Clinical trial publications

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In recent years, there is increasing pressure on academia to develop links with industry and to pursue work of possible commercial value. This pressure results in situations with ethical problems, such as recruitment practices in clinical trials (1), impact on publication of clinical trial data (2-3), and a shift in the focus of research (4). This article reviews the impact of commercial pressures on publication of data from clinical trials.

The conduct of clinical trials

Clinicians study new drugs for various objectives — benefit for their patients, to contribute to advances in medical treatment, the prestige of publication, financial benefits, to attract high quality applicants to their departments, and the opportunity to travel abroad and meet leaders in other countries (5). These are accepted as legitimate benefits of the skills, experience and energy they commit to the work. Until recently, academic clinicians played a key role in the design and conduct of clinical trials. With the increasing cost of developing a new drug (estimated at US$300-600 million), and the need to bring new drugs into market rapidly, the industry's desire to expedite clinical trials has led to a diminishing role for individual academic clinicians in the conduct of clinical trials, and the expansion of control from industry medical departments and contract research organisations (CROs). Today, the industry controls all aspects of the trial from trial design and recruitment rate of participants to data analysis and preparation of publication.

Publication guidelines and policies

Every company follows its own written publication policy, which covers the company's intent to publish the results as a multi-author, multi-centre trial. Companies generally insist on reviewing the article before publication. The investigator must wait for almost a year for publication till the company reviews and analyses trial results. The list of authors may not include investigators who do not recruit the minimum agreed number of patients.

Industry associations support this publication policy. In the UK, the guidelines of the Association of British Pharmaceutical Industry maintain that clinical trial results may be confidential to a company or intended for publication and that "it should always be the intention to publish where warranted." The clinical investigator does not seem to have any responsibility in this (6). The guidelines for good clinical practice (GCP) of the International Conference on Harmonisation do not cover publication as a responsibility of the investigator or sponsor.

The Declaration of Helsinki suggests: "In publication of results the physician is obliged to preserve the accuracy of results". The Royal College of Physicians report concludes: "It is however the responsibility of the investigators to ensure that there is prior agreement with sponsor that the results of the research may be submitted to journals of investigator's choice and the sponsor will not seek to influence the publication of the results of the research" It further adds that "it is unacceptable in principle that the investigators should agree to conditions that may prohibit or impair the chances of publication although some delay may sometimes be acceptable". (6)

Potential problems

For academic investigators, publication in peer-reviewed journals is the coin of the realm. Pharmaceutical firms are more concerned with the approval of new-drug applications from the FDA. Yet publication in prestigious journals is important, to persuade physicians to prescribe the company's products.

Some multi-centre trials have publication committees, which may be dominated by in-house or outside investigators who write up the results for publication. In other cases, the company or CRO writes the reports for publication, circulating draft manuscripts to the investigators who will be listed as authors. Authorship may be determined by such criteria as who participated in designing the study, who enrolled the most patients, and who has a prominent name in the field (3).

Many academic medical centres review contracts between industry and investigators, insisting on the investigator's right to publish the trial's results and allowing the company prepublication review, with a time limit of 60 to 90 days. It is estimated that 30 to 50 percent of contracts submitted by companies have unacceptable publication clauses that must be renegotiated (3). Chalmers argues that the results of many clinical trials are never published at all (7).

Individual investigators who want to inform other clinicians about significant findings such as safety or lack of efficacy face a long drawn-out battle. Betty Dong, who found that her sponsor's brand was not more effective than a generic version, was prevented by the company from publishing her results for nearly seven years. The article was finally published after pressure from the lay press and the US FDA (8).

Nancy Olivieri and associates found that a new drug for thalassemia major could worsen hepatic fibrosis. The sponsor threatened legal action if she published the results. Olivieri did present her findings at several scientific meetings and later in referred journals, despite severe pressure from the company. She was not supported by the hospital or university through this difficult period (2).

Even where there is no conflict, companies' commercial interests delay publication (9,10). According to a survey of 210 US companies, sponsors often require scientists to keep their results secret longer than the patent

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procedure requires.

Fifty-eight per cent of the companies in this survey said they typically require university researchers to refrain from publishing results for at least six months in order to file patent applications. (The US National Institutes of Health requires that its researchers keep results confidential for 30-60 days while patent applications are filed.) Fifty-six per cent admitted that their university-supported research often or sometimes generated information that was kept secret beyond the time required to file a patent. Such information included experimental methods, plans for future experiments, gene products, gene sequences and gene location.

There are also examples of articles whose publication was stopped or whose content was altered by the funding company or company requesting detailed revisions that would have made the manuscript more favourable to the company's official marketing position (3).

The scenario in India is unlikely to be different. Since the introduction of Schedule Y of drug rules in 1988, a Phase III clinical trial is mandatory before the company can obtain registration of a new drug in India (11). Over 300 new drugs have been registered since then. However, the results of most of these trials remain unpublished. Even if published, they are in non-peer reviewed journals. In such a situation, there are unlikely to be reports of conflicts between the investigator and industry.

Single centre publication of a multi-centre trial

One of the unsettled issues in multi-centre clinical drug trials is whether single centres should publish their results independently. Stiller and Mehrel have commented: "We do the scientific community and the public a disservice if we deny them rapid access to potentially important new data, if we require our colleagues to wait until a bureaucracy stumbles through all the cumbersome steps that inevitably delay publication" (12). In fact, the results of less successful multi-centre studies may never be published if an individual investigator does not take the initiative. The medical community has the right to know negative results as well as the more frequently reported successes. Without this information, time and money may be wasted in resuming the same unsuccessful clinical trial.

The statistical dilemma is whether results from a single centre in multi-centre trials will be misleading or non-representative. The science of statistics is sophisticated enough to minimise over-interpretation of data, unless an investigator or statistician misrepresents, misinterprets, or overlooks significant data (12). However, the current practice does not encourage a single centre publication of a multi-centre trial.

Medical journals and publication of trials

At present, most journals require authors of original articles to disclose any financial ties with companies that make products discussed in papers submitted to the journal. Recently, the editors of the *New England Journal of Medicine* found that the financial ties of the authors of a study were so extensive that it would have used too much space to disclose them fully in the journal! Ultimately, the journal summarised them and provided details on their web site (13).

However, editors often have a limited understanding of issues arising out of the relationship between authors and sponsors. In a mail survey of editors of 12 major medical journals, nine requested such a disclosure. Only four inquired about publication rights of the author; only one knew whether the sponsor's written approval was required prior to manuscript submission; only one knew whether the sponsor could delay submission for other than patent reasons; and only one knew whether there was an independent steering committee for the study (14). In India, hardly any major journal insists on declaration of conflict of interest.

Major international journals publish clinical trials and also provide editorial comments. In contrast, few clinical trials are published in peer-reviewed Indian journals. This may reflect the lack of interest of authors and sponsors in publication, or the scientific quality of the clinical trial, or the bias of editors and referees against considering trials high quality research.

Clinical trial investigators' financial bias and clinical trials

Besides the industry, the investigators also face allegations of commercial interest in clinical trials. One aspect concerns trading in pharmaceutical company shares by investigators who may have confidential information about the trial results. This could result in premature or inappropriate communication of research results. Investigators may enter patients who have borderline selection criteria into studies, or fabricate results, or induce patients to enter by offering remuneration or better medical care (5).

To win and retain their clinical trial contracts with industry, investigators must find participants and find them quickly. This pressure may lead to the adoption of questionable practices. Doctors are paid substantial fees by sponsors to get their patients to enrol in trials, which raises questions about conflict of interest. They are also paid for opening their patients' confidential records so recruiters can hunt for eligible subjects. Patients are often unaware that their doctors are paid to recruit them for trials (1).

There is considerable evidence that researchers with ties to drug companies are more likely to report results favourable to the sponsor's products than are researchers without such ties (3). The US FDA is concerned about such bias, and insists on disclosure of all financial arrangements between the investigator and the company.

The Indian perspective

With the patent regime only five years away, several Indian companies have stepped up their efforts to develop new drugs. The estimated cost of drug development is Rs. 150 crore, which is less then one-tenth the international cost. Indian companies' focus of new drug research — asthma, benign prostatic hypertrophy, diabetes and cancer — is similar to multinational efforts. Competitive global pressures on Indian companies will create the need to expedite drug development

time.

India is keen to promote itself as an international centre for clinical trials, emphasising its large pool of well-trained doctors and the ready availability of trial subjects. The government believes that clinical trials could become a significant source of foreign investment. However, concerns have been expressed that the Indian population, with its enormous genetic diversity is in danger of being exploited (15).

Clinical trials are the most expensive part of the total cost of any new drug before it hits the market. As global clinical trials come to India, trial costs will go up with the need to adhere to GCP guidelines, the participation of international CROs and the use of an international central laboratory for monitoring. A clinical trial in a chronic disease requiring frequent laboratory monitoring and GCP monitoring, and involving a CRO, would cost approximately US$ 5,000 per patient. This is more than five times the current cost of a Phase III trial in India for registering a new drug. Of course, this is still cheaper than it would be in the USA or Europe.

International clinical trials will help Indian investigators improve the infrastructure of their centres and get international exposure. Besides, investigators in private set-ups are also able to earn for their time and responsibility. However, as all trials have deadlines, there is pressure on the investigators to expedite recruitment of patients.

In 1999, several multinational and Indian companies filed 24 investigational new drug (IND) applications with the Drugs Controller General of India, of which 17 have been referred to the Indian Council of Medical Research. This was a significant jump from the six IND applications in 1998. Research and development for new drugs and Indian involvement in global clinical trials is in evolution. Once this picks up momentum, we will face a variety of ethical issues.

Conclusions

The US Department of Health and Human Services suggests that government should work with industry, clinical investigators, and institutional review boards, to draw up guidelines on recruiting practices (1), and also strengthen government oversight of institutional review boards.

Nathan and Weatherall recommend, "In any agreement between a clinical scientist and the company, the investigator should have the freedom to inform patients and the scientific community about deleterious effects of agent or procedure under investigation" (2). The hospital or university must immediately offer support to the investigator in case the company takes legal action or harasses him. Similarly, the company must have the opportunity to make its case when there is a disagreement with the scientist. However, they should do so under the conditions of open scientific debate, or at least with a panel of independent experts. The scientific associations and journals must carefully investigate the origin of research papers and to assure that the programme committees, chairman and speakers do not have conflict of interest.

Freestone and Mitchell have proposed guidelines for investigators' investment. They advise that clinical investigators (and their immediate relatives) should not buy or sell shares in pharmaceutical companies whose share price might be affected by their work until this is completed and results have been made public. They should not disclose unpublished price sensitive results of studies in confidence to third parties. Clinical investigators should make a voluntary declaration to ethics committees and to sponsors of any shareholding for which there might be a conflict of interest and undertake not to trade in the relevant company's securities until the studies are completed and the results made public.

Lower research costs and the availability of drug-naive patients encourages the trend to do more trials in developing countries like India. There is an urgent need for the Indian research community, ethics committees, investigators, regulators and national research organisations to discuss the above issues and develop Indian guidelines.

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