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Management of conflict of interest: the example of the Cochrane Collaboration

The Cochrane Collaboration has developed strict rules to protect its systematic reviews from conflicts of interest.

Created in 1993 and now established in nearly 90 countries, the non-profit Cochrane Collaboration has acquired an international reputation for the Cochrane Database of Systematic Reviews, a collection of regularly updated reviews of the efficacy of a growing number of medical therapies and interventions for disease prevention. The Cochrane review methodology is strict and explicit (1-3).

The Cochrane Database of Systematic Reviews is the main documentary resource in the Cochrane Library. It is published four times a year, both on CD-ROM and online (**a**). In the last few years the Cochrane Collaboration has acquired the active support of health authorities in a number of countries (in South and Central America, Australia, Spain, Ireland, Iceland, Finland, Norway and the United Kingdom). Health care professionals and the public in these countries have benefited from free (publicly funded) access to the online Cochrane Library.

Strict and explicit methods

Thousands of contributors (editors, authors and peer reviewers) participate, on an unpaid basis, in the production of systematic reviews for the Cochrane Collaboration.

In general, teams of unpaid authors propose subjects ("titles") for review articles to one of the 50 thematic editorial teams ("collaborative review groups") covering nearly all fields of medicine.

The interventions, target populations and outcomes assessed during systematic reviews are first agreed upon with the editorial team. Once the title has been defined and accepted, the authors write a detailed protocol describing how the data will be analysed. The protocol must be published in the Cochrane Library before the analytical work begins.

The editorial teams maintain the responsibility and the right to approve publication, in the Cochrane Library, of protocols and systematic review articles (and updates) covered by their field of interest (**b**).

Funding sources and conflict of interest: clearly stated for each review

The work of the steering group and coordinating office of the Cochrane Collaboration is funded by subscriptions to the Cochrane Library.

Conflict of interest. Authors, who sometimes work free of charge, generally receive financial support from a variety of sources (mainly universities and government agencies). Funding sources and authors' potential conflicts of interest are always listed at the end of each Cochrane review article.

A section of the Cochrane Handbook for Systematic Reviews of Interventions (an official reference manual intended for authors of Cochrane reviews) deals with conflict-of-interest statements (4). It specifies that "*Cochrane Reviews should be free of any real or perceived bias introduced by the receipt of any benefit in cash or kind, any hospitality, or any subsidy derived from any source that may have or be perceived to have an interest in the outcome of the review. It is a matter of Cochrane Collaboration policy that direct funding from a single source with a vested interest in the results of the review is not acceptable*" (4).

Two review articles jointly funded by a pharmaceutical company rekindled a debate on conflict of interest within the Cochrane Collaboration. In 2001, two reviews, ►►

a- The Cochrane Collaboration also produces a register of comparative trials (the Cochrane Controlled Trials Register), a register of publications which report on methodological issues about controlled trials (Cochrane Methodology Register), and a bank of systematic reviews of methodological studies (Cochrane Database of Methodology Reviews). The Cochrane Library contains all the articles of the Cochrane Collaboration as well as those of three other banks of review articles produced by the NHS Centre for Reviews and Dissemination, a British public organisation (ref 1). Commercial distribution of the Cochrane Library, on CD-ROM and online, is handled by the Anglo-American publisher John Wiley & Sons (http://www.thecochranelibrary.com).

b- A list of the Collaborative Review Groups, their websites, protocol titles and review articles can be found on the Cochrane Collaboration website http://www.cochrane.org/contact/entities.htm#CRGLIST (consulted on 2 March 2005).

a- The study was conducted by members of the International Society of Drug Bulletins (ISDB), including Prescrire, in collaboration with Quality Assurance and Safety of medicines (QSM) of the World Health Organisation (WHO). The analysis focused on information collected by health care professionals participating in the study in 26 countries: in the Americas (Argentina, Brazil, Canada, Colombia, U.S., Mexico, Peru and Venezuela); Europe (Croatia, Spain, Estonia, France, Italy, Poland, United Kingdom and Switzerland); Africa (Egypt, Kenya, Mozambique and Tunisia); Asia (India, Pakistan, Philippines, Syria and Thailand); and Australia (ref 1).

b- BNF literature sources include the Martindale database, a global reference in drug therapy (ref 3).

c- Data that were not published in the BNF were not included in the analysis.

d- "Official" information, available at the time of marketing authorisation (e.g. the summary of product characteristics), was obtained for fluoxetine and nifedipine in 18 countries, and for ciprofloxacin in 14 countries (ref 1).

e- The BNF was used to establish a list of items for each of the four types of information (37 items for ciprofloxacin, 48 for fluoxetine, 22 for nifedipine). The authors compared the number of items on this list with those mentioned in the information collected in each country. These figures served to calculate a "degree of agreement" of information, expressed as scores of 1, 0 or -1, for the indications, precautions and adverse effects. For the dose regimen, the authors awarded a score of 1 when the dose corresponded to that mentioned in the BNF, and 0 when the dose was different. The sum of the scores obtained for the four types of information and for a given drug could therefore range from +4 to -3 (ref 1).

1- Reggi V et al. "Prescribing information in 26 countries: a comparative study" *Eur J Clin Pharmacol* 2003; **59** (4): 263-270.
2- British Medical Association and Royal Pharmaceutical Society of Great Britain "British National Formulary (UK)".
3- The Royal Pharmaceutical Society of Great Britain "Martindale The complete drug reference" 34th ed. The Pharmaceutical Press, London 2005: 2 756 pages.

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SURVEY

► each assessing the efficacy of an antimigraine drug and partly funded by Pfizer, were published in the Cochrane Library (5,6). One of these reviews focused on eletriptan, a Pfizer product (5).

The Conflict of Interest section of the two articles stated that Pfizer was one of several funding sources, and summarised the terms of the contract signed between the authors and the company: Pfizer agreed not to intervene in the preparation of the review or in the publication of its results, and to provide the authors with all published and unpublished individual clinical data on patients having participated in clinical trials of eletriptan (5,6).

Despite the transparency of this statement, some members of the Cochrane Collaboration expressed profound concern and restated their opposition to even partial funding of Cochrane reviews by pharmaceutical firms, fearing it could undermine the image of the Cochrane Collaboration and the credibility of its reviews (7,8).

No funding by for-profit organisations with a vested interest in the conclusions of a review

The debate resulted in a consultation of all members of the Cochrane Collaboration in December 2003 and January 2004 on the funding of its units (author groups, Collaborative Review Groups, etc.) and products (systematic review articles, etc.).

New rules published in April 2004 prohibit the funding of a Cochrane review or its update by a for-profit company that might realise a material advantage from the conclusions of the review (**c**)(9).

The new rules also do not allow such companies to fund Collaborative Review Groups, or related groups such as the Consumer Collaboration, which includes patients involved in the preparation of systematic reviews (http://www.cochrane.org/consumers), the Cancer Collaboration, the Complementary Medicine Field, or the Vaccines Field.

Recognizing the potential financial implications of Cochrane reviews for public health institutions, the new rules allow Cochrane reviews to be funded by government agencies and not-for-profit health insurers. Commercial enterprises with no conflict of interest with a given Cochrane review may also provide financial support. However, no financial contributor to a Cochrane review may exert any influence whatsoever on the preparation of the review or its publication (9).

Arbitration in ambiguous situations

To deal with unforeseen circumstances and problems involving funding sources, a member of the Steering Group was designated as the Funding Arbiter. If necessary, the arbiter can designate and chair a three-member jury. One of the first tasks of this new arbitration service was to re-examine all published Cochrane reviews whose funding sources do not comply with the new rules, and to decide whether or not they should be removed from the Cochrane Library. The arbiter also examines cases in which an author of a systematic review article has been employed by a pharmaceutical company or manufacturer of medical devices.

This new policy now applies to new funding sources for all groups within the Cochrane Collaboration that are involved in the production of systematic reviews (**d**). A two-year delay was allowed so that those whose existing funding sources do not comply with the new rules could seek alternative financing.

Few public or private providers of medical information aimed at health care professionals or the general public have such a clear policy on commercial funding sources. The Cochrane Collaboration provides an excellent example of how to manage conflicts of interest.

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c- *The new Cochrane policy on commercial funding sources clarifies several important issues. For example, the Conflicts of Interest section of each review article must state each author's consulting activities for commercial enterprises, whether they have participated in clinical trials linked to the review, and any stocks and shares they may hold. Persons with a direct financial interest in the use of a therapeutic intervention are forbidden to participate in a systematic review of the efficacy of this intervention, as an author, a member of the peer review committee, or as a member of the Review Group. Authors and Review Groups must not receive authorship rights for the sale of reprints of review articles to which they contributed (ref 9).*

d- *Discussions are ongoing on the question of commercial funding of Cochrane Collaboration conferences and Cochrane Methods Groups. An amendment made in April 2005 to the new Cochrane policy states that "there should be no direct funding of Cochrane Centres (or Branches of Centres) by commercial sources".*

Selected references from Prescrire's literature search.

1- Prescrire Rédaction "La Bibliothèque Cochrane (The Cochrane Library)" *Rev Prescrire* 2001; **21** (219): 545-546.
2- "What is the Cochrane Collaboration?" Website http://www.cochrane.org accessed on 17 March 2005.
3- "Cochrane Collaboration newcomers' guide" Website http://www.cochrane.org accessed on 17 March 2005.
4- "Conflict of interest (Section 2.2.)". In Cochrane Reviewers' Handbook 4.2.3 ed, November 2004: 18-19. Website http://www.cochrane.org/resources/handbook accessed on 2 March 2005.
5- Smith L et al. "Eletriptan for acute migraine (Cochrane Review)". In: *The Cochrane Library*, Issue 2, 2004. Chichester, John Wiley & Sons: 2 pages.
6- Oldman A et al. "Rizatriptan for acute migraine (Cochrane Review)" In: *The Cochrane Library*, Issue 2, 2004. Chichester, John Wiley & Sons: 2 pages.
7- Moynihan R "Cochrane at crossroads over drug company sponsorship" *BMJ* 2003; **327** (7420): 924-926.
8- Lenzer J "Cochrane proposes further limits on commercial funding" *BMJ* 2003; **328** (7436): 366.
9- "Cochrane Collaboration policy on commercial sponsorship". Website http://www.cochrane.org/docs/commercialsponsorship.htm accessed on 18 July 2005.

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