploitation in commercially sponsored research*

1. We believe it is beyond question that the highest ethical standards should be maintained wherever research involving human subjects is performed. In our view this means that procedures and practices that would not be considered ethical in the sponsor's home country are not ethical if performed elsewhere.
2. The ethical imperative to publish applies to research carried out in the developing world no less than elsewhere. We recommend that reports of commercially sponsored research conducted wholly or in part in developing countries should justify the choice of site(s) and population(s), explicitly stating the potential clinical relevance of the results of the study to each community.
3. We recommend that members of IHS should not become involved in commercially sponsored research that cannot ultimately benefit the population in whom it is conducted, and that IHS publications should not carry reports of such research on the basis that it is unethical.

1.3 *Commercially sponsored clinical services*

1. We believe that direct commercial sponsorship of clinical services is undesirable, but it may be the lesser of two evils when the alternative is no services.
2. The solution to the issues of concern lies in recognition by governments of the unmet health-care needs of large numbers of people affected by headache. We recommend IHS, in its strategic planning, give priority to its activities that will lead towards this recognition.

1.4 *Commercially sponsored education*

1. We believe that the remedy to the issues of concern lies less in controlling sponsors' behaviour

(which is subject to general controls) than in setting standards of behaviour in its relationships with commercial sponsors that IHS should wish to follow and should expect of its members.

2. We believe that education is rightly and must remain a priority amongst the strategic objectives of IHS.
3. We recommend that the educational purpose of the IHC should not be compromised. The implication of this recommendation is that the IHC cannot be organized with the aim, primary or secondary, of maximizing profit.
4. We endorse the present rule that no part of the main scientific programme of IHC shall be directly sponsored by the pharmaceutical industry, and we further recommend that no commercially sponsored event be *any part of*, or held *during or in parallel with*, the scientific or educational programme of any other educational event organized or supported by IHS.
5. We recommend that commercially sponsored satellite symposia or other events that IHS may allow to be held, subject to these conditions, at or in association with any IHS-supported educational events should be clearly described as such; and that the sponsor be identified in the main programme, in the programme of the event if separately printed and on all materials relating to it that the sponsor may produce.
6. We recommend that chairmen and members of programme committees for educational events including the IHC may not, within their period of office, be in receipt of personal financial support or deriving any pecuniary advantage from commercial organizations whose products may be mentioned, or from their commercial allies or competitors, that is likely to create an unmanageable conflict of interest. Chairmen and members of programme committees may not accept commercially sponsored engagements at those events.

1.5 *Marketing*

1. We believe the control of advertising lies with regulators and it is not, generally, an issue relating to relationships between IHS and its sponsors. Nevertheless, there are remedies to some of the issues of concern that lie less in controlling sponsors' behaviour (which is subject to these controls) than in setting standards of behaviour in relationships with sponsors that IHS should expect of its members.
2. Accordingly, we recommend that IHS members do not support or give legitimacy to any

marketing activities of companies that do not conform to the Society's objectives and lead to the meeting of patients' needs. In some matters this is a question of observing the Society's *Policy on Conflicts of Interest for IHS Members* (see section 4.1.3). In others, responsibility rests with the individuals concerned as a professional duty.

2.0 The Subcommittee

2.1 Mission and purpose

The Ethics Subcommittee of the International Headache Society (IHS) ('the Subcommittee') is a standing subcommittee of IHS Council.

Its mission is to promote the welfare of people affected by headache by issuing guidance on ethical issues relevant, in the broadest sense, to research into and the provision of healthcare for headache disorders. In pursuit of this, the Subcommittee is charged with identifying such issues of which the Society should be aware. Further, whenever IHS should have views on these issues, it is charged with leading the formulation of them. Its tasks are to:

- enquire into these issues;
- take evidence from interested parties in order to do so;
- report to Council, with recommendations, where appropriate;
- incorporate in those recommendations advice to Council of actions it might need to take.

The first Report of the Subcommittee, *Ethical issues in headache research and management*, was published in *Cephalalgia* in 1998.

2.2 Membership

The following were members of the Subcommittee during the period 2002–2005 when the Report and Recommendations set out here were developed:

T. J. Steiner (<i>Chairman</i>) Division of Neuroscience and Mental Health, Imperial College London, London, UK	Physician member; headache specialist
J. Afra National Institute of Neurosurgery, Budapest, Hungary	Physician member; neurologist

V. M. Harpwood Cardiff Law School, Cardiff, UK	Lay member; academic lawyer and barrister
H. Isler Talstrasse 65, Zürich, Switzerland	Physician member; neurologist and headache and pain specialist
S. Peroutka Synergia Pharma, South San Francisco, CA, USA	Physician member; neurologist
E. O'Sullivan Department of Neurology, Cork University Hospital, Cork, Ireland	Physician member; general practitioner
J. M. Pereira Monteiro Department of Neurology, Hospital Santo Antonio, Porto, Portugal	Physician member; neurologist
K. Ravishankar Headache and Migraine Clinic, Jaslok Hospital and Research Centre, Bombay, India	Physician member; headache specialist
K. Shannon World Headache Alliance, Toronto, Canada	Lay member; Chief operating officer, WHA
P. Tfelt-Hansen Department of Neurology, Bispebjerg Hospital, Copenhagen, Denmark	Physician member; neurologist; Chairman, IHS Clinical Trials Subcommittee
N. Vaiciene Department of Neurology, Kaunas Medical University Hospital, Kaunas, Lithuania	Physician member; paediatric neurologist

2.3 Background to this report

IHS actively seeks commercial sponsorship for many of its charitable activities. In return, it endeavours to provide benefits of association to its sponsors and it is also the case that commercial sponsors share some of the objectives to which their support will be committed.

IHS members and the Society's partners and other agencies with which it works have expressed the belief that, whatever benefits may derive from them, relationships with the pharmaceutical industry should have a sound ethical basis. Such a basis is of value not only to the Society's beneficiaries but also to the pharmaceutical industry. In its second round of deliberations the Subcommittee has, accordingly, focused upon issues arising from these relationships and more generally from commercial sponsorship. In doing so, the Subcommittee

recognized that the pharmaceutical industry has its own controls. An example of these is the voluntary *PhRMA code on interactions with healthcare professionals* (1), adopted in 2002.

In this, its second Report, the Subcommittee sets out its recommendations for ensuring that a sound ethical basis exists and is maintained. It sees these recommendations as a set of *Operational guidelines governing relationships with commercial sponsors* for IHS, its members and its partners.

As before, the Subcommittee has concentrated upon issues specific to headache; those applying generally are avoided unless having particular relevance or application to headache. General ethical issues are dealt with in general texts on ethics.

2.4 Reference

- 1 Pharmaceutical Research and Manufacturers of America. *PhRMA code on interactions with healthcare professionals*. PhRMA 2002. Available at <http://www.phrma.org/publications/policy>

3.0 Introduction

The Society, and those for whose benefit it pursues its charitable objectives, have without any doubt gained enormously over the last several years from commercial sponsorship, much of it given in the form of unrestricted educational grants. As examples of recent achievements, the Society has raised awareness of headache disorders, fostered recognition by the World Health Organization (WHO) of the huge disability burden they impose worldwide, supported research, promulgated its findings, classified and set out detailed diagnostic criteria for all recognized headache disorders, formulated clinical trials guidelines, advised the European Medicines Evaluation Agency, supported the Cochrane Collaboration, provided education at various levels, stimulated interest in headache disorders as a subspecialty amongst young doctors and brought into being the World Headache Alliance. These are substantial, lasting and worthwhile. Their realization has consumed significant resources and, wherever those resources have come from commercial sponsors without conditions attached, the Society is appropriately and unreservedly grateful.

It is correct to acknowledge here that many, although by no means all of these achievements, and the benefits they have brought directly or indirectly to people affected by headache, were facilitated and in some instances made possible by commercial sponsorship. It is also true that they are

the product of commitments of time, energy, skill and expertise by large numbers of volunteers, which should also be acknowledged although not being the subject of this Report.

Given these undeniably desirable outcomes of commercial sponsorship, why are there concerns about it? And are these concerns around relationships between commercial sponsors and the Society or individuals who influence the Society? In this Report, the Subcommittee attempts to separate the issues in order to identify where each cause for concern lies, and what exactly it is, before suggesting remedies wherever it can. These in general are recommendations aimed at the Society and its members and partners, but there are a few instances where solutions that appear obvious lie with the industry.

The Subcommittee hopes that the Society's commercial sponsors will welcome this document, in which it seeks to set out an ethical basis for rules of engagement for pursuing shared objectives in a spirit of partnership and cooperation. The recommendations within it are intended to supplement and support, not replace, commercial sponsors' own codes of practice.

3.1 The approach to ethical analysis

There are no conclusive answers to many of the ethical problems encountered in the practice of medicine. By exposing and confronting dilemmas, it is often possible to generate a consensus that acceptably balances competing values whilst acknowledging pragmatic considerations such as the limited availability of services and resources. In doing this, the Subcommittee's approach was to consider first the interests of people affected by headache, adopting the general rule that nothing, whatever its benefits elsewhere, should be done against their interests. The second consideration was the interests of the Society.

3.2 Ethical principles, human rights and responsibilities

The Subcommittee recognized the several ethical principles established in medical practice. These include *autonomy* of patients, *justice*, with particular reference to resource allocation in a context of limited resources (distributive justice), *non-maleficence* and *beneficence* (1), together with the medical professional ethical principles of *veracity* (truth-telling), *fidelity* (the keeping of promises) and *confidentiality*.

At the same time, the Subcommittee was aware of more general approaches to medical ethics based, for example, on *human rights*, the *needs* of patients, the *responsibilities* of doctors, the *good of society as a whole* and *deserts*.

Although the Subcommittee considered the worldwide context, any discussion on rights is informed by the *European Convention on Human Rights and Fundamental Freedoms* (2) and by the Council of Europe's Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine (3). Of the various statements of patients' rights, probably the most authoritative and relevant is the *European Charter of Patients' Rights* (4), presented in Brussels on 15 November 2002 (5), which proposed the proclamation of 14 such rights. These, summarized below, 'together seek to render the fundamental rights... concrete, applicable and appropriate to the current transitory situation in the health services' and 'must be recognized and respected independently of financial, economic or political constraints, taking the criteria of the appropriateness of care into consideration' (5).

1. **Right to preventative measures** (the right to a proper health service in order to prevent illness);
2. **Right of access** (equal access for everyone to the health services that his or her health needs require);
3. **Right to information** (about health, the health services and all that scientific research and technological innovation make available);
4. **Right to consent** (based on full information and without prejudice to the right to refuse information);
5. **Right to free choice** (between different treatment options, and including the right to decline treatment);
6. **Right to privacy and confidentiality;**
7. **Right to respect of patients' time** (including the right to receive necessary treatment expeditiously and the right to expect doctors to devote adequate time to their patients);
8. **Right to the observance of quality standards;**
9. **Right to safety** (including the right to be free from harm caused by poor functioning of health services, medical errors or misinformation and the right to expect healthcare providers to prevent errors by monitoring precedents and by receiving continuous training);
10. **Right to innovation** (including the right to new treatments and diagnostic procedures, and the

right to expect health services to promote and sustain research in the biomedical field, paying particular attention to rare diseases);

11. **Right to avoid unnecessary suffering and pain;**
12. **Right to personalized treatment** (the right to diagnostic or therapeutic programmes tailored to each individual's personal needs);
13. **Right to complain** (whenever a person has suffered a harm, and including the right to receive a response);
14. **Right to compensation** (for physical or moral and psychological harm caused by a health-service treatment).

The Subcommittee particularly noted this amongst a number of additional Citizens' Rights (5):

15. **Right to participate in policy-making in the area of health** (including the right to participate in the definition, implementation and evaluation of public policies relating to the protection of healthcare rights);

and also identified the following:

16. **Right to be taken seriously;**
17. **Right to have disability recognized.**

It is generally the case that rights are associated with corresponding responsibilities, and this is true in healthcare. The *US President's Advisory Commission on Consumer Protection and Quality in the Health Care Industry* expressed it thus (6): 'In a health care system that protects consumers' rights, it is reasonable to expect and encourage consumers to assume reasonable responsibilities. Greater individual involvement by consumers in their care increases the likelihood of achieving the best outcomes...' The Commission went on to list a number of such responsibilities, of which the most relevant and important in the context of this Report are:

- to become involved in specific healthcare decisions;
- to work collaboratively with healthcare providers in developing and carrying out agreed-upon treatment plans;
- to disclose relevant information and clearly communicate wants and needs;
- to recognize the reality of risks and limits of the science of medical care and the human fallibility of the healthcare professional;
- to be aware of a healthcare provider's obligation to be reasonably efficient and equitable in providing care to other patients and the community;
- to report wrongdoing and fraud to appropriate resources or legal authorities.

3.2.1 Specific relevance to headache

It is argued that some at least of the patients' rights listed above are threatened generally by healthcare spending cuts (5). In the context of healthcare for headache, the *right to preventative measures*, the *right of access*, the *right to information*, the *right to free choice*, the *right to respect of patients' time*, the *right to the observance of quality standards*, the *right to innovation*, the *right to avoid unnecessary suffering and pain* and the *right to personalized treatment* are all clearly and directly threatened by the low priority accorded everywhere to headache disorders.

The *right to be taken seriously* and the *right to have disability recognized* are notably relevant. Probably because there is no objective evidence of illness, people disabled by headache disorders are often not taken seriously.

The *right to safety*, especially the right to be free from harm caused by the poor functioning of health services, medical errors and misinformation, finds special relevance in iatrogenic illness exemplified by medication-overuse headache.

The *right to innovation* implies a right to expect appropriate research to be carried out. Much of the world's resources for therapeutic research in headache have for some years been committed to migraine-dominated and market-dictated studies, with emphasis on triptans, despite that these are not any part of the answer to headache for the majority of the world's headache sufferers.

The *right to innovation* is infringed in children and the elderly because therapeutic research into headache disorders in these groups is difficult and market prospects are small, so it is not done. As a result, both groups are treated with drugs used off-licence and without a good evidence base. The *right to safety* is secondarily infringed.

People with unusual headache disorders (orphan diseases), including trigeminal autonomic cephalalgias, which are not so rare, are similarly disadvantaged.

Curtailling the *right of access*, the *right to free choice*, the *right to personalized treatment* and the *right to avoid unnecessary suffering and pain* are the disappearance from markets of useful and cheap headache drugs with low commercial value, and the selective placement of new headache drugs only in high-value markets. The *right to avoid unnecessary suffering and pain* and the *right to safety* are arguably breached by the advertising of inappropriate drugs or doses of drugs, or of drugs in inappropriate ways, that leads directly or indirectly to headache mismanagement.

The *right to respect of patients' time* is especially relevant given that time is a notable casualty of headache disorders. It is also clear that the nature of headache disorders demands that doctors devote adequate time to their patients affected by them.

3.3 References

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3.4 General sources and materials

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- 3 British Medical Association. Medical ethics today. The BMA's handbook of ethics and law, 2nd edn. London: BMA 2004.
- 4 Council for International Organizations of Medical Sciences. International ethical guidelines for biomedical research involving human subjects. Geneva: CIOMS 1993.
- 5 Council for International Organizations of Medical Sciences. Declaration of Ixtapa: global agenda for bioethics. Geneva: CIOMS 1994.
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- 7 Kant I. *Groundwork of metaphysics of morals*. New York: Harper and Rowe 1958.
- 8 Nuremberg Code (forming part of the judgement in United States vs. Karl Brandt. Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law no. 10, vols 1 and 2: The Medical Case. Military Tribunal I, 1947). Washington, DC: US Government Printing Office 1948–9.
- 9 United States Food and Drug Administration. Final guidance on industry-supported scientific and educational activities. Federal Register 8 December 1997.

- 10 World Medical Association. Declaration of Helsinki: Ethical principles for medical research involving human subjects. Helsinki, Finland: 18th WMA General Assembly, 1964. Revised Tokyo, Japan: 29th WMA General Assembly, 1975; Venice, Italy: 35th WMA General Assembly, 1983; Hong Kong: 41st WMA General Assembly, 1989; Somerset West, South Africa: 48th WMA General Assembly, 1996; Edinburgh, United Kingdom: 52nd WMA General Assembly, 2000.
- 11 World Medical Association. Declaration of Lisbon on the rights of the patient. Lisbon, Portugal: 34th WMA General Assembly, 1981. Amended Bali, Indonesia: 47th WMA General Assembly, 1995.

4.0 Report, and recommendations

4.1 Conflicts of interests in relationships with commercial sponsors

4.1.1 Statement of the problem

In some respects the relationship between sponsors and IHS members is symbiotic, and it is inevitable that conflicts of interest will arise in any such relationship. A conflict of interest exists when personal or other interests have the potential to impair professional objectivity in providing a judgement or taking an action affecting the interests of those to whom a professional duty is owed.

Conflicts of interest are a condition, not an aspect of behaviour (1). Interests that create conflicts are often entirely legitimate, and may be necessary and desirable in an individual's professional life (2). Conflicts of interest are therefore common. They become a problem only when they *inappropriately* influence or appear to influence professional judgement or behaviour, and they concern IHS when these relate to the goals of HIS, including excellence in the provision of healthcare and education and in the conduct of research. Accordingly, the Subcommittee takes the view that a member of IHS has a conflict of interest whenever he or she has personal or other interests that may unduly influence actions or decisions as a member of the Executive Committee, Council or any subcommittee or task force, or in any other way on behalf of IHS, or as a researcher, author, teacher, speaker, reviewer or editor in the field of headache. A conflict of interest may put IHS itself at risk of such influence.

Interests with potential influence include academic competition, intellectual passion, personal relationships and political and religious beliefs. However, those likely to have undue influence are most commonly financial relationships, and these are of particular importance in the context of research, conferences, publications and publicity.

Such conflicts of interest arise in most engagements of headache organizations and individuals with commercial sponsors, but that is not to say they are generally unmanageable. For IHS, the overarching conflict is that it seeks to raise money into a general pool for activities of its choosing, whereas sponsors wish to fund projects with visible outcomes that, in some way, accord with their commercial objectives.

The Subcommittee made the following analysis of the environment.

1. IHS and its members need sponsorship

- IHS needs financial support for its many worthwhile activities that bring benefits to people affected by headache disorders. This is particularly evident in its educational activities, which cannot be supported at their present level but for commercial sponsorship. Income-generating opportunities for IHS are limited to the IHC (itself dependent on commercial sponsorship), the journal *Cephalalgia* and sales of reprints (including guidelines) and fees of paying members. IHS has nothing else to sell except, perhaps, space to commercial advertisers.
- Researchers need sponsorship, not for all research but for some. Necessary headache research is rarely income-generating or cost-free. It always has an opportunity cost: research takes time from patient care.
- Healthcare professionals working in headache management need sponsors, partly to improve service provision and partly to attend meetings contributing to continuing professional development (CPD).

2. Non-commercial sponsorship is not nearly sufficient

- Throughout the world, healthcare for headache and research into the better management of headache have low priority for government support. Funding is rarely provided at any useful level. Oversight of research in the manner necessary to safeguard the interests of people with headache does not exist.
- Public finance for headache education, care and research is available from charitable and patient-led organizations set up with support for these specifically amongst their objectives. These non-commercial sources of sponsorship have been and are of significant benefit to headache sufferers in some countries, but overall are limited and patchy and the support they provide again has no controlling oversight.

- Other sources of non-commercial sponsorship exist: charitable foundations, industry in general (which bears the major costs of headache) and the insurance and lifestyle industries. Resources are needed to develop these.
 - Professional fundraisers bring other problematic issues. High costs, demands for percentage payments (illegal in the charitable sector in some jurisdictions) and the absence of any guarantees of success have militated against their employment.
 - Donations or bequests from individuals are not a likely source of income for IHS and actively to seek them would bring IHS into conflict with lay and national groups.
3. *A subculture of financial dependency upon the pharmaceutical industry affects the headache world*
- This lack of public investment is at the heart of the problem, fostering policies of soliciting commercial sponsorship to meet needs.
 - Lack of motivation has contributed to it. It has been too easy for some time to raise pharmaceutical sponsorship—a situation that is changing.
 - In research, payments to investigators and their departments for commercially sponsored research far exceed (in terms of money for hours) what is received for the conduct of government-funded research.
4. *Commercial sponsors have commercial objectives*
- ‘He who pays the piper calls the tune.’ Because resources are not adequately provided from elsewhere, there is a danger of choices in headache research and education being substantially dictated by the pharmaceutical industry. Sponsors’ commercial interests direct what they will support, which determines in large part the focus of research, educational and other activities that are dependent upon their support (3).
5. *The result is not a fair distribution of resources according to need*
- Educational events are most likely to receive commercial sponsorship when focused upon marketable therapies.
 - Although massive pharmaceutical investment into drug development programmes over the last decade has brought and continues to bring undoubted benefits to sufferers from migraine, these represent fewer than one-fifth of all sufferers from headache. The majority, those with tension-type headache, and the most disabled, those with chronic daily headache, have no comparable levels of expectation from commercially sponsored research.
- Research on orphan drugs and rare diseases is rarely supported.
 - Traditional and complementary medicine and a range of devices marketed for headache are valid topics of research that are unlikely to be sponsored.
 - When commercially sponsored research leads to the marketing of a new treatment, premium pricing to recover costs may mean that many people who might benefit from it have little opportunity to do so.
 - Several patients’ rights (see section 3.2) are jeopardized: the *right to innovation*, the *right to access*, the *right to preventative measures* and the *right to avoid unnecessary suffering and pain*.
- Conflicts of interest arise readily in this environment. They can be listed as follows. Not all are unmanageable or necessarily undesirable, but some self-evidently are.
- A. *Conferences have divided purpose*
- Scientific or educational programme content of conferences can reflect participants’ needs or sponsors’ wants, but not wholly both. In theory, participants are attracted by meeting their needs; in practice, the audiences at these events, including teaching courses, are largely those in receipt of sponsorship.
 - Therefore conferences, especially the IHC, can seek either to educate or to generate income, but one or other of these must be the clear and primary objective.
 - Sponsored satellite symposia hosted by large conferences, especially the IHC, attract large payments. They are seen as part of the event, but there has been little control over content.
- B. *Editorial objectivity has a financial cost*
- Payments, sometimes substantial, are offered in return for the publication in *Cephalalgia* of sponsored supplements. There is no control over content.
 - Reports of sponsored research are submitted for publication in *Cephalalgia* with high prospects for large reprint sales contingent upon acceptance (4, 5).
- C. *Association gives legitimacy*
- The acceptance by IHS of sponsorship from companies sometimes gives undeserved legitimacy by association to practices that those companies may be engaged in.

D. *Advisory boards serve a need, but can be suborned*

- It is highly desirable that the industry, if it is to meet the needs of people with headache, should be properly advised of those needs and how best to meet them by headache experts and/or lay advocates.
- Advisory boards may serve this purpose well by informing commercial planning.
- Equally, since sponsors control the advisory process, advisory boards and expert clinicians are sometimes used only to give a semblance of respectability to a company's commercial planning, or to 'create a climate of opinion favourable to a new agent' (6).
- Members of advisory boards are paid for their advice and continued membership may be contingent upon the advice that is given.

E. *Commercial sponsors and lay groups*

- Lay groups are of great potential value to people with headache and, sometimes, they have significant influence. For example, in Ireland there would not be headache clinics if there had been no lay group to lobby government to set them up.
- Lay groups have conflicts of interest when directly supported by sponsor companies—particularly when there is reliance upon one. In reality, small organizations may owe their existence to a commercial sponsor, whilst many larger organizations are in part dependent on one or more. For this not to be a problem requires sophistication to recognize and strength to resist unwanted influence in what is invariably an unequal partnership (7). Why do pharmaceutical companies support patients' organizations? One commentator believes it is because they seek their help in achieving market expansion and first-line use of their own rather than their competitors' products, and in lobbying against restrictive regulation, and they gain corporate social responsibility points (7). None of these is necessarily contrary to patients' interests.
- Recent comment has been critical of the use of 'front' groups by the pharmaceutical industry (8). The Subcommittee believes such groups flourish in the headache field.
- Lay groups have clear conflicts of interest when offered educational funding in return for public endorsement of a single marketed product without reference to others of similar efficacy.

- Lay groups may have conflicts of interest when asked by drug companies to give their endorsement to trials or other research, including market research, with commercially useful outcomes. Often these are already completed, so that there can be no input into or control over (or sometimes even knowledge of) the methodology. Even when no direct financial inducement is attached to such requests, they may imply contingent favourable consideration for future much-needed sponsorship. Lay groups may similarly have conflicts of interest when asked to conduct or give their names to trials involving devices and other non-pharmaceutical treatment options at the behest of manufacturers. These may be done with good intent to inform members and others, or for financial reward. In either of these cases, non-scientific methodology can produce misleading results.

Secrecy has been identified as the real cause for concern (6)—since it suggests intent and therefore reason to hide something—and transparency as the key to its remedy (1). At issue therefore is the extent to which, if at all, declarations of conflicts of interest disarm them (9). There are those who think not sufficiently (10).

In addition to all of the above issues, offers by drug companies, and the acceptance by doctors, of gifts and hospitality, whether with conditions or not, are bound to cause those looking on to wonder if such doctors might be influenced in any way (11). The nature and scale of what appears acceptable varies widely around the world (12, 13).

It is not easy to propose 'one-size-fits-all' global ethical solutions, as though the issues and their implications were constant worldwide. Clearly they are not (14).

4.1.2 *References*

- 1 Smith R. Beyond conflict of interest. *BMJ* 1998; 317: 291–2.
- 2 Thompson DF. Understanding financial conflicts of interest. *N Engl J Med* 1993; 329:573–6.
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- 11 McGuaran A. Royal college issues new guidelines on gifts from drug companies. *BMJ* 2002; 325:511.
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- 14 Ana J. Doctors and journals in the South cut off drug companies at their peril [letter]. *BMJ* 2003; 327:341–2.

4.1.3 Recommendations

1. We believe that the ultimate solution to unmanageable conflicts of interest is removal of the context that gives rise to them.
2. We recommend therefore that IHS actively seek funding from other sources than the pharmaceutical industry, promoting the message that it is in the interests of society and employers to manage headache better. Although it may not be exploited easily, we believe this opportunity exists to reduce dependence on commercial sponsorship, because so much of the burden of headache is economic, borne by society and employers.
3. We recommend that IHS formally adopt the following as the Society's *Policy on Commercial Sponsorship*.

Policy on commercial sponsorship

IHS welcomes commercial sponsorship of its activities as an opportunity to work with its partners in the pharmaceutical industry towards shared objectives. As a registered charity, and in the interests of transparency, the Society sets out its policy for acceptance of commercial sponsorship.

1. The Society will endeavour always to be fair and non-discriminating in its dealings with commercial sponsors.
2. Sponsorship, whether in the form of unrestricted or restricted financial support or in-kind product or service donations, will be accepted by the Society solely for the pursuit of its charitable objectives.

3. The Society recognizes that commercial sponsors may legitimately be seeking to serve their other interests when making donations, but the Society will not feel obliged to act in those interests or be steered in its decisions by them.
4. The Society will decline or limit sponsorship that creates risk of dependence upon any single commercial sponsor.
5. The Society will not accept sponsorship from one pharmaceutical company intended to have the effect of giving it a competitive advantage over another or others.
6. The Society will not accept sponsorship in return for product endorsement.
7. The Society will not accept sponsorship from companies connected with industries that, in its opinion, directly damage human health.
8. Commercial sponsorship arrangements will be managed transparently, and publicly acknowledged.

4. We recommend that IHS endeavour to extend its relationships with industry based on equal partnership rather than dependent upon sponsorship.
5. We recommend that, within the context of its strategic planning, IHS review and state unambiguously the primary objective of the IHC. Our preference is that this event should be returned uncompromisingly to its original mission of education. Further reference to this is made in section 4.4.
6. We recommend that IHS, together with the Editor-in-Chief of *Cephalalgia*, develop and publish a policy with respect to the review and acceptance of articles likely to generate substantial income from reprint sales.
7. We recommend that IHS, through this Ethics Subcommittee, develop and publish a *Statement of Values* that it will hold as non-negotiable in all its dealings, to which it will adhere in the pursuit of its objectives and to which as a matter of policy it will expect its members (whether individuals or national societies) and partners, including sponsors, to subscribe.
8. We recommend that every member of IHS who has a position of leadership or influence in the Society or in the headache field more generally be required to read, understand, sign and comply with the Society's policy on conflicts of interest.
9. We recommend the following be adopted as the Society's *Policy on Conflicts of Interest for IHS Members*.

Policy on conflicts of interest for IHS members

This policy applies to all members, but Members of Council (the Society's Trustees) have in addition a general duty to act in the best interests of the Society. They have a conflict of interest whenever they may act in order to gain financial or other benefits for themselves, their families, friends, colleagues, institutions or organizations.

Because a conflict of interest may impair integrity of judgement, or cause reasonable persons to believe that judgement has been improperly influenced (1, 2), the Society is of the view that conflict-of-interest situations should be regulated. The three main controls are:

- (a) disclosure that a conflict of interest exists;
- (b) avoidance of conflicts of interest that might be unmanageable; and
- (c) prohibition of situations that would give rise to clearly unmanageable conflicts of interest or to the perception that such conflicts are highly probable.

The Society's policy with respect to these controls is to achieve transparency—thus protecting the Society and those with whom it has dealings—with least encroachment upon its members' personal and professional freedoms.

(a) Disclosures

By acknowledging financial conflicts of interest, IHS members and office-holders take the *minimum* step necessary in mitigating any undue influence.

Disclosures of relevant financial interests are required from all members of IHS committees, subcommittees and task forces, all authors and editors of IHS publications, all reviewers of content of IHS publications and meetings, and all speakers and poster presenters at IHS events.

A relevant financial interest exists whenever personal remuneration having a significant financial value has been received from or promised by a company whose products (or whose allies' or competitors' products) may be discussed in or affected by those publications, meetings or committee or task-force proceedings. In this context, 'personal remuneration' includes hospitality, personal sponsorship for professional purposes and payments into a research fund under the person's control. 'Significant

financial value' is intended to mean that small gifts, but nothing more, may be ignored.

Belief, however confident, that a conflict of interest does not influence judgement does not excuse failure to disclose a relevant financial interest (3). In determining what is relevant to be disclosed, a general declaration (suggesting that no conflicts of interest therefore exist) of 'relationships (whether specified or not) with all or most companies is not sufficient.

Disclosures should be made as follows:

- IHS committee and task force members: disclosure on the IHS website of all relevant financial interests, as they occur, throughout the period of office;
- Editor and associate editors of *Cephalalgia*: disclosure annually in the journal of all relevant financial interests in the preceding 12 months and disclosure on the IHS website of the same, as they occur, throughout the period of office;
- Reviewers of IHS publication content: disclosure, at the time of commissioning of the review, of all relevant financial interests to the commissioning editor or associate editor, who is charged with using judgement to decide whether any of these creates so unmanageable a conflict as to disbar the reviewer;
- Reviewers of IHS meeting content: disclosure on the IHS website of all relevant financial interests, as they occur, throughout the period of influence;
- Authors and poster presenters: disclosures of all relevant financial interests within the published paper or poster;
- Speakers: relevant disclosures at the commencement of their talks; abstracts, if published, should carry the words 'The author(s) declared a financial conflict of interest';
- For all IHS-supported lectures and publications referring to commercial products: a list should be provided that clearly differentiates those in which, through any financial relationship with a commercial company, the speaker/author has an interest from those in which no such interest exists.

Specifically, in each of the above, members should identify each relationship with commercial sponsors within the following categories:

- (a) research grant or contract support administered through an academic or research institution;

- (b) personal compensation (as opposed to institutional salary support) through:
 - i. consultancy or advisory board contracts;
 - ii. grants;
 - iii. honoraria, fees or salary;
 - iv. hospitality;
- (c) personal financial investment including ownership, equity or other financial holdings; and
- (d) direct paid employment.

IHS will maintain a 'Conflicts of interest' section on its website; all disclosures will be listed there and repeated in relevant (e.g. committee) pages.

Ghost authorship. Mandatory disclosure of every conflict of interest applies to all authors. Omission from the list of authors of an individual who qualifies for authorship—and may have played an important role in drafting the manuscript and 'shaping' its message—has been documented in review articles (4). The perception is that these individuals are often employees or representatives of pharmaceutical companies (5), whilst their omission from the authorship list avoids disclosure of their conflicts of interest.

This practice is academic misconduct. A statement to this effect will be included in the *Guidelines to authors* published in *Cephalalgia*: 'In all submissions to *Cephalalgia*, including supplements to *Cephalalgia*, the corresponding author is charged with identifying all individuals who qualify for authorship and with verifying that all such individuals are listed as authors.'

(b) *Avoidance of conflicts of interest*

Avoidance is necessary of conflicts of interest that might be unmanageable. Members of IHS with positions of leadership or influence in the Society, including editors, reviewers, speakers and committee members, are expected to decline to undertake any activities involving such conflicts.

For example, members of the IHC scientific programme committee, or any other person in a position to determine programme content, should exclude themselves from any content decisions involving the products of companies that currently provide them with financial support or those of their competitors.

(c) *Prohibition*

The Society wishes to keep prohibitions to a minimum, relying upon members' good faith.

There is one. Members of the scientific programme committee of any IHS meeting, including and particularly the IHC, are prohibited from speaking publicly on behalf of a commercial sponsor during that meeting.

References

- 1 Thompson DF. Understanding financial conflicts of interest. *N Engl J Med* 1993; 329:573–6.
- 2 International Committee of Medical Journal Editors. Conflict of interest. *Lancet* 1993; 341:742–3.
- 3 Smith R. Beyond conflict of interest. *BMJ* 1998; 317:291–2.
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- 5 Rennie D, Flanagan A. Authorship! Authorship! Guests, ghosts, grafters, and the two-sided coin. *JAMA* 1994; 271:469–71.

10. We make no recommendation on the acceptance of gifts and hospitality other than that these should be reasonable, unconditional and, if appropriate, declared. Worldwide cultural variation makes any general statement difficult. Doctors, wherever they are, may consider this test question: 'Would you wish your patients, your employer and/or the local press to witness the gift or hospitality being received?' If the response is 'yes', there is unlikely to be a problem.

4.2 *Commercially sponsored research*

The Subcommittee defines *sponsored research* as any clinical trial or other research conducted at the behest of, and the costs of which are at least in part covered by, a company or organization that retains a commercial interest in the results.

It should, by way of introduction to this section, first be noted that much of the therapeutic innovation of the last two decades and more has been the result of industry-sponsored research. This is true generally (1, 2) and it is true in the headache field. The pharmaceutical industry continues to drive clinical research and, if some commentators find this undesirable, they attribute blame in part to others, including academia (3).

4.2.0.1 References

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- 2 Bonaccorso S, Smith R. In praise of the devil. *BMJ* 2003; 326:1220.
- 3 Remuzzi G, Schieppati A, Boissel J-P, Garattini S, Horton R. Independent clinical research in Europe. *Lancet* 2004; 364:1723–6.

4.2.1 Compensation for injury to subjects of commercially sponsored research

4.2.1.1 Statement of the problem

This issue is clearly relevant to patients' *right to safety, right to avoid unnecessary suffering and pain and right to compensation* (see section 3.2). Although the last was envisaged in a therapeutic rather than a research context, the patient who enters a commercially sponsored research study does not thereupon cease to be a patient needing treatment. Compensation of subjects harmed during the course and as a result of their sponsored research is therefore an important responsibility of sponsors. It is subject to legislation and other regulations and less formal controls that vary across and even within countries in both developed and developing worlds (1–4). In some jurisdictions, a distinction is made between harms arising with and without fault. Around the world there is no uniformity and varying formality in the provision of no-fault compensation, which is the most desirable remedy for patients put at risk primarily for the benefit of others.

Difficulties are foreseen in attempting to impose change. A demand that arrangements for compensation in sponsored research should be backed by law is not an achievable solution if it depends on legislation to be enacted in every country. A recommendation that sponsored research should not be carried out by IHS members in countries where compensation is not regulated at all, or adequately, may go too far. A requirement for sponsors to make contractual commitments to compensation may be proposed, provided that a contract will be binding as between all relevant parties.

An aspect of particular concern is presented when investigators carry out research or other activities other than in accordance with the agreed experimental protocol. It is usual for sponsors who underwrite compensation arrangements to exclude the consequences of such acts, whilst patients who may be affected cannot know what is and what is not laid down in the protocol. When such a situation arises, apart from any other harm that may be suffered, there has been a breach of the patient's *right to consent* based on full information (see section 3.2). The concern does not merely relate to 'add-on' experiments by investigators pursuing their personal interests opportunistically, although

these are worrying. Patients recruited to sponsored research in violation of exclusion criteria, for example, may find themselves both at greater risk of harm and without remedy from the sponsor if they sustain harm. No specific cases are known to the Subcommittee of harms that have not been compensated, but a solution to this problem is needed before such a case arises.

4.2.1.2 Specific relevance to headache

The particular relevance to headache is that clinical research is generally conducted in people with little prospect of direct benefit as trial participants. They may be required to travel to research centres whilst unwell during acute attacks, when they would otherwise stay at home. All research that takes new chemical entities into patients carries unknown risks, whilst the pathophysiological mechanisms of the primary headache disorders, and the potential for unexpected pharmacodynamic interaction, remain unclear.

4.2.1.3 Recommendations

1. We believe that compensation for harm to patients and healthy volunteers arising from sponsored research should be a requirement, regardless of fault, everywhere in the world where sponsored research is conducted.
2. We recommend therefore that sponsors voluntarily apply the highest standards everywhere, without variation and regardless of local less-demanding requirements.

Highest standards in our view include commitment to compensate fully with or without legal liability whenever harm occurs and the test for causation (see below) is met. They require that the scope of compensation include financial losses resulting from, and costs of medical care to remedy (to the extent possible), harms to health as well as financial compensation for physical or mental injury.

Highest standards also require that patients be fully informed of their rights to compensation, and the scope and limits of this compensation should be clear to them at the time of entry to research. Sponsors may not derogate from the obligation to pay compensation on the basis of a patient's apparent consent to forego it.

The *test for causation* should rest on whether the harm arose because the patient or volunteer was involved in the research (i.e. 'but for the research, it would not have occurred'). We accept that the scope of this cannot be unlimited. For

example, the inclusion of journeys to and from a research centre during an acute attack is reasonable and in our view necessary, but similar journeys for routine visits may be thought too remote.

3. We recommend that IHS members should not undertake sponsored research where these arrangements are not in place.
4. Investigators who undertake 'add-ons' to a sponsored study must accept and make due provision for their responsibility to provide compensation, or otherwise explain very carefully to research subjects that compensation may not be available.
5. Nevertheless, patients who suffer harm should not be involved in disputes between sponsor and investigator over whether or not harm may be attributed to activities 'outside-protocol'. In all cases where the sponsor may seek to shift responsibility for compensation to the investigator, 'highest standards' require that compensation be paid first; the sponsor may then seek to recover from the investigator.

4.2.1.4 References

- 1 Barton JM, Macmillan MS, Sawyer L. The compensation of patients injured in clinical trials. *J Med Ethics* 1995; 21:166-9.
- 2 Guest S. Compensation for subjects of medical research: the moral rights of patients and the power of research ethics committees. *J Med Ethics* 1997; 23:181-5.
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4.2.2 *Payments to participants in or parties to commercially sponsored research*

4.2.2.1 Statement of the problem

Many clinical trials nowadays, and some other research involving patients, are carried out not for academic interest but as contract research. Investigators may have neither input into the protocol nor any prospect of being an author of publications from it. Such trials are conducted for financial reward, with payments usually at high levels, albeit often (but not always) to support a clinical service or other research. This being so, the following issues are perceived to arise.

1. *Payments to investigators*

Payments *per capita* have become the accepted norm. Despite concerns about trafficking in

human individuals and inducement to recruit perhaps unsuitable patients (1), they are the only practical and feasible basis for compensating for work done.

Arguably, subjects of research should be informed of both the fact and the amount of these payments to investigators when their consent to participate is sought (2), since this falls within their *right to consent* based on full information (see section 3.2). However, the Subcommittee found this to be subject to cultural variation and irreconcilable differences of opinion. In different circumstances the information might make prospective subjects more or less inclined to participate.

Sponsor companies who give investigators a financial stake in the success of a product undergoing trial create a situation of conflict of interest that is likely to prove unmanageable, and it is unethical behaviour by both parties. It is said to be 'not uncommon', at least in the USA (3).

2. *Payments to institutions*

It is entirely reasonable that overhead costs of research should be fully covered in sponsors' payments to institutions. But overheads charged by institutions that do not fairly reflect their contribution to a study—sometimes by institutions that accept no responsibility at all towards the study—impede research. If the research is worthwhile, that inflicts a harm and infringes, or is a third-party interference in, patients' *right to innovation*.

3. *Payments to subjects*

Payments by sponsors to subjects of research are not a problem to the extent that they reimburse out-of-pocket expenses. They raise ethical issues when intended to pay for time, effort and commitment because of the potential inducement to some if not all subjects. Inducement threatens patients' *right to free choice* (see section 3.2).

4.2.2.2 Specific relevance to headache

These issues are general. However, activity amongst pharmaceutical companies developing antimigraine drugs remains high. Competition for the services of investigators reflects a shortage of experienced clinical trials facilities. Sponsors are looking more and more to investigators, sites and geographical areas new to the conduct of clinical trials in headache. Thus it is particularly true of headache that few trials now are carried out primarily for academic interest.

4.2.2.3 Recommendations

1. We recommend that, in commercially sponsored research undertaken by IHS members and involving patients as subjects:
 - (a) all participation should be appropriately recompensed, in a manner that reflects work done and at rates and through payments declared to and approved by the relevant ethics committee;
 - (b) payments *per capita* should be the basis of reimbursement to investigators for most clinical trials (this slightly modifies the reserved recommendation in our first Report (4));
 - (c) disclosure to subjects of research of payments to investigators should be a matter for local ethics committees;
 - (d) payments to institutions should fully cover the overhead costs and no more.
2. We believe that payments to research subjects are matters for local regulation and local ethics committees.

4.2.2.4 References

- 1 Steiner TJ. Ethical aspects of headache treatment trials. In: Olesen J, Tfelt-Hansen P, editors. *Headache treatment: trial methodology and new drugs*. Philadelphia: Lippincott-Raven 1997:71–8.
- 2 Rao JN, Sant Cassia LJ. Ethics of undisclosed payments to doctors recruiting patients in clinical trials. *BMJ* 2002; 325:36–7.
- 3 Wadlund J. Heading off a clinical trial liability lawsuit. *Appl Clin Trials* 2003; 12:50–3.
- 4 Ethics Subcommittee of the International Headache Society. *Ethical issues in headache research and management. Report and recommendations*. Cephalalgia 1998; 18:505–29.

4.2.3 Commercial confidentiality and constraints upon freedom of information

4.2.3.1 Statement of the problem

Issues of *patient confidentiality* were considered in our first Report (1). Patients' *right to privacy and confidentiality* is identified in section 3.2. The principle of medical confidentiality, set out in the Hippocratic Oath, finds support in virtually all guidance to doctors on matters of ethics throughout history and across the civilized world. It is deeply rooted in pragmatism and belief in mutual trust and respect as essential ingredients of the doctor/patient relationship. Patients who are not assured of confidentiality—and therefore fail to disclose relevant details—may not receive effective treatment. Whilst patient confidentiality needs protection in

sponsored research, these issues will not be discussed again in this Report.

Concerns exist also about the security of health and healthcare information held about patients given that some of this information has commercial value and has become a tradable commodity. Such concerns are magnified in the light of electronically held data that may be accessible by fraudulent means. This is a general issue, relevant but not specifically so to headache.

Throughout the world, protection is also given to commercially sensitive information. Whilst therefore clinical trials frequently depend for their effectiveness on the free flow of information about patients, the commercial companies behind them have an interest in maintaining secrecy during the development of new pharmaceutical products. This issue of *commercial confidentiality* requires extensive discussion, not because of the value the Subcommittee attaches to it but because of the far-reaching consequences it has had.

In summary, the conflict is this. Commercial sponsors have strong commercial reasons for controlling the information flow from their research on the one hand. On the other, publication of research is an ethical imperative (2). This means full publication, not hiding a study that has produced 'inconvenient' results behind only a misleading abstract (3).

Failure to publish research involving patients is unethical because the research will have put participating patients at risk for no purpose. Failure to publish vitiates patients' consent if this was given on the understanding that the research was for the future benefit of others. Failure to publish is unethical because it creates knowledge bias. Medical understanding worldwide is developed in part on the published results of previous research work (4), whilst future research properly takes into account all that has been done before. Both are at risk of being misled if what is published presents only a partial account of past research, especially if the part that is missing is 'selected' (5). Failure to publish research permits its suppression and, should fraud be intended, permits that too (6). Patients' *right to consent*, their *right to information*, their *right to respect of their time*, their *right to innovation*, their *right to avoid unnecessary suffering and pain* and their *right to safety* (see section 3.2) are all actually or potentially infringed by failure to publish.

For all these reasons, anything less than full adherence to the principle of public availability of clinical trial reports lets down the patients who take

part in them (7) and those who might benefit from them in future or be protected against what has been shown to be unhelpful. This is true generally and it is true of commercially sponsored trials, but current regulations and practice may not prevent some sponsors delaying or preventing the dissemination of findings that do not support their commercial, professional or managerial interests (8–12). Sponsored research is less likely to be submitted for publication when results do not fit the sponsors' marketing strategy (13).

The solution with regard to sponsored clinical trials lies in registration, and there have been voluntary stalled and re-started attempts to set up a register of trials (14–16). Clinical trials should be publicly registered at their inception, as the Cochrane Collaboration now urges (17). Whilst no existing comprehensive system supports the organization and dissemination of information about ongoing clinical trials which would help in tracking them from start to publication (18), important developments are achieving change. WHO, since April 2004, has been registering on-line all trials approved by its ethics review board (19) and is now urging research institutions and sponsor companies to follow suit. The USA through the National Institutes of Health has a publicly funded register at <http://www.clinicaltrials.gov> (20). In Europe, the EU requirement for national ethics committees gives impetus to one possible solution: that, since ethics committees are moving towards making their records public, trials registers are becoming feasible even without full industry cooperation (21). The compulsory register of all trials of medicinal products in Europe (EUDRACT) is not public, but again is a move in the right direction. These developments and some bad publicity (e.g. (16)) have led to moves towards voluntary public registration of trials despite that many arguments are mounted against disclosure (22). Agreement was reached between the world's main pharmaceutical industry trade associations and key pharmaceutical companies in January 2005 to disclose, on free and publicly accessible databases, regardless of outcome, the summary results of completed industry-sponsored trials of any medicine approved for marketing in at least one country (23). In addition, details of trials (other than exploratory trials) will be registered within 21 days of starting patient enrolment (24).

Publication of completed sponsored research depends upon its being written up. This task clearly belongs as a professional duty to the investigators, or an agreed subgroup of them (25), but the

self-discipline to do it is not always found. Authors have academic responsibility for what is published in their name. Co-authorship may involve an element of trust, but this does not relieve any author of this responsibility. Use of medical writers is controversial because they do not have to defend their writing as named authors and do not share this responsibility. Their allegiance is to those who pay them, and it is unsurprising if this becomes reflected in their presentation of results—some omitted and others emphasized—to set them in a 'helpful' light. Bias of this sort in published work may be more misleading than non-publication.

The protective intervention of academic institutions might be a solution, but they have become commercial enterprises in their own right (26), and appear unhelpful. A recent survey in the USA concluded: 'Academic institutions routinely engage in industry-sponsored research that fails to adhere to [International Committee of Medical Journal Editors] guidelines regarding . . . publication rights' (27). And it should in fairness be added that selective reporting of trial outcomes is not limited to sponsored trials (28).

Once research is written up, publication is in the hands of journal editors who reject much of what is submitted. The grounds include poor methodology, poor writing, irrelevance to the journal, adverse comment from reviewers who are not always impartial, and a host of other reasons (2, 29, 30). These problems are outside the scope of this Report. On the other hand, it is relevant that the prospect of large numbers of reprint sales is an inducement to a journal to accept a manuscript for publication (see section 4.1.3).

There is evidence that clinical trials with positive results are more likely to be written up as manuscripts, submitted for publication when written and published when submitted (31). All of these influences work against studies that confirm null hypotheses, although such findings may be clinically important. They also undermine (or thwart) overview analyses by preselection of favourable data for deposition in the public domain (7, 29, 32, 33).

Poor research is not worthy of publication. The ethical issue in such cases lies not in non-publication but in the undertaking and conduct of poor research and was discussed in our first Report (1).

4.2.3.2 Specific relevance to headache

Headache treatment, as any other, should be based as far as is possible on evidence of efficacy and safety. The most reliable evidence is from

randomized controlled trials, and the best evidence is gained by overview of all such trials that have been done. This requires the results of all such trials to be in the public domain. In the headache field they are not. For example, a review of the literature on prophylactic trials found that every class of prophylactic was, apparently, 40% better than placebo (34). The likely explanation is a 'threshold' for publication.

Large numbers of sponsored multicentre (often multinational) studies are recently completed, underway or being planned in the headache field. The principal objective of many of these studies is to meet regulatory requirements for marketing authorizations in various parts of the world. The second objective is to support marketing. For this purpose, non-peer-reviewed collations are commonly favoured, bringing together selected clinical research reports (whilst sometimes claiming to contain all important data). They are given respectability by editorial endorsement and publication as supplements to journals such as *Cephalalgia* and they serve well as handouts to prescribing physicians. Publication for the scientific community is of lesser priority: references in advertising and in information to prescribers can be listed as 'data on file'.

4.2.3.3 Recommendations

1. We recommend that sponsors and investigators commit at outset, in contract within the research protocol, to the principle of trial reports being made publicly available as soon as is reasonably practicable.
2. We support 'a universal condition among institutional ethics committees that there is an intention to publish' (2), although this will be unnecessary if our first recommendation is put into effect.
3. We recommend that IHS, as a matter of policy, endorse moves towards compulsory registration (35), *before the first patient is enrolled*, of all headache trials conducted from now on throughout the world. We further recommend adoption of the criteria proposed by Abbasi (36) for a suitable registry.

Meanwhile we urge all sponsors to recognize the changing climate and pre-empt enforcement by voluntarily registering their trials.

The International Committee of Medical Journal Editors (ICMJE) have adopted a policy of refusal for publication of reports of clinical trials that were not publicly registered at or before the

onset of patient enrolment (37, 38). They exhort all other biomedical journal editors to follow suit. We considered but do not recommend that IHS adopt a policy of preference for publication in its journal of trials so registered. This would erect a barrier to publication.

4. Like others (39), we do not wholly endorse the 2001 statement *Sponsorship, Authorship, and Accountability* issued by the ICMJE (4), and do not recommend its adoption by *Cephalalgia*. In our opinion it goes too far in its expectations of what must be done independently of the sponsor company, particularly with regard to statistical analysis.
5. We recommend that IHS consider a system of 'name and shame' in known cases of non-publication of sponsored research. A trial may be deemed non-published 1 year after data-lock if there is not at least one published and citable abstract describing the principal efficacy analysis. We believe that, if such an intention is advertised, it will encourage and be a contribution towards free information flow. The system will require safeguards, discussed and agreed with sponsors, who should welcome it.

In such a system IHS members and others may be invited to lodge complaints with IHS (which must be signed, but which IHS will treat confidentially) against companies for suppression of results of completed trials. If *prima facie* such complaints are found to have substance (by the Ethics Subcommittee or Clinical Trials Subcommittee) and the company complained against produces no acceptable defence, IHS may, after writing of its intent to the company, consider sanctions against the company such as 'black-boxing' in *Cephalalgia* (a black-framed and prominently published *Notice of Non-publication*). In any such instance, IHS should offer a right of reply, with any reasonable reply also published. We considered but do not recommend further sanctions such as preventing discussion of any of the sponsor company's products at IHS meetings or in its journals. This would suppress information flow.

6. We recommend that IHS consider, now and perhaps again in the future, a clinical trials amnesty (40). This would in essence be an offer to consider for publication, perhaps in a special peer-reviewed supplement of *Cephalalgia*, trials completed some time ago for which the acceptable time-window for publication had passed. The amnesty might need to take a flexible approach to the CONSORT guidelines.

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4.2.4 Exclusion of children from commercially sponsored research

4.2.4.1 Statement of the problem

Children and adolescents have special needs and vulnerabilities because of their incomplete development. At the same time, there are especial difficulties in performing clinical trials in these age groups, and pharmaceutical companies generally need persuasion to undertake them (1). End-points in clinical trials that are appropriate for adults are not

necessarily so for children or adolescents. Placebo-control raises particularly troublesome ethical issues in children, who cannot protect their own interests through the giving or withholding of valid informed consent. The *Declaration of Helsinki* forbids research in people unable to consent, including children, 'unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons' (2). Other guidance, however, mandates the inclusion of children in research unless there is good scientific or ethical cause for their exclusion (3).

The actual result is a lack of therapeutic research and few appropriate treatments and formulations for these age groups, who have been described as 'therapeutic orphans' (4). Because of this failure to recognize their needs and to perform appropriate research, children are denied access to safe and effective treatments that adults demand as a fundamental right. UNICEF, in a preamble to the United Nations *Convention on the Rights of the Child*, observes that 'human rights apply to all age groups—they do not magically begin with a child's passage into adulthood' (5). Accordingly, Article 24 of the Convention recognizes 'the right of the child to the enjoyment of the highest attainable standard of health and to facilities for the treatment of illness and rehabilitation of health' (5), and children and adolescents have equal entitlement to patients' *right of access, right to preventative measures, right to avoid unnecessary suffering and pain* and, of course, *right to personalized treatment* (see section 3.2). The desire to protect children as individuals from exposure to research risk arguably has the effect of harming children as a class by inhibiting research into paediatric health and diseases (infringing their *right to innovation*). The same result is achieved by excluding children from research for any other reason, including commercial interest.

Further than this, children and adolescents, lacking treatments developed for them, are put in danger (a breach of their *right to safety*) when treated by doctors using drugs off-licence and without good evidence or by parents guided by advertising information provided by pharmaceutical companies which is intended, and suitable, for adults. Studies throughout Europe have shown that children receive medications not licensed for their use, or at different doses or for different indications or by different routes from those recommended (6). In a survey of five European countries, two-thirds of children received drugs prescribed off-label, with analgesics amongst those most frequently given (6).

4.2.4.2 Specific relevance to headache

Headache disorders are common in children and adolescents, whereas very few of the marketed drugs are licensed for use by them.

IHS has set out guidelines for clinical trials of drugs in various headache disorders (7–9), none of which specifically consider trials in children and adolescents.

4.2.4.3 Recommendations

1. We recommend that IHS, in its strategic planning, consider the unmet needs of children and adolescents with headache and find ways to demonstrate to industry the size and potential commercial value of the market in remedies for childhood and adolescent headache. We believe this will lead to investment in this area.
2. We recommend that the Clinical Trials Subcommittee produce and publish specific recommendations on end-points for trials in these age groups.
3. We recommend that the World Headache Alliance be brought into this arena, applying pressure from the general population upon sponsors to address these needs.

4.2.4.4 References

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4.2.5 *The developing world, and its exploitation in commercially sponsored research*

4.2.5.1 Statement of the problem

The developing world is exploited by any research conducted in developing countries that:

- investigates questions of interest only to the developed world;
- does not reflect the different needs, different problems and different (e.g. traditional) treatment methods of the developing world;
- prefers their populations only because they are naive to the treatments being tested (which simplifies patient enrolment and trial management (1)).

Most such research is commercially sponsored. Developing countries offer low research costs, with neither patients nor doctors and their institutions rewarded at the same (absolute) levels as in developed countries. Strong financial incentives are created to conduct research in developing countries that may be more difficult or more expensive elsewhere.

In addition, controls are often less effective and ethics committees underdeveloped or absent (2). They may not prevent the conduct of trials of drugs in developing countries despite that the treatments will not be marketed to their populations. Research of this nature breaches rights enshrined in the *Declaration of Helsinki* (3).

4.2.5.2 Specific relevance to headache

These issues are general (2). Furthermore, headache disorders are ubiquitous and therefore of interest worldwide. Nonetheless, headache-related needs, problems and treatment methods do vary and these issues become important in headache for two reasons. First, whereas headache disorders are common in developing countries, they attract very low priority for allocation of healthcare resources or are entirely unrecognized. This creates a readiness to embrace sponsored research that is based in high vulnerability. Second, large triptan-naive populations are easily found.

4.2.5.3 Recommendations

1. We believe it is beyond question that the highest ethical standards should be maintained wherever research involving human subjects is

performed. In our view this means that procedures and practices that would not be considered ethical in the sponsor's home country are not ethical if performed elsewhere. Whilst there must be recognition and acceptance of cultural differences (4), this is not a *carte blanche* for ethical relativism (5).

2. The ethical imperative to publish (see section 4.2.3) applies to research carried out in the developing world no less than elsewhere. We recommend that reports of commercially sponsored research conducted wholly or in part in developing countries should justify the choice of site(s) and population(s), explicitly stating the potential clinical relevance of the results of the study to each community (6).
3. We recommend that members of IHS should not become involved in commercially sponsored research that cannot ultimately benefit the population in whom it is conducted, and that IHS publications should not carry reports of such research on the basis that it is unethical.

4.2.5.4 References

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4.3 *Commercially sponsored clinical services*

4.3.1 *Statement of the problem*

In certain countries, notably the UK, some specialist headache clinics rely on direct commercial sponsorship, for example to employ nurses. This is not unique to headache (1). When clinical services are otherwise inadequate, commercially supported services fill a vacuum.

This may be of major and direct benefit to patients.

On the other hand, there is possible influence over prescribing. It is not known what impact, if any, this has. Also, a service may become established through commercial sponsorship that is then withdrawn, forcing the allocation to it of public healthcare resources. This may be perceived as a good outcome, but normal service development processes and priority determination are undermined along with the citizens' *right to participate in policy-making in the area of health* identified in section 3.2.

4.3.2 Specific relevance to headache

These issues are especially relevant to headache because of the lack of health service provision for it.

4.3.3 Recommendations

1. We believe that direct commercial sponsorship of clinical services is undesirable for the reasons given, but it may be the lesser of two evils when the alternative is no services.
2. The solution lies in recognition by governments of the unmet healthcare needs of large numbers of people affected by headache. There is now sound evidence of this worldwide (2). We recommend IHS, in its strategic planning, give priority to its activities that will lead towards this recognition.

4.3.4 References

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4.4 Commercially sponsored education

4.4.1 Statement of the problem

Patients' *right to safety* includes, specifically, the right to expect healthcare providers to prevent errors by receiving continuous training. Patients themselves have a *right to information* about health and about all that scientific research and technological innovation make available (see section 3.2). These are two separate issues.

Even when the professional education agenda is controlled by regulators (1) or by apparently independent bodies, it appears to need commercial sponsorship. Many educational efforts are under-resourced unless 'backed by the deep pockets of the private sector' (2).

Responsibility for this situation does not lie with sponsors, who support a great many educational initiatives that would otherwise not be possible. Nor is this situation of itself harmful. For example, education on some aspects of the therapeutic use of drugs and related research may best be given by people in industry who have most familiarity with them. Doctors within industry are bound by the same professional ethical principles as those in clinical practice, whereas pharmaceutical companies are subject to self- and external regulation that require ethical conduct.

On the other hand, there is a perceived if not actual conflict between the commercial interests of pharmaceutical companies who sponsor education and the *prima facie* requirement that education be unaffected by considerations other than the needs of patients, balanced and non-promotional (3). Where the content of educational meetings and events is directly influenced by the industry, this tension is likely to be most in evidence. Thus, this influence is overt in commercially sponsored satellite symposia, but more covert in other events such as those organized for primary care continuous professional development (CPD) that preferentially highlight a sponsor's drug (4). Covert influence may be less easily managed.

Additionally, industry's interests in research and development indirectly influence the content of large meetings that report this research. Themes are selected by organizers to attract sponsorship, and speakers likely to be personally sponsored can be invited at no cost. Both these influences are covert. Industry substantially determines, through sponsorship of registration fees, travel and accommodation, who attends which meetings. As a result, industry influences the choice of venue for large meetings. This has the potential to disenfranchise large parts of the world.

Concerns apply similarly to lay meetings: even where there is no direct influence on content, speakers may be chosen from an industry-favoured short list because they will be supported by industry.

In these ways a situation exists that, although offering many benefits in a vacuum of provision by those whose responsibility it should be, encourages bad practices. At the same time, the effectiveness of controls varies from one part of the world to another. Where problems actually occur, their origins lie as much with those who engage in these bad practices as in the context that allows them, whilst the latter may be beyond immediate remedy.

'Educational' websites for the general public are discussed in section 4.5.

4.4.2 Specific relevance to headache

These issues are of general relevance, but pervade the headache field and need to be considered so that the Subcommittee may make recommendations as to what IHS should allow at its meetings (5), in its publications or otherwise in its name.

At the heart of this issue is the lack of government priority for and investment in headache, and therefore in education in this field. Education is often deficient in headache, leading to mismanagement of large numbers of people. Adequate education of healthcare providers at all levels in the diagnosis and management of headache disorders will bring huge benefits to people affected by them. Education about headache is of key importance in primary and community care because most headache disorders, if managed at all, are managed in primary care. Education issues arise with pharmacists also. They are frequently consulted for headache, and should not, for example, indiscriminately recommend analgesics.

A central question is whether the content and indeed the educational objectives of IHCs are compromised by the drive to use these as income generators for the Society's other good purposes. Industry influence on content is self-evident according to those who argue that the IHC has for some years been inappropriately dominated by triptanology. It is doubtful, while IHS remains dependent upon profit from the IHC for many of its activities, that it will take the congress to a venue that potential sponsors will choose to avoid.

4.4.3 Recommendations

1. We believe that the remedy to these issues lies less in controlling sponsors' behaviour (which is subject to general controls) than in setting standards of behaviour in its relationships with commercial sponsors that IHS should wish to follow and should expect of its members.
2. We believe that education is rightly and must remain a priority amongst the strategic objectives of IHS.
3. We recommend that the educational purpose of the IHC should not be compromised. The implication of this recommendation is that the IHC cannot be organized with the aim, primary or secondary, of maximizing profit.
4. We endorse the present rule that no part of the main scientific programme of IHCs shall be directly sponsored by the pharmaceutical industry (5), and we further recommend that no commercially sponsored event be *any part of*, or held

during or in parallel with, the scientific or educational programme of any other educational event organized or supported by IHS.

5. We recommend that commercially sponsored satellite symposia or other events that IHS may allow to be held, subject to these conditions, at or in association with any IHS-supported educational events should be clearly described as such; and that the sponsor be identified in the main programme, in the programme of the event if separately printed and on all materials relating to it that the sponsor may produce.
6. We recommend that chairmen and members of programme committees for educational events including the IHC may not, within their period of office, be in receipt of personal financial support or deriving any pecuniary advantage from commercial organizations whose products may be mentioned, or from their commercial allies or competitors, that is likely to create an unmanageable conflict of interest. Chairmen and members of programme committees may not accept commercially sponsored engagements at those events.

4.4.4 References

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4.5 Marketing

4.5.1 Statement of the problem

Marketing targets healthcare providers and/or consumers. Marketing initiatives generally seek to raise awareness not only of a product but also of need for treatment for which the product is a candidate for use.

In most countries, the advertising of prescription drugs is restricted. Direct-to-consumer (DTC) advertising of prescription drugs in the USA has been associated with benefits and adverse effects (1). In Europe and other parts of the world DTC advertising is not and will not be permitted. Advertising to the general public or intended users of over-the-counter (OTC) medications is universal. Control lies with regulators, whose

influence and effectiveness are variable throughout the world.

The following are examples of practices pursuing commercial advantage that are not to the benefit of patients:

- all efforts (including rewards for prescribing (2)) to increase market share for a particular drug or treatment option at the expense of others with better claims;
- all marketing claims, whether to healthcare professionals or intended consumers, that are not impartial reflections of the truth (3); promotional and advertising claims with skewed emphasis or using selected or manipulated end-points from clinical trials or selectively reporting variable success rates achieved across multiple trials; provision to prescribers by pharmaceutical representatives of selective information in order to influence prescribing (4);
- off-label promotion.

When rewards are offered for prescribing, they have the specific intent of subverting clinical judgment, which doctors should exercise in their patients' interest and not any other—least of all their own financial interest (5). Rewards may be direct—in the form of monetary or other gifts or hospitality (6, 7)—or more commonly indirect. The latter include support for attendance at educational meetings, which itself may have secondary benefits to patients. Marketing does sometimes masquerade as education (see section 4.4), particularly in primary care, and the devolution of pharmaceutical sponsorship for education to marketing budgets can only encourage this. Marketing initiatives targeted at primary-care prescribers have been under close scrutiny in many regions (4, 8).

4.5.2 Specific relevance to headache

Marketing initiatives and, indeed, marketing objectives are not necessarily at odds with and may even support the objectives of IHS.

However, they come into conflict with the Society's objectives when they create demand that is not backed by clinical need, support treatments that are inappropriate to needs that do exist or promote one treatment having no advantage over another. A good example of clinically misplaced promotion is the huge expenditure aimed at increasing use of triptan X rather than triptan Y when, in most populations, the needed message is that headache treatments, including triptans, are under-utilized.

DTC advertising and the promotion of OTC products are especially relevant to headache because of its high general-population prevalence and the low levels of contact between doctors and affected people. Advertising to the general public of OTC painkillers for headache is particularly widespread and often intensive. Messages for example that product Z is the 'rapid and complete solution to headache' may mislead by inappropriately suggesting a diagnosis or, alternatively, suggesting efficacy regardless of diagnosis. With its potential to generate uncontrolled demand, such advertising may and almost certainly does contribute to medication-overuse headache—a major public health problem (9).

Controversial initiatives are commercially sponsored websites for the general public and people affected by headache. The Ethical Issues Working Group of the UK Faculty of Pharmaceutical Medicine distinguished, in 1998, between providing information and offering advice, admitting then that patients' interests might not be best served in this area (10). Their concerns, in the headache field at least, would probably be greater now. Many manufacturers of migraine treatments maintain websites with, for example, self-completion questionnaires that generate 'disability scores'. They are 'successful', in the sense of being much-visited and apparently popular, because they are the main or only source of information about their illness consulted by large numbers of the headache-affected public. Their stated purpose—to promote awareness of the possible *need* for treatment—sits uncomfortably with their commercial objective to increase *demand* for treatment.

Healthcare providers including IHS members can support and thereby perpetuate these practices in the following ways:

- by direct association, usually for payment of a fee, with biased claims made in sponsored articles or at sponsored meetings;
- by conducting and publishing sponsored research with flawed design likely (and sometimes intended) to lead to biased outcomes;
- by accepting rewards for prescribing.

4.5.3 Recommendations

1. We believe the control of advertising lies with regulators and it is not, generally, an issue relating to relationships between IHS and its sponsors. Nevertheless, there are remedies to some of the issues identified above that lie less in

controlling sponsors' behaviour (which is subject to these controls) than in setting standards of behaviour in relationships with sponsors that IHS should expect of its members.

2. Accordingly, we recommend that IHS members do not support or give legitimacy to any marketing activities of companies that do not conform to the Society's objectives and lead to the meeting of patients' needs. In some matters this is a question of observing the Society's *Policy on Conflicts of Interest for IHS Members* (see section 4.1.3). In others, responsibility rests with the individuals concerned as a professional duty.

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