

Ethical issues in headache research and management*

Report and recommendations of the ethics subcommittee
of the International Headache Society

May 1998

1.0 SUMMARY OF RECOMMENDATIONS

Consent to participation in research, and inducement by offers (explicit or implicit) of free or enhanced care, or by payments

1. Wherever possible, there should be common standards throughout the world in relation to consent to research in headache.
2. Where these standards are not already imposed by law, they should be imported by sponsors, trial coordinators, and investigators.
3. The IHS should adopt Guideline 1 of the International Guidelines of CIOMS (6) as a minimum standard for investigators.
4. As an exception, the use of medical records is acceptable *without consent* in certain circumstances and with safeguards.
5. With regard to potential inducement to participate, Guideline 4 of CIOMS (6) should be adopted.
6. The possibility of efficacy of a trial treatment is *not* a benefit, and trial information given during the consenting process should not identify it as such.
7. IHS publications should not include accounts of clinical research unless a specific statement is included that, with respect to the issue of consent, these recommendations were adhered to.

Headache awareness and the impact of public opinion, state-funded healthcare, and health insurance

1. The autonomy of people with headache should be respected. Researchers should beware of offering hidden “inducements” to patients to participate in research.
2. The socioeconomic impact of headache pleads forcefully for a larger share of healthcare resources than it currently receives. Private insurers should include care for headache disorders.
3. The IHS should adopt a positive role in informing governments, employers, insurers, patients, and the general public about the nature of headache, research into headache, and its effective treatment.

Confidentiality

The IHS should adopt Guideline 12 of the International Guidelines of CIOMS (6).

Choices in research: what therapeutic areas, what drugs, what studies, and by whom?

1. The IHS must promote the message that it is in the interests of society and employers to support headache research, and not to let it rest entirely with the pharmaceutical industry.
2. The IHS should directly solicit funding from other sources than the pharmaceutical industry to support a wider range of studies.
3. Economic evaluation should accompany the introduction of every new therapy to inform rational prescribing, and should be sufficient to show how the treatment contributes to cost-containment.
4. Audit procedures should be put into place within healthcare systems to discover gaps in headache care.

* Address for correspondence: Dr Timothy J. Steiner (Chairman), IHS Ethics Subcommittee, Division of Neuroscience and Psychological Medicine, Imperial College School of Medicine, St. Dunstan's Road, London W6 8RP, UK

Clinical trials as part of development programs: the right balance between numbers put at risk and levels of risk

1. Trials whose aim is solely to support marketing, if they present any risk to patients, or direct resources away from other more worthwhile trials, are *unethical*. IHS publications should not accept reports of such trials.
2. Efficacy endpoints in clinical trials should be clinically relevant, respecting patients' values. Unless there are good reasons to do otherwise, trialists should use endpoints recommended by the IHS (15–17).

Costs and risks of “non-benefit” procedures in clinical headache research, especially where protocols appear contrary to good management or where patients are used essentially as volunteers

1. Institutional review board or ethics committee approval is required for every procedure that constitutes research on human subjects. Approval is specific to the submission. Additional procedures to an approved protocol require additional approval.
2. Explanations to subjects of the risks and possible benefits of additional procedures must be to the standard generally required, *and* set in the context of what is accepted practice in the management of headache.
3. The investigator must recognize that the purpose(s) of the original protocol and additional procedure(s) may conflict. The permission of the sponsor should be sought.
4. Publications of research emanating in this way should cite the context of the research and the source of support.

Payments (especially “per capita” payments) to investigators

1. The Subcommittee accepts with reservations that payments *per capita* should be the basis of reimbursement for most clinical trials. Payments should reflect work done at rates that are locally appropriate to the professional expertise applied to it.
2. All payments tied to recruitment rates should be approved by an ethics review committee and, ideally, made to institutions and not to individual investigators.
3. The Subcommittee has no view on whether patients should be informed of payments to the investigator's service or institution contingent upon their recruitment.

Qualifications of investigators and coordinators of headache trials

1. It is *unethical* for investigators, unless subject to appropriate supervision, to undertake clinical research without the necessary competence in the condition being studied *and*, in the case of sponsored clinical trials, in Good Clinical Practice (GCP).
2. It is *unethical* for sponsors to put clinical research in the hands of investigators who do not have the necessary competence.
3. Every investigator should meet the approval of the sponsor and an institutional review board or local research ethics committee.
4. Primary-care physicians willing to conform to GCP, provided that they are reasonably competent in the therapeutic area, may carry out clinical trials in headache and need not be supervised by specialists.
5. An investigator who is not responsible for the management of the patient has a *duty* to establish and maintain communication with the primary-care physician and other medical practitioners involved in the patient's medical care.
6. The IHS Classification Subcommittee should include, in future guidelines, advice on levels of competence needed for correct and reliable application of their diagnostic criteria.

Quality control and quality assurance of clinical trials and other headache research (sponsored or not); GCP guidelines and their application to headache trials

1. Wherever possible, there should be common standards throughout the world in relation to quality of sponsored and non-sponsored clinical research in headache.
2. The Subcommittee endorses the application of GCP as set out by the International Conference on Harmonization (13) to pharmaceutically sponsored research.
3. The Subcommittee calls upon the Scientific, Clinical Trials, and Education Subcommittees of the IHS to promote high standards by publication of methodological guidelines wherever possible.

Worthless or poorly designed trials

1. It is *unethical* for investigators to attempt research which they are not qualified to do, unless adequately supervised.
2. For clinical trials of drugs in migraine (17), tension-type headache (15), or cluster headache (16), the guidelines of the IHS Clinical Trials Subcommittee should be followed.
3. In other areas of headache research, the IHS Scientific Subcommittee should consider the need for guidelines.

Use of placebo in headache studies

1. The use of placebo requires justification in all cases.
2. Ethical use of placebo in headache trials always hinges on informed consent. The term "placebo" and the twin concepts of placebo-response and placebo-control require careful explanation if a patient is to be *informed*. Details of other treatment options that a patient foregoes in a placebo-controlled study are a necessary part of the information to potential subjects.
3. Placebo controls may and should be used to establish efficacy of a new drug, acute or prophylactic, that is expected to have some benefit over accepted therapies.
4. The use of placebo is more problematic in long-term studies, but the issues are similar. Use of placebo depends on *continuing* consent.

Stopping rules for clinical trials, and the role of expert advisory committees

1. Protocols should specify the reasons for which a trial might be stopped prior to completion. These might be ethical, statistical, methodological, legal, regulatory, or commercial (e.g., a decision to cease development of the drug altogether).
2. Statements such as "the sponsor reserves the right to stop the trial with or without cause" cannot ethically be justified, and they are unnecessary. Ethics committees should not approve and investigators should not undertake research where such restrictions are placed on its completion.
3. Where an interim analysis is planned, statistical rules should be written beforehand to govern any decision to stop a trial.

Rights of ownership of data; impediments to free flow of information, including feedback of information from clinical trials (especially multicenter) to investigators

1. Responsibility for ensuring proper data handling and analysis cannot be separated from the ethical responsibility of the investigator conducting research. Investigators and sponsors should agree about data management and analysis policies of multicenter trials in the protocol.
2. Where a contract exists between investigator and sponsor, the sponsor's *duty* to ensure full analysis and subsequently facilitate publication should be written into it.
3. Institutional review boards and research ethics committees should make these matters conditions of approval and, in cases of subsequent default, should notify regulators.
4. Newsletters sent periodically to investigators during a trial might be continued through data clarification and cleansing, and analysis, to publication.

Publication bias; establishment of a registry of headache trials (both drug trials and others)

1. Responsibility for publication cannot be separated from the ethical responsibility of the investigator. The Subcommittee agrees that: "Scientists have an ethical obligation to submit creditable research results for publication, and ... should not enter into agreements that interfere with their control over the decision to publish."
2. Investigators and sponsors should agree on publication policy of multicenter trials in the protocol and, if necessary, institutional review boards and ethics committees should use their powers to enforce it. Ideally, responsibility for publication should be irrevocably devolved to a publication committee of named investigators.
3. As a general rule, every methodologically sound randomized controlled trial should be published in such a way as to allow evaluation of the results; publication solely as an abstract or in non-peer reviewed supplements is unacceptable.
4. Notwithstanding this, the Subcommittee agrees that commercial sponsors of research may need time to gain some advantage over competitors by delaying publication of results.
5. Editors of IHS publications, including *Cephalalgia*, should have in mind the public interest in considering whether or not to accept a trial for publication.

6. As this cannot be a complete solution to publication bias, a registry of clinical trials is ethically desirable. The Subcommittee endorses initiatives to set up a headache review group or subgroup within the International Cochrane Collaboration, and recommends that IHS and sponsoring companies give full support.

Inappropriate publication and inappropriate media interpretation

1. Responsibility for publication cannot be separated from the ethical responsibility of the investigator conducting the trial.
2. Authors must regulate themselves. In the absence of other realistic penalties for neglect of this responsibility, it should attract the disapproval of peers. Editors of IHS publications discovering undeclared duplicate publication should declare it in print.
3. Publication should be first in an appropriate scientific medium.
4. Where trials feature in multiple publications, the protocol number, acronym, or other unique identifier should appear in every title.
5. Cooperation with interested lay or financial media enhances the opportunity for correct representation.

The educational/promotional interface; sponsorship of headache education; declarations of interest

1. The IHS should pursue a policy of openness in its dealings with sponsors.
2. The IHS should accept sponsorship from the pharmaceutical industry as far as possible in accordance with the advice of the Legal Department of the European Federation of Pharmaceutical Industries' Associations (10) and the FDA (24).
3. International Headache Congresses (IHCs) should be organized in accordance with IHS guidelines (14). The Subcommittee specifically endorses the resolution of the IHS Council that *no part of the main scientific program of IHCs shall be directly sponsored by the pharmaceutical industry*. Satellite sessions outside and never parallel to the main program may be sponsored and, if so, should be clearly so identified.
4. Organizers of IHCs or other IHS meetings should establish a menu of sponsorship options, setting out precisely what is purchased by the sponsor for each level of sponsorship and available to each potential industry sponsor with the options taken on a first-come first-served basis.
5. Pharmaceutical companies, whether sponsors of the event or not, may organize their own activities around an IHS educational event *in consultation with* the event organizers. Such activities are not expected to be staged at the same time as or in competition with any part of the IHS event.
6. Industry sponsorship of individuals to attend events, and the influence this may have on who attends, are general issues. Possible but partial solutions lie in redirecting this sponsorship to organizers of events, to national societies or to the IHS itself, for distribution as bursaries.

2.0 THE SUBCOMMITTEE

2.1 Membership

T.J. Steiner (<i>Chairman</i>) Division of Neuroscience and Psychological Medicine, Imperial College School of Medicine, London, UK	Academic physician
G. D'Andrea Department of Neurology, San Bortolo Hospital, Vicenza, Italy	Physician
F.J. Gabbay Gabbay Ltd, Southampton, UK	Academic pharmaceutical physician; director, clinical research organization
V.M. Harpwood Cardiff Law School, Cardiff, UK	Academic lawyer and barrister

H. Isler Neurologische Klinik und Poliklinik, Universitatsspital, Zurich, Switzerland	Academic physician
K.M. Lloyd International Medical Affairs, Glaxo Wellcome Plc, Uxbridge, UK	Pharmaceutical physician
K.R. Merikangas Genetic Epidemiology Research Unit, Yale University School of Medicine, New Haven, CT, USA	Academic epidemiologist
J.M. Pereira-Monteiro Department of Neurology, Hospital Santo Antonio, Porto, Portugal	Academic physician
J. Priban Department of Legal Philosophy and Sociology, Charles University, Prague, Czech Republic	Academic legal philosopher
K.R. Reeves Central Research Division, Pfizer Inc, Groton, CT, USA	Pharmaceutical physician
D. Rothner Department of Neurology, Cleveland Clinic Children's Hospital, Cleveland, OH, USA	Pediatrician
D. Russell Department of Neurology, Rikshospitalet, Oslo, Norway	Physician
S. Solomon Department of Neurology, Montefiore Hospital and Medical Center, Bronx, NY, USA	Physician
P. Tfelt-Hansen Department of Neurology, Bispebjerg Hospital, Copenhagen, Denmark	Physician; Chairman, IHS Clinical Trials Subcommittee

2.2 Background

The Ethics Subcommittee ("the Subcommittee") of the Council of the IHS is a standing committee. It is charged with identifying issues of ethical concern in headache research and management, and its tasks are to enquire into these, taking evidence from interested parties, and to report from time to time with recommendations where appropriate. It was formed in response to IHS members' concerns that relationships with the pharmaceutical industry should have a sound ethical basis, but other issues too were recognized as having an ethical dimension, on which the IHS should have views.

The Subcommittee first met as presently constituted in Zurich in May 1993, to set out its mission, scope, and objectives.

2.3 Mission, scope, and objectives

The *mission* of the Subcommittee is to promote the welfare of headache sufferers by drafting advice, guidelines, and recommendations on ethical issues relevant to research into and treatment of headache.

The *scope* of the Subcommittee is:

1. To identify existing ethical issues pertaining to headache.
2. To address any new ethical problems in relation to headache as they arise.
3. To receive comment from and consider the ethical concerns of interested parties.
4. To draft statements which will bring the relevant ethical concerns to the attention of governments, the

medical, and allied professions, the pharmaceutical and insurance industries, lay and charitable organizations, and any other relevant parties.

The Subcommittee welcomes comment from members of the IHS and other interested parties.

The first *objectives* of the Subcommittee have been to identify, deliberate upon, and formulate recommendations on issues arising in headache *research* (see below). The Subcommittee restricted itself to issues specific to headache; those applying to research generally were avoided unless they had specific or particular relevance or application to headache. General ethical issues are dealt with in general texts on ethics.

2.4 Issues in headache research

The following relate to the *rights of and duties towards subjects* of headache research, or to the *interests of the population* of headache sufferers as a whole.

1. Consent to participation in research, and inducement by offers (explicit or implicit) of free or enhanced care, or by payments.
2. Headache awareness and the impact of public opinion, state-funded healthcare and health insurance.
3. Confidentiality.
4. Choices in research: what therapeutic areas, what drugs, what studies, and by whom?
5. Clinical trials as part of development programs: the right balance between numbers put at risk and levels of risk.
6. Costs and risks of "non-benefit" procedures in clinical headache research, especially where protocols appear contrary to good management or where patients are used essentially as volunteers.
7. Payments (especially "per capita" payments) to investigators.
8. Qualifications of investigators and coordinators of headache trials.
9. Quality control and quality assurance of clinical trials and other headache research (sponsored or not); GCP guidelines and their application to headache trials.
10. Worthless or poorly designed trials.
11. Use of placebo in headache studies.
12. Stopping rules for clinical trials, and the role of expert advisory committees.
13. Rights of ownership of data; impediments to the free flow of information, including feedback of information from clinical trials (especially multicenter) to investigators.
14. Publication bias; establishment of a registry of headache trials (both drug trials and others).
15. Inappropriate publication, and inappropriate media interpretation.
16. The educational/promotional interface; sponsorship of headache education; declarations of interest.

2.5 General sources and materials

1. American Psychological Association. Ethical principles in the conduct of research with human participants. APA, 1973:58–69
2. Beauchamp TL, Childress JF. Principles of biomedical ethics, 3rd ed. New York: Oxford University Press, 1989
3. Braithwaite J. Corporate crime in the pharmaceutical industry. London: Routledge and Kegan Paul, 1984 (repr 1986)
4. British Medical Association. Medical ethics today. Its practice and philosophy. BMA, 1995
5. Committee on Ethical Issues of the International Association for the Study of Pain. Ethical guidelines for pain research in humans. Pain 1995;63:277–8
6. Council for International Organizations of Medical Sciences. International ethical guidelines for biomedical research involving human subjects. Geneva: CIOMS, 1993
7. Council for International Organizations of Medical Sciences. Declaration of Ixtapa: Global agenda for bioethics. Geneva: CIOMS, 1994
8. Dukes MNG, Swartz B. Responsibility for drug-induced injury. Amsterdam: Elsevier, 1988
9. Ethics Ad Hoc Committee of American Association for the Study of Headache. Report. Headache 1993;33:115–7
10. European Federation of Pharmaceutical Industries' Associations. EC Directive on the advertising of medicinal products. A reading of the current texts (a note by the legal department). EFPIA, 1992
11. Harris J. The value of life: an introduction to medical ethics. London: Routledge, Kegan and Paul, 1985
12. Harry J, McInnes G, editors. Drug development and clinical trials. Prescribers' J 1991:219–57
13. International Conference on Harmonisation. ICH harmonised tripartite guideline for Good Clinical Practice. Good Clin Pract J 1996;(4):S2–27

14. International Headache Society. Rules and guidelines for the organization of the IHS International Headache Congress (IHC). *Cephalalgia* 1997;17:896–9
15. International Headache Society Committee on Clinical Trials. Guidelines for trials of drug treatments in tension-type headache. First edition. *Cephalalgia* 1995;15:165–79
16. International Headache Society Committee on Clinical Trials in Cluster Headache. Guidelines for controlled trials of drugs in cluster headache. *Cephalalgia* 1995;15:452–62
17. International Headache Society Committee on Clinical Trials in Migraine. Guidelines for controlled trials of drugs in migraine. First edition. *Cephalalgia* 1991;11:1–12 (revision expected 1998)
18. Kant I. *Groundwork of metaphysics of morals*. New York: Harper and Rowe, 1958
19. Neuburger J. Ethics and health care: the role of research ethics committees in the United Kingdom. King's Fund Institute Research Report No. 13; 1992;1–49
20. Nuremberg Code (forming part of the judgment 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)
21. Spilker B. *Guide to clinical trials*. New York: Raven Press, 1991
22. 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
23. Tranoy KE. Research ethics: a European perspective. *Bull Med Eth*, October 1993:28–33
24. United States Food and Drug Administration. Final guidance on industry-supported scientific and educational activities. Federal Register, Dec. 8th, 1997
25. World Medical Assembly. Declaration of Helsinki: Recommendations guiding medical doctors in biomedical research involving human subjects. Helsinki, Finland: 18th WMA, 1964. Revised Tokyo, Japan: 29th WMA, 1975; Venice, Italy: 35th WMA, 1983; Hong Kong: 41st WMA, 1989; Somerset West, South Africa: 48th WMA, 1996
26. World Medical Assembly. Declaration of Lisbon: the rights of the patient. Lisbon: 33rd WMA, 1981

3.0 INTRODUCTION

Ultimately, there may be no “correct” answers to many of the ethical problems encountered in the practice of medicine, but it is possible to expose and confront dilemmas. More often than not, the best that can be achieved is a consensus balancing competing values and often dependent upon pragmatic considerations such as the availability of services and resources. Conflicts clearly existed in many issues before the Subcommittee (listed above in section 2.4). The Subcommittee’s approach in its endeavors to resolve these was to consider first the interests of the individual subjects of research, whether patients or not. The general rule was that nothing should be done *against* the interests of the individual.

3.1 Ethical principles

Lead authors: Vivienne M. Harpwood and Jiri Prihan

The Subcommittee, in deliberating upon the ethical issues arising in headache research and management, recognized a number of ethical principles established in medical practice and declared in guidelines or recommendations produced by other national and international bodies. The views of these bodies were taken into account. Where appropriate, the Subcommittee referred to and adopted their recommendations in relation to headache research.

The ethical principles 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 accepted that, in recent years, there has been a challenge to the notion of “principlism”, or the view that the approach to medical ethics should be on the basis of a set of ethical principles (1). This challenge favors a more general approach to the ethics of both care and research based, for example, on the *needs* of patients, the *responsibilities* of doctors, the *good of society as a whole*, and *deserts*.

The term “needs of patients” is something more general than the needs of *the patient*. Participation in clinical research may rarely be in the direct interests of the subject whereas it may (or, to be ethically justified, must) serve “the good of society as a whole” (2). This more general approach to determining

what is ethical creates a more comfortable climate in which to propose clinical research. It is already apparent in long-established ethical doctrine (3).

3.2 References

1. Beauchamp TL, Childress JF. Principles of biomedical ethics, 3rd ed. New York: Oxford University Press, 1989
2. 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: 71-78
3. World Medical Assembly. Declaration of Helsinki: Recommendations guiding medical doctors in biomedical research involving human subjects. Helsinki, Finland: 18th WMA, 1964. Revised Tokyo, Japan: 29th WMA, 1975; Venice, Italy: 35th WMA, 1983; Hong Kong: 41st WMA, 1989; Somerset West, South Africa: 48th WMA, 1996

4.0 REPORT AND RECOMMENDATIONS

4.1 Consent and inducement

Lead authors: Vivienne M. Harpwood and Jiri Priban

4.1.1 Statement of the problem

It is now accepted that the consent of patients should be obtained to treatment and research wherever possible. This principle pervades medical ethics and should underpin the practice of medicine in the modern world. It is stated explicitly or implicitly in virtually all Codes of Ethics and documents of guidance on ethical practice that have been drafted since the Nuremberg trials. It accommodates the principle of autonomy, or the right to self-determination, the freedom of patients to make choices about their treatment. It encompasses the notion of respect for persons (1) as against utilitarian arguments based on paternalism which promote doctors' rights to make decisions for their patients. In research, patients are partners rather than experimental subjects (2-4).

Nonetheless, full autonomy—the ability in all circumstances to give or withhold consent to proposed treatment or research—is an ideal which cannot always be achieved. There are a number of circumstances in which a patient's autonomy may be eroded (5-7). A possible example in the headache field is extreme youth and a limited ability to make decisions. Patients newly confronting a life-threatening illness cannot easily be asked to consent to randomization between treatments (8). Other factors that may affect autonomy include limits to the availability of a treatment and any inducement, direct or indirect, financial or otherwise, that may have been offered or perceived to be an offer to patients who require medication and other forms of care. For example, it may be the case in countries that do not have state-supported healthcare that the only means of obtaining treatment is to enter a clinical trial. Even where care would be available outside a trial, involvement in well-designed research may be a gain to patients because of the promise of care in its widest sense. "Participation in trials seems to ensure more real professional fulfillment of this promise than most patients get from conventional practice" (9).

Whilst the *ethical* principles underpinning consent to medical interventions are almost universally accepted, there is no international *legal* standard. Codes of guidance do not bind individuals or States in the same way as rules of law, and each State needs to adopt such guidance in a formal manner before it will be legally binding. Some jurisdictions have produced specific legislation on consent to clinical trials and others are still in the process of developing their law incrementally through the decisions of their courts.

Accordingly, the manner in which the principle of autonomy has been adopted in relation to consent to medical interventions varies from one country to another. Some jurisdictions require that patients and other subjects of research be given the fullest possible information about the interventions proposed ("informed consent"), but others leave to the doctor the decision as to how much information should be supplied to individual or all patients.

4.1.2 Specific relevance to headache

Even in the so-called developed countries, services for people with headache are commonly perceived to be less good than they might or ought to be. Access to specialist services is often very limited, and to new treatments haphazardly or systematically restricted. These factors may generate willingness amongst patients to participate in research as a means of gaining or maintaining access, although this "trade" is not

openly discussed between investigator and patient. The higher cost of new treatments is likely to exacerbate this problem in headache.

In less developed cultures, the situation may be more extreme and open to exploitation.

4.1.3 Recommendations

1. Wherever possible, there should be common standards throughout the world in relation to consent to research in headache. This is of particular importance in clinical trials.
2. Where these standards are not already imposed by law, they should be imported by sponsors, trial coordinators, and investigators.
3. The IHS should adopt Guideline 1 of the International Guidelines of CIOMS (10) as a minimum standard for investigators: "For all biomedical research involving human subjects, the investigator must obtain the informed consent of the prospective subject or, in the case of an individual who is not capable of giving informed consent, the proxy consent of a properly authorized representative."

Adults who are guardians of children not capable themselves of giving informed consent may consent on their behalf. Not all jurisdictions recognize proxy consent for adults. Cases in headache research where an adult subject is not capable of giving informed consent are extremely rare. They are likely to arise only in the context of a primary condition presenting as an acute medical emergency or with altered level of consciousness.

(Guidelines 2 and 3 of CIOMS (10) set out the nature of the information that is required to be given. In headache research this is no different from what is required in clinical research generally.)

4. As an exception, the use of medical records (e.g., in epidemiological research) is acceptable *without consent* in the circumstances and with the safeguards proposed by Doyal (7): (a) consent is not practicable; (b) the research is of sufficient merit to balance against the moral wrong of access without consent, and access to the records is essential for the completion of the research; (c) specific approval is obtained from the appropriate research ethics committee, and permission from the clinician responsible for the patient's care; (d) the research pertains to some future planning, preventative or therapeutic initiative that may benefit the patient whose records are studied; (e) where possible, identifiers have been removed, and it is not intended that contact will be made with the patient as a result of research findings; (f) a duty of confidentiality (see section 4.3) is formally accepted by the researcher(s).
5. With regard to potential inducement to participate, Guideline 4 of CIOMS (10) should be adopted: "Subjects (whether patients or healthy volunteers) may be paid for inconvenience and time spent, and should be reimbursed for expenses incurred, in connection with their participation in research; they may also receive free medical services. However, the payments should not be so large or the medical services so extensive as to induce prospective subjects to consent to participate in the research against their better judgment ("undue inducement"). All payments, reimbursements, and medical services to be provided to research subjects should be approved by an ethical review committee."
6. With the exception of some post-marketing trials, the possibility of efficacy of a trial treatment is *not* a benefit (since by definition the treatment is not known to be more and may be less beneficial than standard treatment and, in controlled studies, subjects may not anyway receive it); trial information given during the consenting process should not identify it as a benefit.
7. IHS publications should not include accounts of clinical research unless a specific statement is included that, with respect to the issue of consent, these recommendations were adhered to.

4.1.4 References

1. Kant I. Groundwork of metaphysics of morals. New York: Harper and Rowe, 1958
2. Herxheimer A. The rights of the patient in clinical research. *Lancet* 1988;ii:1128-30
3. Goodare H, Smith R. The rights of patients in research (Editorial). *Br Med J* 1995;310:1277-8
4. Chalmers I. What do I want from health research and researchers when I am a patient? *Br Med J* 1995;310:1315-8
5. Harris J. The value of life: an introduction to medical ethics. London: Routledge, Kegan and Paul 1985
6. Green R. Method in bioethics: a troubled assessment. *J Med Phil* 1990;15:179-97
7. Doyal L. Journals should not publish research to which patients have not given fully informed consent—with three exceptions. *Br Med J* 1997;314:1107-11
8. Baum M. New approach for recruitment into randomised controlled trials. *Lancet* 1993;341:812-3
9. Hart JT. Recruitment to randomised controlled trials (Letter). *Lancet* 1993;341:1539
10. Council for International Organizations of Medical Sciences. International Ethical Guidelines for Biomedical Research Involving Human Subjects. Geneva: CIOMS, 1993

4.2 Headache awareness and impact of public opinion

Lead authors: Vivienne M. Harpwood and Timothy J. Steiner

4.2.1 Statement of the problem

Competition for limited resources in many countries means that patients with some illnesses are less likely to receive treatment than those suffering from other conditions. Distributive justice calls for allocation of resources in fair shares to all who *need* them. The general (public) perception of "headache" is unsophisticated, denying the condition its appropriate share of resources. In some countries headache is not regarded as a disease at all; in others it is seen as relatively benign and given low priority, like the common cold not deserving of major resource input by governments. Such views are not justifiable in the light of the high cost of working-days lost to industry and commerce through headache (current estimates in Europe are between ECU 10 billion and ECU 30 billion per annum). The consequences and ethical implications of not treating headache as a disease are potentially very far-reaching, and may be outlined as follows:

1. People in countries with no state-funded healthcare, or which largely rely on private healthcare, and even those in some countries which do have state-supported healthcare systems but in which headache is not perceived as deserving any priority, may receive no treatment for headache. They may resort to self-treatment that is inappropriate, or use untested alternative medicinal products. They are in danger of exposure to aggressive marketing and misleading advertising of proprietary treatments for headache.
2. People may be induced to enter clinical trials or other research (see section 4.1) when they would not otherwise have done so as a means of obtaining care and follow-up to which they would not, in normal circumstances, have access. In this situation autonomy has been restricted, since people have limited freedom to withhold unreserved consent to research and trials.

4.2.2 Specific relevance to headache

Whilst non-treatment or limited treatment of headache patients might bring advantages by releasing resources for treatment of other conditions, there is a question of balance. The drive towards self-treatment is not necessarily desirable given the potential for exploitation of people with headache by the manufacturers of untested headache "remedies". Because people with headache are a major part of the general population, they represent an attractive (potentially highly lucrative) market opportunity and a great encouragement to these manufacturers.

4.2.3 Recommendations

1. The autonomy of people with headache should be respected. Researchers should be aware of the reality of any situation that offers hidden "inducements" to patients to participate in research, and beware of offering treatment (or enhanced treatment) as a benefit of entry to headache trials (see section 4.1).
2. Figures available on socioeconomic impact of headache and, in particular, the effect of headache on the workforce plead forcefully for a larger share of healthcare resources than it currently receives in many countries. Private insurers should be encouraged to include care for headache disorders in their schemes.
3. All of these issues are matters for objective information and education. The IHS should adopt a positive role in informing governments, employers, insurers, patients, and the general public about the nature of headache, research into headache, and its effective treatment.

4.3 Confidentiality

Lead authors: Vivienne M. Harpwood and Jiri Priban

4.3.1 Statement of the problem

Support for the principle of medical confidentiality, set out in the Hippocratic Oath, is common to virtually all documents giving guidance to doctors on matters of ethics throughout history and across the civilized world. The doctrine of confidentiality is deeply rooted in pragmatism and the arguments that promote medical confidentiality have a fundamental bearing on the doctor/patient relationship. Mutual trust and respect are essential ingredients in that relationship, as patients who are not assured of confidentiality—and therefore fail to disclose relevant details—may not receive effective treatment.

However, few codes of ethics place unqualified emphasis on the principle of confidentiality. Most permit exceptions based on "the interests of society as a whole" or on the "general public good". The very existence of such exceptions indicates that ethical dilemmas will inevitably arise whenever a doctor is faced with the decision as to whether to divulge information that has been confided by a patient.

While most *legal* systems protect confidential information, the majority also permit exceptions to medical confidentiality in special circumstances.

Throughout the world, not only is information about *patients* protected by the principle of confidentiality, but so also is *commercially sensitive* information about clinical trials and the development of new pharmaceutical products. Clearly, for pragmatic reasons, clinical trials frequently depend for their effectiveness on the free flow of information about patients, whilst commercial concerns have an interest in maintaining secrecy during the development of new products.

Thus exceptions to medical confidentiality are frequently framed in codes of professional guidance to include information obtained in clinical trials and research (1). Whilst temporary or permanent records can and should be made anonymous wherever possible so that individual patients cannot be identified in the course of future disclosure, permission should always be obtained from patients if there is likely to be a breach of their privacy. One circumstance in which this commonly occurs is in the access to medical records by clinical trials monitors, which is central to Good Clinical Practice (GCP) (see section 4.9).

As a further exception, the use of ordinary medical records for purposes of research is accepted *without consent* in certain defined circumstances (see section 4.2).

4.3.2 *Specific relevance to headache*

Relevance lies in the sudden expansion of interest in headache. Controls have difficulty keeping pace with the large numbers of sponsored clinical trials currently being conducted and their spread to parts of the world where GCP codes are not formally adopted and where medical confidentiality may not be protected by law. Furthermore, resources are stretched to carry out these trials. The increasing use of third-party monitors (contract research organizations), some with lesser professional qualifications (see section 4.8), widens the range of people required to have direct access to patients' medical records.

4.3.3 **Recommendation**

The IHS should adopt Guideline 12 of the International Guidelines of CIOMS (2): "The investigator must establish secure safeguards of the confidentiality of research data. Subjects should be told of the limits to the investigator's ability to safeguard confidentiality and of the anticipated consequences of breaches of confidentiality."

4.3.4 *References*

1. General Medical Council. Professional guidance and fitness to practice. London: GMC, 1994
2. Council for International Organizations of Medical Sciences. International Ethical Guidelines for Biomedical Research Involving Human Subjects. Geneva: CIOMS, 1993

4.4 **Choices in research**

Lead author: Jose M. Pereira Monteiro

4.4.1 *Statement of the problem*

It is not obvious who makes choices according to what agenda(s) with respect to what research into disease and its treatment is needed, and what is undertaken. Relevant factors are public need and/or demand, interest of potential investigators, and availability of resources to support research.

Whereas what the public *need* (and, to a lesser extent, what the public *want*) should be dominant, public opinion in these matters has no clear means for coherent expression. Doctors endeavoring to treat specific conditions may be aware of deficiencies in provision, and have sufficient interest to undertake research that may lead to improvements, but be unable to secure financial support for it. The pharmaceutical industry has the means to support research across most therapeutic areas but is market-driven in the choices it makes. It is not evident that market forces are just, in the sense of leading to a distribution of fair shares to all in need (1). Pharmaceutical industry research must be complemented by public-funded research, overseen to ensure distributive equity as far as is possible.

4.4.2 *Specific relevance to headache*

Throughout the developed world, government-supported research into the better management of headache has low priority (see section 4.2). Funding is rarely provided at any useful level, and oversight of research in the manner necessary to safeguard the interests of people with headache does not exist.

Public finance for research is available to a limited extent from charitable and patient-led organizations set up with support for research into headache as one of their objectives. Whilst these sources of support have been and are of significant potential benefit to headache sufferers, again there is no controlling oversight.

Massive pharmaceutical investment into drug development programs over the last decade has brought

and continues to bring undoubted benefits to sufferers from migraine. These represent less 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 research in the pharmaceutical industry. Furthermore, where research leads to the marketing of a new treatment, premium pricing, if deemed too high, may mean that many people who might benefit from it have little opportunity to do so.

4.4.3 Recommendations

1. The Subcommittee accepts that choices in headache research are substantially dictated by the pharmaceutical industry because research resources are not adequately provided from elsewhere. The Subcommittee further recognizes the realities of market forces, but much of the burden of headache is economic, borne by society and employers. The IHS must promote the message that it is in the interests of society *and employers* to support headache research that spreads benefits more equitably.
2. The IHS should directly solicit funding from other sources than the pharmaceutical industry to support the following:
 - (a) different *types* of study—epidemiological, pathophysiological, and therapeutic—given the lack of firm knowledge needed to underpin a just provision of healthcare for all people with headache;
 - (b) different *areas* of study, extending to causes of headache, including intrinsic (pain mechanisms related to the head, genetic and constitutional factors) and extrinsic (environmental triggers and predisposers), and embracing all major headache types (tension-type headache, migraine, cluster headache, chronic daily headache);
 - (c) *therapeutic* studies directed at both pharmacological treatments (preventative, abortive, and symptomatic) and non-pharmacological treatments.
3. *Economic evaluation*, setting added costs (of the therapy and any foreseeable consequences of its use) against its calculable impact on all illness costs (direct and indirect), should accompany the introduction of every new therapy to inform rational prescribing and should be sufficient to show how the treatment contributes to cost-containment.
4. In relation to headache, *audit procedures* need to be put into place within healthcare systems to discover gaps in care.

4.4.4 Reference

1. Crisp R, Hope T, Ebbs D. The Asbury draft policy on ethical use of resources (and following commentaries). *Br Med J* 1996;312:1528–33

4.5 Drug development programs: achieving the right balance

Lead authors: Vivienne M. Harpwood and Timothy J. Steiner

4.5.1 Statement of the problem

Drug development programs primarily address safety and efficacy. Some regulators have additional requirements with respect to comparative efficacy against “standard” treatment(s) and pharmacoeconomic implications. It is usually necessary to establish the minimum effective dose, and sometimes the maximum tolerated dose. Pharmaceutical companies need data to support marketing. Each of these may apply separately to different races, patient groups, and/or a variety of circumstances of use.

The over-riding ethical requirement is that the number of people exposed to a new drug *in research* should be:

1. not excessive;
2. enough to demonstrate efficacy and safety.

For the satisfaction of regulatory need there are no clear guidelines.

Efficacy is often measurable in a number of different ways, encompassing indices both of disease and of health (e.g., “quality of life”). Safety in clinical trials can be determined (and demonstrated) only up to a point. In practice, in order to collect a reasonable amount of safety data, more patients receive a drug during most drug development programs than are needed to show efficacy, and open long-term treatment protocols may be undertaken, either appended to efficacy studies or standing alone. Even so, the reality is that rare and possibly serious problems may not come to light before very large numbers of patients are exposed to a drug post-marketing.

4.5.2 *Specific relevance to headache*

Efficacy and safety in migraine and perhaps other headache conditions may each have to be demonstrated for more than one dosage in children, adults, and the elderly, in patients from specialist clinics and from primary care. The clinical characteristics of headache (including need for and response to drug treatment) as well as the safety issues may differ between these groups. Efficacy of migraine treatment may depend on when it is taken, and on what associated symptoms are present. The effects of repeated doses are likely to require examination, and to some extent those of misuse. Duration of use (minimum and maximum) must be investigated in trials of prophylaxis. Full evaluation of therapy may require testing within a number of permutations of circumstances.

Proof of efficacy in headache conditions requires relatively large numbers because endpoints are subjective whilst placebo-response rates are commonly high. Efficacy is proved more efficiently if endpoints are clinically relevant as well as statistically sensitive. There is no agreement on what are the best measures of efficacy in headache trials, although recommendations exist (1–3).

Where pharmaceutical companies compete for clinical trials resources, as they are currently in migraine, each trial has an opportunity cost affecting other planned trials. This adds to the need for economy of patients.

4.5.3 *Recommendations*

1. Investigators should have regard to the purpose of a trial. Those whose aim is solely to support marketing, if they present any level of risk to patients, or direct resources away from trials properly investigating safety or efficacy (or, in some cases, comparative efficacy or pharmacoeconomics), are *unethical*. IHS publications should not accept reports of trials undertaken primarily to support marketing if they yield no useful new knowledge.
2. Efficacy endpoints in clinical trials should be clinically relevant, respecting patients' values (4). Trialists who use endpoints other than those recommended by the IHS (1–3) should have stated reasons for doing so.

4.5.4 *References*

1. International Headache Society Committee on Clinical Trials in Migraine. Guidelines for controlled trials of drugs in migraine. 1st ed. Cephalalgia 1991;11:1–12 (revision expected 1998)
2. International Headache Society Committee on Clinical Trials. Guidelines for trials of drug treatments in tension-type headache. 1st ed. Cephalalgia 1995;15:165–79
3. International Headache Society Committee on Clinical Trials in Cluster Headache. Guidelines for controlled trials of drugs in cluster headache. Cephalalgia 1995;15:452–62
4. 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

4.6 Costs and risks of “non-benefit” procedures in clinical research

Lead author: Kathleen R. Merikangas

4.6.1 *Statement of the problem*

An informal review of the major journals publishing headache research over three recent consecutive years revealed that many projects are conducted without open statements concerning sponsorship of the research. A non-systematic confidential survey of 15 authors who had published without acknowledging sponsorship revealed that the sources of funding were diverse. Most unsponsored research had been conducted using the resources of private clinical practices, university or hospital units, or in the context of ongoing or completed clinical trials for which the investigator had received financial support from a pharmaceutical company.

In many cases of procedures conducted in the context of clinical trials, these had not been included in the original study protocol for which the subject had given consent, nor had the sponsor of the study been informed of the additional procedures. Furthermore, most of the procedures had been administered with only the verbal consent of the subjects, and the approval of institutional review boards or ethics committees had not been sought for them. This was particularly true in non-university settings.

In addition to the participants in the original protocols, the subjects of these studies included dropouts from the original protocol, subjects screened for the original protocol who failed to meet its entry criteria, relatives of participants in the original protocol, and institutional staff. The types of procedure were diverse and included questionnaire studies, interviews, psychophysiology, biofeedback, venepuncture, spectral

electroencephalography, and neuroimaging (CT, MRI, and SPECT). The costs and risks to subjects ranged from mere inconvenience or discomfort to serious potential harm from exposure to radiation.

Arrangements for compensation for harm to research subjects put in place by a sponsor are unlikely to extend to unauthorized "add-on" studies. Subjects may be unaware of this.

There are several issues generated by research that cannot directly benefit the subject(s) conducted in the context of a clinical trial or with use of resources allocated for that trial:

1. selection of subjects;
2. provision of essential information to prospective participants for purposes of consent;
3. specification of the risks and possible benefits;
4. compensation for harm caused;
5. review by institutional review boards or ethics committees;
6. the source(s) of financial support.

4.6.2 *Specific relevance to headache*

These issues obtain prominence in headache research because the number of sponsored clinical trials has increased dramatically over the last few years and continues to do so. This greatly increases the opportunity for "add-on" projects whilst, at the same time, lessening investigators' time for separately conceived studies.

4.6.3 *Recommendations*

1. Institutional review board or ethics committee approval is required for each and every procedure that constitutes research on human subjects. Approval is specific and restricted to the submission placed before the board or committee, not an "umbrella" for procedures conducted in the context of an approved protocol but not part of it when submitted.
2. Explanations to subjects of the risks and possible benefits of additional procedures must be to the standard generally required, *and* set in the context of what is accepted practice in the management of headache (e.g., brain scanning is not routine in headache management). Specific consent of subjects (see section 4.1) must be obtained following provision of information to all procedures not part of routine care.
3. The investigator must recognize that the purpose(s) of the original protocol and the additional procedure(s) may conflict. The permission of the sponsor should be sought, particularly but not only when the additional procedures are conducted using the resources of the sponsor.
4. Publications of research emanating in this way should cite the context of the research and the source of support.

4.7 **Payments to investigators**

Lead author: Timothy J. Steiner

4.7.1 *Statement of the problem*

Relatively few trials are now carried out for academic interest, with protocols originated by the investigator(s). Most are done as contract research, and investigators may have no input into the protocol nor any prospect of being an author of publications from it. Such trials are conducted for financial reward, albeit often to support a clinical service or other research.

There can be no doubt that payments to investigators *per capita* are an encouragement to recruit. In 1990, the Royal College of Physicians of London (RCP) in their guidelines to research ethics committees stated (1): "payments made on a per capita basis ... are unethical." This was vigorously challenged by the Association of the British Pharmaceutical Industry. In 1992, the RCP advice was amended (2), recommending payments to practices or departments that related to realistic estimates of workload. It is difficult to see how these can avoid being based on numbers of patients recruited and followed-up, but whether this amounts to pressure to recruit inappropriately is not certain. Even if payments fairly reward work done and no more, the presumption tends to arise (especially when "finder's fees" are mooted (3), paid to other clinicians for referring potentially suitable patients). The unease that can never be wholly dispelled is about "selling" patients (4).

It is wholly reasonable that sponsors wish to pay only for work done, and to acceptable standards of quality. In the past, there is no doubt, sponsors have been defrauded by investigators paid in advance who have not delivered, but recourse to law for performance of a contract is unhelpful since the conduct of clinical trials cannot be made subject to compulsion.

4.7.2 *Specific relevance to headache*

Activity amongst pharmaceutical companies developing antimigraine drugs is at an unprecedented level. Competition for the services of investigators reflects a shortage of experienced clinical trials facilities. Sponsors are looking more and more to investigators 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: most are done as contract research.

4.7.3 *Recommendations*

1. The Subcommittee accepts with reservations that payments *per capita* should be the basis of reimbursement for most clinical trials. Payments should reflect work done in terms of time spent at rates that are locally appropriate to the professional expertise applied to the work.
2. All payments tied to recruitment rates should be declared to and approved by an ethics review committee and, ideally, made to institutions and not to individual investigators.
3. The Subcommittee has no view on whether patients should be informed of payments to the investigator's service or institution contingent upon their recruitment. This is normal and expected practice in some countries but not in others. In different circumstances the information may make prospective subjects more or less inclined to participate.

4.7.4 *References*

1. Royal College of Physicians of London. Guidelines on the practice of ethics committees in medical research involving human subjects. London: RCP, 1990
2. Royal College of Physicians of London. Addition to Guidelines on the practice of ethics committees in medical research involving human subjects, section 17. London: RCP, 8th April 1992
3. Lind SE. Sounding board: finder's fees for research subjects. *N Engl J Med* 1990;323:192-5
4. 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

4.8 *Qualifications of investigators in clinical trials*

Lead authors: Seymour Solomon and Karen R. Reeves

4.8.1 *Statement of the problem*

Physicians are not, by virtue of their medical training, necessarily competent in research. Those who are not have neither reason nor inducement to engage unsupervised in clinical trials or other research of their own.

In sponsored drug trials, payments to investigators, even if made to their service or institution (see section 4.7), are a potential or actual inducement to become involved. Pharmaceutical companies base their choice of investigator on evidence of research experience and ability to generate accurate data, and/or expectation of enrolling sufficient numbers of subjects (1). In some jurisdictions there is legal accountability governing the choice (2). A wide spectrum of investigators may be used, including academic physicians, research physicians, physicians in non-academic service centers and community or primary-care physicians who have day-to-day contact with patients.

No matter their background, all investigators should conform to Good Clinical Practice (GCP) (see section 4.9). Experience in GCP has to be gained; it cannot always be expected if new investigators are to become experienced.

Investigators should be well qualified in the management of the condition to be studied (1, 3, 4), firstly because patients reasonably expect to be appropriately managed and secondly because sponsor companies are not expected to be the source of specialist expertise in this area. Training may be necessary in the performance of measurement scales used in research but not in routine management.

One important question, which may be illness-specific, is whether trials should be conducted by specialists or by primary-care practitioners. A separate issue is whether or not the investigator should be responsible for clinical management of the patient during and after the trial.

Many of these principles apply to trial monitors, who need skills in several areas: scientific (research and trial methodology), clinical (understanding disease and patients), and GCP, as well as interpersonal relationships. There is increasing use of third-party monitors from an increasing variety of backgrounds, some with qualifications that do not appear relevant (5).

4.8.2 *Specific relevance to headache*

There is no subspecialty qualification in headache medicine, nor board to assess professional skills in the diagnosis and treatment of headache patients or competence in headache research. Since anyone can claim

to be a "headache specialist" and open a headache clinic, the danger of enlisting unqualified investigators is apparent. Furthermore, because of the number of simultaneous drug development programs in headache currently underway or being planned, pharmaceutical companies compete for investigators with adequate experience, facilities, and patients. There may not be enough. Priorities may be directed towards speed of recruitment, to complete trials as quickly as possible.

A related issue concerns the IHS diagnostic criteria (6). Does the application of these require the expert competence of fully trained specialists, or can they sensibly be used by general neurologists, non-specialist physicians, primary-care physicians, doctors in training, nurses, lay investigators (conducting surveys, for example) or patients themselves (5)? This appears to be happening in some research, although diagnostic criteria are not generally expected to be reliable when set out as a list to be "ticked" by non-experts.

Headache is ubiquitous and most sufferers are receiving only primary care. Communication links between investigators and patients' primary-care physicians may not be well established, particularly if research subjects are recruited by advertisement to the general public.

4.8.3 Recommendations

1. It is *unethical* for investigators, unless subject to appropriate supervision, to undertake clinical research without the necessary competence in the condition being studied *and*, in the case of sponsored clinical trials, in Good Clinical Practice (GCP).
2. It is *unethical* for sponsors to put clinical research in the hands of investigators who do not have the necessary competence. Some indicators of competence in the headache field are: evidence of expertise attained in past training; a track record in previous research (including well-conducted clinical trials); peer-reviewed authorship in the headache field; evidence of an interest in the field manifested by membership of a professional headache society.
3. Every investigator should meet the approval not only of the sponsor but also of an institutional review board or local research ethics committee.
4. Primary-care physicians willing to conform to GCP may carry out clinical trials. Provided that they are reasonably competent in the therapeutic area, primary-care physicians conducting headache studies need not be supervised by specialists, who are not involved with the majority of headache sufferers.
5. An investigator who is not the physician responsible for the management of the patient during and after the study has a *duty* to establish and maintain free and open communication with the primary-care physician and any other medical practitioner actively involved in the patient's medical care.
6. The IHS Classification Subcommittee are asked to include, in their future guidelines, advice on levels of competence needed for correct and reliable application of their diagnostic criteria.

4.8.4 References

1. Cocchetto DM, Wallace JR. Qualifications of investigators for clinical investigations conducted under an IND: a discussion paper. *Drug Inform J* 1992;26:167-73
2. United States Government. Title 21, Code of Federal Regulations, part 312.50. Washington DC: US Government Printing Office, 1990
3. World Medical Assembly. Declaration of Helsinki: Recommendations guiding medical doctors in biomedical research involving human subjects. Helsinki, Finland: 18th WMA, 1964. Revised Tokyo, Japan: 29th WMA, 1975; Venice, Italy: 35th WMA, 1983; Hong Kong: 41st WMA, 1989; Somerset West, South Africa: 48th WMA, 1996
4. United States Food and Drug Administration. General considerations for the clinical evaluation of drugs. Washington DC: US Government Printing Office, 1977
5. 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
6. International Headache Society Classification Committee. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. *Cephalalgia* 1988;8 Suppl 7:13-96

4.9 Quality control and quality assurance of headache research, and Good Clinical Practice guidelines

Lead authors: Timothy J. Steiner and Felicity J. Gabbay

4.9.1 Statement of the problem

Clinical research undertaken to support drug registration, particularly clinical trials, is subject to well-developed codes of external quality assurance usually referred to as Good Clinical Practice (GCP) (1). Various regulatory agencies or in some cases the pharmaceutical industry itself have put GCP guidelines into place. These are being brought into line by the International Conference on Harmonization (ICH) (1).

Clinical researchers carrying out research of this nature have a *duty* (often reinforced in contract) to be familiar and fully comply with the principles and practice of GCP (see section 4.8).

There are problems related to the application of GCP (2) but it has done much to ensure ethical conduct in pharmaceutical research and prevent or uncover fraud (3). It has little effect in promoting good scientific (as opposed to administrative) method, nor does it stand in the way of studies with a poor rationale.

No comparable *formal* codes of practice protect the quality of non-sponsored or academic clinical research, although it would be unacceptable if such research were of lesser quality. The quality guarantee of academic research rests, with little safeguard, on a combination of academic competence, diligence, and integrity. It is not evident that this is sufficient, but no-one knows the extent to which it is not. Poor quality can and probably does arise in the absence of any one of these, being either unintentional or deliberate (fraudulent).

Even if much needed, research involving human subjects or research that may, in future, affect the management of patients is *unethical* if not conducted to the highest reasonably achievable standards (4) (see section 4.10). The argument that it is better to do research half-well (for example because of limited time or resources) than not to do it at all requires proof in the particular circumstances of the case, and in most cases is likely to be unacceptable.

4.9.2 *Specific relevance to headache*

Section 4.4 identifies the need for headache research extending widely beyond what is supported by the pharmaceutical industry.

4.9.3 *Recommendations*

1. Wherever possible, there should be common standards throughout the world in relation to quality of sponsored and non-sponsored clinical research in headache.
2. The Subcommittee endorses the application of Good Clinical Practice (GCP) as set out by the International Conference on Harmonization (1) to pharmaceutically sponsored research.
3. The Subcommittee calls upon the Scientific, Clinical Trials, and Education Subcommittees of the IHS to promote high standards by publication of methodological guidelines wherever possible.

4.9.4 *References*

1. International Conference on Harmonisation. ICH harmonised tripartite guideline for Good Clinical Practice. *Good Clin Pract J* 1996;3:S2-27
2. 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
3. Various authors. The problem of unreliable data and fraud in clinical research. *Good Clin Pract J* 1994;1:4-27
4. Altman DG. The scandal of poor medical research (Editorial). *Br Med J* 1994;308:283-84

4.10 *Worthless or poorly designed studies*

Lead authors: Timothy J. Steiner and Vivienne M. Harpwood

4.10.1 *Statement of the problem*

Numerous studies of both general and specialist medical journals have shown that researchers commonly do the following: use wrong techniques (willfully or in ignorance), or the right techniques wrongly, misinterpret their results or report them selectively, and draw unjustified conclusions (1). One reason has been identified: "... much poor research arises because researchers feel compelled for career reasons to carry out research that they are ill-equipped to perform, and nobody stops them" (1).

Worthless studies are *unethical* because they put patients potentially at risk, and consume resources (with opportunity cost), without possibility of benefit to anyone. Data from methodologically poor studies may be worthless or, even worse, misleading.

Good Clinical Practice (GCP) (see section 4.9) applies external quality control to the ethical conduct of studies (principally, those sponsored by the pharmaceutical industry), and often to data management, but does not address the rationale or methodological design of the study. GCP is seldom applied to non-sponsored research.

4.10.2 *Specific relevance to headache*

The IHS Clinical Trials Subcommittee, in 1991, identified the poor quality of many *published* trials in headache as a reason for the formulation of guidelines (2). Presumably, these were of better quality than others not published. There is no reason to suppose that the problem was, or is, restricted to this type of research.

4.10.3 Recommendations

1. Responsibility for good design and conduct of research rests primarily with the investigator. It is *unethical* for investigators to attempt research which they are not qualified to do, unless adequately supervised (see section 4.8).
2. For clinical trials of drugs in migraine (2), tension-type headache (3), or cluster headache (4), the guidelines of the IHS Clinical Trials Subcommittee should be followed.
3. In other areas of headache research, the IHS Scientific Subcommittee should consider the need for guidelines.

4.10.4 References

1. Altman DG. The scandal of poor medical research (Editorial). *Br Med J* 1994;308:283–4
2. International Headache Society Committee on Clinical Trials in Migraine. Guidelines for controlled trials of drugs in migraine. 1st ed. *Cephalalgia* 1991;11:1–12 (revision expected 1998)
3. International Headache Society Committee on Clinical Trials. Guidelines for trials of drug treatments in tension-type headache. 1st ed. *Cephalalgia* 1995;15:165–79
4. International Headache Society Committee on Clinical Trials in Cluster Headache. Guidelines for controlled trials of drugs in cluster headache. *Cephalalgia* 1995;15:452–62

4.11 The use of placebo control in headache trials

Lead authors: Seymour Solomon and Karen R. Reeves

4.11.1 Statement of the problem

Placebos are commonly used in two circumstances: firstly, as a direct comparator with a trial treatment, usually following randomization to treatment groups; secondly, during a run-in period prior to a comparative phase of treatment to establish a baseline and/or identify placebo-responders or non-compliers. In either case, there may be partial deceit to foil patients' presumptions as to when they might be receiving placebo.

Confusion over the use of placebos in clinical trials has been identified (1). The Declaration of Helsinki (2) states: ". . . in any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method." This appears to rule placebo unethical (3).

Placebo controls may be demanded by regulatory authorities, especially FDA, as proof of drug efficacy, and marketing authorization may otherwise be refused. Practitioners wish to know what advantage, qualitatively and quantitatively, a new treatment may offer over current alternatives (4, 5). Patients may be fruitlessly exposed to risk from an experimental drug if a trial is unable from the outset to produce unequivocal results because of inappropriate or inadequate control. Studies with active comparators tend to require larger numbers of patients than placebo-controlled studies either to demonstrate equivalence or establish superiority. These larger studies may expose more patients to an experimental drug which eventually proves ineffective and before there is good evidence of its safety (see section 4.5). If a new drug and an active comparator evoke similar responses without placebo control, it cannot be claimed categorically that either was effective in improving outcome over natural history in this particular experiment conducted in this particular population (6).

Instead of placebo, some studies have used a low dose of the drug under study. This may be appropriate in phase II dose-finding. In formal efficacy studies it may distort the results if the low dose actually has some activity, and if it does not then it is no different from placebo.

Informed consent (see section 4.1) is central to ethical deliberate use of treatments less efficacious than standard treatments (3). It has been argued that providing information necessary for consent to a placebo run-in (i.e., "everyone will be on placebo for the first month") is not compatible with its purposes (7), either of prospectively observing an "untreated" baseline or of stabilizing patients under trial conditions.

4.11.2 Specific relevance to headache

Standard treatments exist for both acute and prophylactic treatment of headache. Symptom frequency, intensity, and duration are the most important factors in choosing headache therapy. Intensity and duration of pain are pertinent to acute therapy and frequency of attacks to prophylactic treatment. "Response rates" to medication for acute migraine are now as high as 75%, whereas efficacy of prophylactic therapy is often only slightly better than placebo effect, with response rates at best in the range of 50 to 60%. Proposed new therapies are developed in this context, and should promise some advantage over accepted therapies: if not greater efficacy then fewer adverse effects, better quality of life or, arguably, lower cost.

Some claim that, given the patient's consent, the ethical issues arising from use of placebo are unimportant

in headache. The illness occurs transiently, and withholding active therapy will not lead to any significant or long-term harm that an autonomous patient might not reasonably accept (8). Rescue medications are readily available. These arguments appear to have merit.

4.11.3 Recommendations

1. The use of placebo requires justification in all cases.
2. Ethical use of placebo in headache trials always hinges on informed consent (see section 4.1). The Subcommittee rejects the argument, in headache trials, that "even informed patients may not be disinterested enough to decide rationally whether it is tolerable to be deprived of an accepted treatment" (3). The term "placebo" and the twin concepts of placebo-response and placebo-control are not easily understood by the public and require careful explanation if a patient is to be *informed*. Details of other treatment options that a patient foregoes in a placebo-controlled study are a necessary part of the information to potential subjects.
3. Placebo controls may and should be used to establish efficacy of a new drug, acute or prophylactic, expected to reduce symptom-burden either more effectively, or with fewer or less troublesome adverse effects, or possibly at lower cost, than accepted therapies.
4. The use of placebo is more problematic in long-term studies or when quality-of-life is a principal efficacy parameter, but the issues are similar. Use of placebo for such studies depends on consent, and success of the trial will depend on *continuing* consent until completion. The likelihood of this being given must be judged on a case-by-case basis.

4.11.4 References

1. Collier J. Confusion over use of placebos in clinical trials (Editorial). *Br Med J* 1995;311:821-2
2. World Medical Assembly. Declaration of Helsinki: Recommendations guiding medical doctors in biomedical research involving human subjects. Helsinki, Finland: 18th WMA, 1964. Revised Tokyo, Japan: 29th WMA, 1975; Venice, Italy: 35th WMA, 1983; Hong Kong: 41st WMA, 1989; Somerset West, South Africa: 48th WMA, 1996
3. Rothman KJ, Michels KB. Sounding board. The continuing unethical use of placebo controls. *N Engl J Med* 1994;331:394-8
4. Hill AB. Medical ethics and controlled trials. *Br Med J* 1963;1:1043-9
5. Henry D, Hill S. Comparing treatments (Editorial). *Br Med J* 1995;310:1279
6. Spriet A, Dupin-Spriet T, Simon P. Choice of the comparator: placebo or active drug? In: *Methodology of drug trials*, 2nd ed. New York: Karger, 1994
7. Senn S. Are placebo run ins justified? *Br Med J* 1997;314:1191-3
8. 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

4.12 Stopping rules for clinical trials

Lead author: Timothy J. Steiner

4.12.1 Statement of the problem

Early trial stop is a complex ethical issue (1), with potential impact on other trials in progress addressing similar questions.

Clinical research recruits patients who consent on the basis that it is useful and worthwhile (not, perhaps, to them but to future patients). This implies that the research will proceed to its conclusion. There may be good reasons, nonetheless, why a trial or other research may have to be abandoned prior to completion (2). Examples are new data reflecting upon the safety of a trial drug, or practical problems that indicate that the study cannot be completed (generally, or only at one center that finds itself unable to recruit, for example). A decision by a company on commercial or other grounds to cease development of a drug means that future patients cannot benefit. This may justify stopping trials in progress, since there is no prospect of benefit to set against any risk, but sponsor companies have "a moral responsibility to ensure that the commitments shown by physicians to their patients in the research setting and the commitments made by patients to advance clinical knowledge are not subject to the vagaries of commercial restructuring" (3).

A special case for stopping a trial midway is when a planned interim analysis shows one or other compared treatment to be more efficacious or safer (4). Such analyses are invariably conducted on fewer patients than were estimated to be needed to show a difference, with some only partially followed up. Unless the finding is statistically irrefutable (5), there is usually an ethical dilemma (1) requiring the interests of patients who might still be entered to be balanced against those of patients who have already

contributed to the research and the needs of future patients who might benefit from the results of the completed research. Failure to achieve a clear result may itself be unethical.

A complication for a study underway is the publication of results from similar trials (6). The weight of other evidence has to be taken into account in determining whether or not there is still clinical equipoise (the point at which there is no preference for treatment A over treatment B) (7) so that the trial might be continued. Regardless of this, some investigators may become less motivated, as may participating or prospective trial subjects (8), and continuation may be difficult.

4.12.2 *Specific relevance to headache*

Protocols for sponsored multicenter trials are commonly presented to prospective investigators already "set in stone". The headache "market" may be perceived as uncertainly profitable yet competitive ("high economic risk"), leading to commercial sensitivity. It is not unusual to find clauses in protocols for headache trials, or in the associated agreements between sponsor and investigator, along the lines of "the sponsor reserves the right to stop the trial at any time, with or without cause".

4.12.3 *Recommendations*

1. Protocols should specify the reasons for which a trial might be stopped prior to completion. These might be *ethical* (e.g., discovery of undue toxicity, or emergence of a more effective or safer alternative therapy), *statistical* (planned interim analysis [see below] shows that the question addressed by the trial has been irrefutably answered), *methodological* (e.g., failure of the study to proceed according to the protocol), *legal* (e.g., misuse of trial supplies or other serious breach of the protocol by the investigator), *regulatory* (e.g., at the behest of a licensing authority), or *commercial* (e.g., a decision to cease development of the drug altogether).
2. Statements such as "the sponsor reserves the right to stop the trial with or without cause" cannot ethically be justified, and they are unnecessary. Ethics committees should not approve and investigators should not undertake research where such restrictions are placed on its completion. Concerted refusal to do so will end this practice.
3. Where an interim analysis is planned, with the prospect of trial stop, statistical rules should be written beforehand to govern the decision, which, preferably, should be made independently of investigators and sponsor (1, 2).

4.12.4 *References*

1. Pocock SJ. When to stop a clinical trial. *Br Med J* 1992;305:235-40
2. McNamee D. Stopping trials early. *Lancet* 1994;344:327
3. Editorial. A curious stopping rule from Hoechst Marion Roussel. *Lancet* 1997;350:155
4. Spilker B. Guide to clinical trials. New York: Raven Press, 1991:124-8
5. Editorial. On stopping a trial before its time. *Lancet* 1993;342:1311-2
6. Fletcher A, Spiegelhalter D, Staessen J, Thijs L, Bulpitt C. Implications for trials in progress of publication of positive results. *Lancet* 1993;342:653-7
7. Johnson N, Lilford RJ, Brazier W. At what level of collective equipoise does a clinical trial become ethical? *J Med Ethics* 1991;17:30-4
8. Brewin CR, Bradley C. Patient preferences and randomised clinical trials. *Br Med J* 1989;299:313-15

4.13 **Rights of ownership of data, and restrictions on information flow**

Lead author: Timothy J. Steiner

4.13.1 *Statement of the problem*

It is commonplace for protocols for sponsored clinical trials and some other research to state that all data produced by the research are the *property* of the sponsor. By paying the investigator under what amounts to a research contract, the sponsor contends, he has bought the data. This presupposes that clinical data are purchaseable in this way, and that no-one else (the health authority, for example, or the patient) might claim to own them.

Does this matter? One theoretical concern is that scientific investigators denied intellectual interest in data generated by their research lose interest in the research. Clinical investigators may lose interest in the subjects of the research whose management, if they are patients, is determined by the trial protocol.

Ethically, the most important issues may arise not over ownership of the data but over control of them (1), which is likely to rest with ownership. In a multicenter study, individual investigators without access to the whole of the data cannot judge whether they have been analyzed appropriately. A single principal

investigator chosen to sign off the study report has a mammoth burden and probably an undischageable responsibility. The opportunity for invisible "data massaging" may be limited where those data are to be submitted to regulatory agencies, but still the situation invites claims that companies commission clinical studies in a number of countries and submit to regulators only the data from those reporting favorably (2). Furthermore, having control of data may allow publication in a particular way or place, or not at all (see section 4.14). Data-massaging and selection for publication in a way that best supports marketing (1) are likely to be undetectable.

Whether or not these things happen, there are legitimate concerns that they might in a context where the pharmaceutical industry does not have a blemish-free record (3).

4.13.2 *Specific relevance to headache*

With the sudden expansion of interest in headache, large numbers of sponsored multicenter (often multinational) studies are underway or being planned. Often the emphasis is on rapid completion, with investigators moving on to new studies unmindful of those completed. Such controls as there are have difficulty keeping pace, especially as studies spread to parts of the world where codes of practice are not formally adopted and regulation is less rigorous.

4.13.3 *Recommendations*

1. Responsibility for ensuring proper data handling and analysis cannot be separated from the ethical responsibility of the investigator conducting the trial in the first place (4). Investigators and sponsors should agree about data management and analysis policies of multicenter trials in the protocol.
2. Many multicenter trial protocols are the subject of performance contracts between investigators and sponsor, which bind both. Where such a contract exists, the sponsor's *duty* (5) to ensure full analysis according to the protocol and subsequently facilitate publication (subject to the considerations in section 4.14) should be written into it.
3. Institutional review boards and research ethics committees should make these matters conditions of approval. In the case of subsequent default there should be no presumption of innocence; they should notify regulators of the facts.
4. Many sponsor companies laudably send regular newsletters to investigators during the currency of a trial. This aid to greater involvement in aspects outside the investigators' own centers might be continued through data clarification and cleansing, and analysis, to publication.

4.13.4 *References*

1. Hampton JR, Julian DG. Role of the pharmaceutical industry in major clinical trials. *Lancet* 1987;ii:1258-9
2. Braithwaite J. Corporate crime in the pharmaceutical industry. London: Routledge and Kegan Paul, 1984 (repr 1986)
3. Dukes MNG, Swartz B. Responsibility for drug-induced injury. Amsterdam: Elsevier, 1988
4. Wheatley D. Clinical trial results: whose responsibility? Report of meeting of Royal Society of Medicine Forum on Clinical Pharmacology and Therapeutics, 18th March 1991. *J Roy Soc Med* 1992;85:242-4
5. Dukes MNG, Swartz B. Responsibility for drug-induced injury. Amsterdam: Elsevier, 1988: 303-5

4.14 **Publication bias; registry of headache trials**

Lead authors: Peer Tfelt-Hansen, Felicity J. Gabbay, and Timothy J. Steiner

4.14.1 *Statement of the problem*

Publication of research is an ethical imperative (1). Medical knowledge worldwide is developed in part on the published results of previous research work. Future research properly takes into account all that has been done before. Both are at risk of being misled if publications present only a partial account of past research, especially if the part that is missing is "selected".

Too much research undertaken with patients is not published because results are perceived as boring or, alternatively, do not fit the marketing strategy of the sponsors (2). A greater proportion of clinical trials with positive results are (a) written up as manuscripts; (b) submitted for publication; (c) published (3). This works against studies that confirm null hypotheses, although such findings may be clinically important. It also undermines (or thwarts) overview analyses, by pre-selection of favorable data (4-7).

Anything less than full adherence to the principles of independent analysis and public availability of trial reports lets down the patients who took part in research (5) (see section 4.1). "What is required is a universal condition among institutional ethics committees that there is an intention to publish" (1). Even if this were realized, and investigators found the self-discipline always to analyze and write up, publication

is in the hands of journal editors who reject much of what is submitted on grounds of poor methodology, unprofessional writing, irrelevance to the journal, adverse comment from reviewers, and a host of other reasons (1, 4).

Current regulations and practice may not prevent a sponsor of clinical research from delaying or preventing the dissemination of findings that do not support his or her commercial, professional, or managerial interests (8, 9).

4.14.2 *Specific relevance to headache*

Headache treatment, as any other, should be based as far as is possible on evidence of efficacy and safety in the proposed use. 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 all such trials to be in the public domain. A review of the literature on prophylactic trials (10) found that every class of prophylactic was, apparently, 40% better than placebo. The most likely explanation is a "threshold" for publication.

With the current interest in the development of new drugs and new formulations for migraine treatment, many sponsored large multicenter trials are being conducted. The principal objective is to meet regulatory requirements for marketing authorizations in various parts of the world. The second objective is to support marketing, for which non-peer reviewed supplements bringing together selected clinical research reports are commonly favored, these serving well as handouts to prescribing physicians. Publication for the scientific communication is of lesser priority: references in advertising and in information to prescribers can be listed as "data on file". Recent examples of this have been seen with antimigraine drugs.

4.14.3 *Recommendations*

1. Responsibility for publication cannot be separated from the ethical responsibility of the investigator conducting the trial in the first place (11). The Subcommittee shares the view of the Vancouver Group that: "Scientists have an ethical obligation to submit creditable research results for publication, and should expect to do so. As the persons directly responsible for their work, the authors as individuals should not enter into agreements that interfere with their control over the decision to publish" (12).
2. Investigators and sponsors should agree to a publication policy of multicenter trials in the protocol, not after trial completion, to be binding on all parties and, if necessary, institutional review boards and ethics committees should use their powers to enforce it (8). Ideally, responsibility for early and full publication should be irrevocably devolved to a publication committee of named investigators, with access to all data and setting out the analysis plan.
3. As a general rule, every methodologically sound randomized controlled trial should be published (and only such trials should be carried out: see section 4.10). Publication should be in such a way as to allow evaluation of the results; publication solely as an abstract or in non-peer reviewed supplements is unacceptable.
4. Notwithstanding this, the Subcommittee shares the view of the Committee of Vice Chancellors and Principals of the Universities of the UK, and recognizes that commercial sponsors of research may need time to gain some advantage over competitors by delaying publication of results (13).
5. Editors of IHS publications, including Cephalalgia, should have in mind the public interest in considering whether or not to accept a trial for publication.
6. As this cannot be a complete solution to publication bias, a registry of clinical trials (14–16) is ethically desirable, to include all non-sponsored trials and all phase III and phase IV sponsored trials. The Subcommittee endorses initiatives to set up a Headache review group or subgroup within the International Cochrane Collaboration (17), and recommends that the IHS and sponsoring companies give full support.

4.14.4 *References*

1. Pearn J. Publication: an ethical imperative. *Br Med J* 1995;310:1313–5
2. Goodare H, Smith R. The rights of patients in research (Editorial). *Br Med J* 1995;10:1277–8
3. Spilker B. Guide to clinical trials. New York: Raven Press, 1991:813
4. Levy G. Publication bias: its implications for clinical pharmacology. *Clin Pharmacol Ther* 1992;52:115–9
5. Newcombe RG. Toward a reduction in publication bias. *Br Med J* 1987;295:656–9
6. Begg CB, Berlin JA. Publication bias and dissemination of clinical research. *JNCI* 1989;81:107–15
7. Hetherington J, Dickerson K, Chalmers I, Meinert CL. Retrospective and prospective identification of unpublished controlled trials: lessons from a survey of obstetricians and paediatricians. *Paediatrics* 1989;84:374–80
8. Munro AJ. Publishing the findings of clinical research. *Br Med J* 1993;307:1340–1

9. Rennie D. Thyroid storm. *J Am Med Assoc* 1997;277:1238–43
10. Tfelt-Hansen P, Welch KMA. Prioritizing prophylactic treatment. In: Olesen J, Tfelt-Hansen P, Welch KMA, editors. *The headaches*. New York: Raven Press, 1993:403–4 (and references therein)
11. Wheatley D. Clinical trial results: whose responsibility? Report of meeting of Royal Society of Medicine Forum on Clinical Pharmacology and Therapeutics, 18th March 1991. *J Roy Soc Med* 1992;85:242–4
12. Horton R. Sponsorship, authorship, and a tale of two media (Editorial). *Lancet* 1997;349:1411–2
13. Powell AMA. Publishing the findings of clinical research (Letter). *Br Med J* 1994;308:342
14. Simes RJ. Publication bias: the case for an international registry of clinical trials. *J Clin Oncol* 1986;4:1529–41
15. Spilker B. *Guide to clinical trials*. New York: Raven Press, 1991:816–9
16. Easterbrook PJ. Directory of registries of clinical trials. *Stat Med* 1992;11:345–423
17. Steiner TJ. Treating headache from an evidence base: the Cochrane Collaboration. *Cephalalgia* 1998;18 Suppl 21:63–5

4.15 Inappropriate publication, or media interpretation

Lead authors: Felicity J. Gabbay and Peer Tfelt-Hansen

4.15.1 Statement of the problem, and specific relevance to headache

The release of data to regulatory authorities from trials of unregistered drugs or drugs used for unregistered indications is rigorously controlled, especially in the USA. Not only must a full research report be submitted afterwards but details of a proposed trial and its statistical analysis plan are deposited with the FDA before it starts. Manipulation of data by drug companies or investigators is monitored by teams of internal and government inspectors, and the FDA is charged with ensuring that promotional activities are truthful, balanced, and not misleading (1).

The same is not true of drugs used in accordance with a marketing authorization. Data from post-marketing trials do not, in general, have to be submitted to a regulatory authority. Controls over use of data exist only to the extent that they apply to fraud or to standards of advertising (which may be stringent, as in the UK Medicines Act). Peer review is intended to regulate the quality of published data from all sources, but is not without problems and may be circumvented, for example by publication in non-reviewed journal supplements (see section 4.14).

Medical reports published in journals are *very* much shorter than research reports submitted to regulators. In the 1940s, when the first comparative trials were published, rarely were more than 20 patients entered. Now it is commonplace for in excess of 200 evaluable patients to come from 20 centers in five countries, and not unusual for each of these to be multiplied fivefold. The volume of data, enormously increased, is published in articles of the same length. What is said or left unsaid must be carefully selected if it is not to mislead, but individual investigators are not in a position to check all of the original data to find out whether offered data fairly represent the “whole truth” (2). If they cannot, peer reviewers cannot either. Academic investigators in any event are under pressure to publish, and these factors together can lead to a second example of inappropriate publication: multiple publication of the same trial, or subsets of data from one trial without making clear their common origin (3). It can be very difficult for readers and reviewers to establish how many patients have been studied, and by whom.

The media take passing interest in clinical issues; headache is common, so apparent discoveries or therapeutic developments raise interest which may be heightened (often a media objective) by inventive (as opposed to factual) presentation. The financial press are interested in new pharmaceutical products: data from clinical trials (or even news that trials are in progress, or stopping) may be financially sensitive. Stock Exchange rules require that price-sensitive information be published at the earliest date. But this precludes the scientific claim to priority of publication in appropriate medical or scientific journals (4), the clinical imperative to get therapeutic information to prescribers first, and controls that minimize the dangers of inappropriate emphasis or interpretation.

The following are predictable consequences of inappropriate publication, which may deliberately or inadvertently be manipulated: increased or decreased sales of a marketed drug; increase or decrease in company share price; wrong perceptions of safety and/or efficacy; increased adverse events; litigation by patients misled on safety and/or efficacy; lack of further work or sponsorship in a therapeutic area or on a class of drug.

4.15.2 Recommendations

1. Responsibility for publication cannot be separated from the ethical responsibility of the investigator conducting the trial in the first place (5) (see section 4.14).

2. Authors must regulate themselves. In the absence of other realistic penalties for neglect of this responsibility, it should attract the disapproval of peers. Editors of IHS publications who discover undeclared duplicate publication should declare it in print.
3. Publication should be first in an appropriate scientific medium.
4. Where trials feature in multiple publications, the protocol number, acronym, or other unique identifier should appear in every title.
5. Cooperation with interested lay or financial media enhances the opportunity for correct representation.

4.15.3 References

1. Kessler DA. Drug promotion and scientific exchange. The role of the clinical investigator. *N Engl J Med* 1991;325:201-3
2. Munro AJ. Publishing the findings of clinical research. *Br Med J* 1993;307:1340-1
3. Huston P, Moher D. Redundancy, disaggregation, and the integrity of medical research. *Lancet* 1996;347:1024-6
4. Freestone DS, Mitchell H. Inappropriate publication of trial results and potential for allegations of illegal share dealing. *Br Med J* 1993;306:1112-4
5. Wheatley D. Clinical trial results: whose responsibility? Report of meeting of Royal Society of Medicine Forum on Clinical Pharmacology and Therapeutics, 18th March 1991. *J Roy Soc Med* 1992;85:242-4

4.16 The importance of education, and the interface between education and promotion

Lead authors: David Russell and Kate M. Lloyd

4.16.1 Statement of the problem

There is a perceived or actual conflict between the commercial interests of pharmaceutical companies and the *prima facie* requirement that education provided or sponsored by the pharmaceutical industry be balanced and non-promotional (1, 2).

Imbalance may arise indirectly, since ability to attend at some events may depend on sponsorship of individuals to cover costs of registration fees, travel, and accommodation. Who does and does not attend which events is at risk (made greater by the increasing number and cost of events) of being determined by pharmaceutical sponsors. The practical management of access to this sponsorship by pharmaceutical companies is a concern. An undeclared link between access and promotional activity is unacceptable.

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. Pharmaceutical companies are subject to self- and external regulation that require ethical conduct. The effectiveness of controls may vary from one part of the world to another.

Regardless of other considerations, dealings with sponsors should be open, and fair.

4.16.2 Specific relevance to headache

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

4.16.3 Recommendations

1. The IHS should pursue a policy of openness in its dealings with sponsors.
2. The IHS should accept sponsorship from the pharmaceutical industry as far as possible in accordance with the advice of the Legal Department of the European Federation of Pharmaceutical Industries' Associations (3) and the FDA (4):

With regard to scientific events, EC Directives do not prevent pharmaceutical companies from sponsoring events for purely professional and scientific purposes, or from offering hospitality at such events, directly or indirectly. Such hospitality must always be *reasonable* in level and remain *subordinate* to the main scientific objective of the meeting. Hospitality may not be extended to persons other than health professionals.

The FDA policy states: "The FDA will not regulate (sponsored) scientific and educational activities provided they are independent of influences from the sponsoring company ... A written agreement is needed between the CME provider and the sponsoring company that stipulates that the company will have no role in the design or conduct of the program other than acceptance of the topic."

3. International Headache Congresses (IHCs) should be organized in accordance with IHS guidelines (5). The Subcommittee specifically endorses the resolution of the IHS Council that *no part of the main scientific program of IHCs shall be directly sponsored by the pharmaceutical industry*. Satellite sessions outside and never parallel to the main program may be sponsored and, if so, should be clearly so identified.
4. Organizers of IHCs or other IHS meetings seeking industry sponsorship should establish a menu of sponsorship options, setting out precisely what is purchased by the sponsor for each level of sponsorship. The same menu should be available to each potential industry sponsor with the options taken on a first-come first-served basis. Thus there is clarity in advance and transparency to participants; all potential sponsors compete on equal terms; the organizers declare their sources of funding; there should be no opportunity for scientific veracity to be compromised by funding.
5. Pharmaceutical companies, whether sponsors of the event or not, may organize their own activities around an IHS educational event *in consultation with* the event organizers. Such activities are not expected to be staged at the same time as or in competition with any part of the IHS event.
6. The sponsorship of individuals by pharmaceutical companies, and the influence this may have in determining who attends an event, are general issues. Possible but partial solutions lie in redirecting this sponsorship to organizers of events, to national societies, or to the IHS itself, for distribution in the form of bursaries. This would separate sponsors from the choice of who attends (but not what is attended).

4.16.4 References

1. Council on Ethical and Judicial Affairs of the American Medical Association. Gifts to physicians from industry. *J Am Med Assoc* 1991;265:501
2. Kessler DA. Drug promotion and scientific exchange. The role of the clinical investigator. *N Engl J Med* 1991;325:201–3
3. European Federation of Pharmaceutical Industries' Associations. EC Directive on the advertising of medicinal products: a reading of the current texts (a note by the legal department). EFPIA, 1992
4. United States Food and Drug Administration. Final guidance on industry-supported scientific and educational activities. *Federal Register*, Dec 8th 1997
5. International Headache Society. Rules and guidelines for the organization of the IHS International Headache Congress (IHC). *Cephalalgia* 1997;17:896–9