Publishing the findings of clinical research

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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. Pharmaceutical trials are particularly subject to this concern, but the issue of non-publication has a wider significance. Patients participate in research on the understanding that it will be of public benefit. To be fair to these patients we must confirm that data will be analysed without bias and that findings will be regarded as being in the public domain and hence available to interested reviewers even if the results do not justify publication. Clinical investigators and ethics committees have the power and the duty to enforce this outcome.

Adam and Oswald recently revealed in the *BMJ* that adverse findings on triazolam obtained from clinical trials remained in the manufacturer's files until a specific reanalysis by drug licensing authorities resulted in their public disclosure.¹ Unfortunately the procedures in place for the conduct of pharmaceutical trials are inadequate to prevent this problem of non-publication. Nor may it be unique to pharmaceutical trials. The budget for operational research in the NHS is increasing but it is controlled by politicians and their appointees. The public and the clinical investigators who manage such research need an explicit requirement that findings lie in the public domain and are to be reported free of bias.

We also need to address the problems of reviewers who need access to information that may not justify publication in journals for a general readership. At present, publication bias by researchers, sponsors, and editors limits their knowledge of and access to relevant information.

Current guidelines

The Association of the British Pharmaceutical Industry's guidelines on good clinical research practice maintain that clinical trial results may be either confidential to the company or intended for publication and that "it should always be the intention to publish results where this is warranted."² They do not suggest that the clinical investigator has any responsibilities in this respect.

The Declaration of Helsinki maintains that "biomedical research involving human subjects should be conducted only by scientifically qualified persons under the supervision of a clinically competent medical person" and that "in publication of the results of his or her research the physician is obliged to preserve the accuracy of the results."³

The Royal College of Physicians' report on research involving patients has it that "it is however the responsibility of the investigator to ensure that there is prior agreement with any financial sponsor that the results of the research may be submitted to journals of the investigator's choice and that the sponsor will not seek to influence the publication of the results of the research."⁴ The college's guidelines on the practice of ethics committees also suggest that "it is unacceptable in principle that an investigator should agree to conditions that may prohibit or impair the chances of

publication although some delay may sometimes be acceptable."⁵

Multicentre pharmaceutical trials—the current situation

Many clinical trials are multicentre projects. Pharmaceutical companies or their agents are the paymasters, and their protocols and correspondence may be very guarded on the subject of publication. Their employees or agents analyse and report the data. Publication thereafter may be a matter of the sponsoring company's discretion. I remember, from the days when I worked in pharmaceutical company clinical research departments, non-committal remarks from my seniors if I raised the topic of a duty to publish trial reports regardless of the outcome. Commercial considerations certainly played a part in the pacing of the trials, and more than half of the clinical research departments' projects were considered not to justify publication, usually on grounds that they were inconclusive or of interest only to reviewers or competitors. It is commonly acknowledged that results of many pharmaceutical trials are of minority interest only and do not justify publication in major refereed journals.

Most companies will agree at the outset to circulate a report of the data to the clinical investigators while denying them the freedom to publish it unilaterally. They will also usually involve one or several of the clinical investigators in drafting the report or the statistical summary if it is to be published. Their medical information departments are usually helpful to inquirers but may not be a reliable source of comprehensive information on an issue that is commercially sensitive.

Suggested reforms

What can be done? We need to establish the principle that if a medicine or device is marketed anywhere in the world the clinical trial data on it must be analysed independently and findings made accessible to interested reviewers. The same requirement may be made of any audit, survey, or clinical trial sponsored by government, health service management, a professional body, or a charity which involves the participation of patients.

To meet the needs of reviewers we need an additional computer database of findings of uncirculated clinical research, under the guardianship and editorship of a public body. Clinical researchers may then be required to submit reports of their work to this database. To make this system credible, local and national ethics committees will need to take a larger role in quality assurance and maintaining registers of research in progress. An electronic bulletin board linked to a database will be needed to provide for peer review and right of reply from the interested readership. Exceptions to the requirement for timely conclusion and reporting of research to the database will require guidelines to be interpreted by ethics committees.

Steps in the right direction

The pressure of publicity may achieve something. Individual companies may accept the principle that

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BMJ 1993;307:1340-1

Are clinical trials worth doing if the results are left to languish in the drug manufacturer's files?

data from their clinical trials are a public as well as a private resource that needs to be made available for review.

Industry associations can achieve more by including in their guidelines a requirement for publication (if necessary in journals circulated at the cost of the writers rather than the recipients). They might also set up an international register of results of pharmaceutical trials and an authoritative external inspectorate. The sanctions on miscreants would be expulsion from the industry association and being reported to drug regulatory authorities. These measures would benefit the public reputation of pharmaceutical research and all involved in it.

Drug regulatory authorities are increasingly making clinical trial reports on marketed products in their files available for public inspection. This trend is to be encouraged.

Ethics committees are expected to ensure that patients and the public are not bothered to take part in research that is likely to prove futile. Research findings that remain under wraps are fruitless, and ethics committees may include this concern in their agenda.

What can clinical investigators do?

Patients give freely of their time to take part in clinical trials on the unspoken understanding that the work is being conducted for public benefit. Anything less than adherence to the principles of independent analysis and public availability of trial reports on marketed products lets these patients down. However, many clinical investigators in multicentre trials are content to regard their responsibility as limited to producing accurate and complete case reports. They may not know who the other clinical investigators are. They may feel that if they put pressure on the sponsor to publish the results regardless of the outcome they may be dropped in favour of another trialist. I hasten to add that I have never known this to happen.

In the absence of adequate procedures I suggest that clinical investigators in multicentre projects ask sponsors the following questions and be prepared to persist with the inquiry and withhold their collaboration until satisfactory answers emerge.

- Who are the other clinical investigators?
- Do any of the clinical investigators have the knowledge required to act as independent monitors of the data analysis and reporting?
- Will one or more clinical investigators be appointed to monitor the data analysis and reporting, and will their identities be made known to the others?
- If there is an organising committee, who is the

chairman; and who is in the majority, clinical investigators or company employees or agents?

- Will the original data and the statistical report be inspected by an independent statistician chosen by the clinical monitor?
- Will the report of the results of the trial be submitted to a journal that is abstracted by one or more of the medical reference computer indexing services?

- 1 Adam K, Oswald I. Unpublished manufacturers' research unfavourable. *BMJ* 1993;306:1475-6.
- 2 Association of the British Pharmaceutical Industry. *Guidelines on good clinical research practice*. London: ABPI, 1988.
- 3 World Medical Assembly. *Declaration of Helsinki—recommendations guiding medical doctors in biomedical research involving human subjects*. Hong Kong: WMA, 1989.
- 4 Royal College of Physicians of London. *Research involving patients*. London: RCP, 1990.
- 5 Royal College of Physicians of London. *Guidelines on the practice of ethics committees in medical research involving human subjects*. London: RCP, 1990.

(Accepted 19 October)

Update box for *Oxford Handbook of Clinical Medicine* (3rd ed), p 362

Obstructive sleep apnoea syndrome

The obstructive apnoea syndrome is characterised by intermittent and recurrent closure of the pharyngeal airway, with partial or complete cessation of breathing during sleep. This apnoea is terminated only by partial arousal. The typical patient is a middle aged overweight man who presents because of snoring or daytime somnolence. The spouse or partner usually volunteers that the patient stops breathing frequently during sleep.

Mechanism: The normal decrease in tone of the oropharyngeal musculature during sleep, in association with a small starting size or external loading by neck obesity, results in collapse of the upper airway (at the level of the pharynx). Partial narrowing causes snoring. Arousal is provoked mainly by increased respiratory effort to overcome the blockage; thus heavy snoring without apnoea can also disturb sleep. In children, narrowing of the airway by enlarged tonsils may cause apnoea.

Clinical features are loud snoring, daytime somnolence, poor sleep quality, headache in the mornings, decreased libido, and impaired cognitive performance. Features of type II respiratory failure (p 352) may be evident if there is associated chronic obstructive lung disease. Patients are at increased risk of developing cardiovascular diseases and being involved in road traffic accidents.

Tests: Polysomnography (monitoring oxygen saturation, airflow at the nose and mouth, electrocardiograms, electro-oculograms, and electromyograms of movement of chest and abdominal walls during sleep). Simpler studies (oximetry and video recordings) will often be all that is required for diagnosis. The occurrence of 15 or more episodes of apnoea or hypopnoea during an hour of sleep is the conventional indicator of significant sleep apnoea, but severe symptoms occur with lower or normal rates of apnoea when snoring alone is provoking sleep disruption.

Management: Continuous positive airway pressure via a nasal mask during sleep is the best treatment for symptomatic patients willing to use this cumbersome device. Weight reduction also helps. Tonsillectomy, uvulopalatopharyngoplasty, and tracheostomy are rarely needed.—M K SRIDHAR

PRINCIPAL SOURCE
Douglas NJ. The sleep apnoea/hypopnoea syndrome and snoring. *BMJ* 1993;306:1057-60.

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