Current Controlled Trials in Cardiovascular Medicine

BioMed Central

Commentary

Balancing commercial and public interests

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Published: 07 July 2004

Current Controlled Trials in Cardiovascular Medicine 2004, **5**:6 doi:10.1186/1468-6708-5-6

Received: 05 May 2004
Accepted: 07 July 2004

This article is available from: http://cvm.controlled-trials.com/content/5/1/6

Abstract

A large number of randomized clinical trials with important health outcomes are completed each year. Those with favorable findings are typically reported and published rapidly, while the publication of those with unfavorable results is often delayed or given a positive "spin." This observation applies primarily to industry-sponsored trials. Our objectives are to discuss the responsibility of pharmaceutical firms to the public with respect to timely, complete, and unbiased information from all randomized clinical trials and to propose solutions for improvements. We believe that in addition to financial obligations to their shareholders, pharmaceutical companies have social responsibilities to the public and to health care providers. However, private markets do not reward or compel optimal disclosure of drug safety or inferiority information on a voluntary basis.

A problem which has not previously been identified relates to non-comparability of drugs. A case report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) illustrates how public interests may be violated due to failure to inform about drug inferiority. The current system for dissemination of relevant medical information could be improved if all involved parties collaborated fully. However, full disclosure of trial results is unlikely when research results are unfavorable to the firm. We conclude that expanded government regulations will be required for a satisfactory solution to the problem.

Introduction

A large number of randomized clinical trials of patient care and public health importance are completed each year. It is essential that their findings, favorable or unfavorable, be published and disseminated in a timely, complete and unbiased manner. Not surprisingly, trials with positive results tend to be reported more quickly, and the sponsor, if a pharmaceutical company, typically and appropriately has an active involvement in this process.

Regrettably, trials with unfavorable findings – neutral or suggestive of harm in placebo-controlled designs, or indifferent or inferior in active-control designs – tend to be treated differently. One strategy is to delay or withhold publication. Ioannidis [1] reported that for negative trials, the time from trial completion to publication was almost twice that for positive trials. Many negative trials are never published [2]. In rare instances, manufacturers have used legal means to try to block the publication of unfavorable trial results [3,4]. Another strategy is to try to use a publication as "an advertisement in the clothing of science" [5]. At times, manufacturers exert undue pressure on investigators to give trial results a more positive "spin" [6,7]. The observation from a large survey that as many as 96–99% of trials from China, Russia/USSR, and Taiwan reported positive findings also suggests the possibility of sponsor

interference [8]. Leading medical journals have responded to these concerns by announcing plans to reject articles "conducted under conditions that allow the sponsor sole control of the data or to withhold publication" [9]. A problem not previously identified relates to trials comparing two or more drugs. Is information about drug superiority and inferiority properly disseminated to physicians and patients?

The Food and Drug Administration (FDA) is charged by Congress to approve drugs for clinical use and to provide essential drug information through labeling to clinicians and patients. Its mandate to protect the public from unsafe drugs does not, however, extend to assessing comparative efficacy or to warning physicians or patients about inferior products. The problem of inadequate dissemination of unfavorable safety information exists, since FDA is reactive in its mission and has no systematic approach to detect omissions.

Given the weaknesses in the dissemination process, it is the pharmaceutical industry that has assumed the major role of directly informing individual health professionals and the public about drug trial results. Through large networks of pharmaceutical representatives, sponsorship of promotional meetings, continuing medical education programs and advertisements, the industry has the capacity to control this function not only when the results are favorable but when they are unfavorable as well. However, can we trust that the knowledge and resources they have are used to provide timely, complete and unbiased information when the results are unfavorable?

The social responsibility of the pharmaceutical industry

Ideally, a socially responsible drug company would be expected to take the following four steps in the dissemination of all relevant trial results to all relevant parties:

(1) Initiate timely and complete updates of the package inserts. According to current regulations, it is the manufacturer's responsibility to inform the FDA regarding relevant, new trial documentation, favorable or unfavorable, and to collaborate with the agency to revise inserts accordingly. Findings from drug trials that show clinical benefit or comparative superiority/inferiority could be added under the insert heading "Indications and Usage," while adverse reactions – depending on their severity – might be included under such headings as "Contraindications," "Warnings," "Precautions" or "Adverse Reactions." An important improvement would be to require that labeling changes be highlighted to show new information. Updated package inserts serve as source material for clinicians seeking specific drug information. By mandate, the FDA has no direct role in this dissemination process.

(2) Concurrently contact health care providers with direct written communications. The manufacturer ought to inform health care providers directly about major labeling changes that are relevant to patient care. These changes could include new drug indications, stronger supportive evidence of clinical benefit, but also evidence of safety concerns and comparative superiority/inferiority. However, the impact of such written communications and labeling changes alone have little or no impact on physician prescribing behavior and on recommended patient monitoring [10-13].

(3) Concurrently reinforce research messages verbally to individual clinicians. The most effective way to inform physicians about new and important drug information is through face-to-face encounters [14,15]. This type of detailing is already being used effectively to promote trial results to increase drug sales. Although equally important, unfavorable results are commonly either minimized or not presented by the representatives. Legal actions taken against manufacturers of drugs shown to cause harm have revealed that critical safety information sometimes is withheld from both clinicians and regulatory agencies [16-18].

(4) Concurrently employ mass media approaches to reach patients. The industry has refined ways of reaching patients through direct to consumer advertising of drugs. This is an important way of increasing sales and informing the public. Public health authorities mount various media campaigns to change unhealthy behaviors. Similar techniques should be used to inform the public about drug safety and inferiority concerns since it has the right to know. This could be paid for through sources similar to those that support public health campaigns, or funds could come through an ear-marked assessment targeted to the pharmaceutical industry or the sale of its products.

Acceptance and implementation of these responsibilities would markedly reduce our societal problem of drug safety and inferiority. Can we presume that all companies are good citizens?

Case report: ALLHAT

In 1994, the National Heart, Lung, and Blood Institute (NHLBI) launched the Antihypertensive and Lipid Lowering to prevent Heart Attack Trial (ALLHAT), designed to guide clinicians in making educated selections of antihypertensive agents by providing outcome data related to risk-benefit balance and cost-effectiveness. Specifically, ALLHAT was designed to determine whether the newer and more costly agents – ACE inhibitors, calcium channel blockers, and alpha-blockers – were more effective than inexpensive low-dose generic diuretics (chlorthalidone) in reducing the risk of major coronary events and other

cardiovascular outcomes [19]. Chlorthalidone was shown to reduce the risks of cardiovascular events by 25% and to cut the risk of heart failure in half compared to the alpha-blocker, doxazosin. The ALLHAT results were so convincing that the doxazosin treatment arm was terminated early and all patients assigned to this drug were advised to switch to other medications [20]. The findings were published in the *Journal of the American Medical Association* in April, 2000 following an expedited review [21].

The ALLHAT findings have important health and cost implications. If the excess absolute risk of fatal, hospitalized, and non-hospitalized heart failure of using doxazosin (Cardura) is 1%/yr (as shown in ALLHAT) and there are 500,000 Cardura users in the United States, there will be 5,000 unnecessary initial heart failure cases every year. This number would almost double if the ALLHAT findings also apply to other alpha-blockers and to patients prescribed Cardura for indications other than hypertension. There were also higher risks of stroke, angina and coronary revascularizations. According to a recent Medical Letter [22], Cardura, for example, was priced at $30.90 per month compared to generic chlorthalidone at $5.40 per month. The adverse events themselves require additional health care expenditures, making the total societal cost of Cardura even higher.

How did Pfizer respond?

(1) Pfizer never submitted the ALLHAT data or the *JAMA* article [21] to the FDA, in order to initiate a labeling change. The FDA only got involved through a Citizen Petition [23] that was filed after a failed lawsuit against Pfizer by two patients. An FDA Hearing [24] was held more than 14 months after the ALLHAT results were made public through an NHLBI press release [20]. A revised package insert for Cardura ought to state clearly that in elderly patients with hypertension, the drug is inferior to low-dose diuretics (chlorthalidone) in the prevention of congestive heart failure, stroke, angina, and coronary revascularizations.

(2) Pfizer never issued a "Dear Doctor" letter to inform health care professionals about the important findings from ALLHAT, in spite of the fact that it agreed with the NHLBI decision to stop the doxazosin arm in ALLHAT. If human subject protection obligations required the ALLHAT investigators to inform participants and switch them from doxazosin to another agent, it follows that the company also had obligations to inform the public of the trial findings. If the size of a trial or the passage of time makes contacting individual patients impractical, informing the relevant community of physicians is the next best alternative, since they have a professional obligation to pass this information on to patients for whom it is medically relevant.

(3) The company did not take advantage of its large cadre of pharmaceutical representatives to inform relevant groups of clinicians directly and in a timely manner about Cardura's inferiority compared to low-dose diuretics (chlorthalidone). In contrast, according to internal Pfizer documents included in the Citizen Petition to the FDA [23], the company developed a "Cardura ALLHAT Preparation Plan." As reported in the petition, though Pfizer was fully aware of the ALLHAT results, its plan emphasized that "Cardura is one of the Magnificant 7 products that counts for significant revenue and profit." It aggressively continued to assure all "high-prescribers of Cardura" that Cardura was an "exceptionally safe drug." Further, according to the petition and internal company documents, the ALLHAT results were seen by Pfizer as a potential threat to its business, regardless of whether the trial findings were in the hands of its "competitors," "governments . . . requesting label or price changes," or the "press." Proactive steps were, therefore, needed. According to testimony by a senior Pfizer executive quoted in the petition, "the sales representatives to the best of my knowledge are not proactively discussing ALLHAT" [23]. It appears that the trial results were treated as a marketing problem rather than a public health issue.

(4) Pfizer did not inform the public through newspaper ads or on TV about the inferiority of Cardura compared to low-dose diuretics (chlorthalidone) for treatment of hypertension. According to testimony by a senior Pfizer executive, the company made a conscious decision "not to issue a [public] statement on the ALLHAT results, because doing so "would draw more attention to the situation." [23]. Related to these failures, Pfizer was sued by two patients as representatives of a class action lawsuit, requesting in part that the company inform health care professionals and the public about the inferiority of Cardura in the prevention of cardiovascular complications of hypertension.

Market failure in information dissemination

It is no surprise to market theorists that the pharmaceutical industry has not lived up to social ideals in releasing product information. The literature on the obligations of corporations to society is large. The most widely quoted author on the subject, Milton Friedman [25,26], claims that corporate social responsibility is none other than that of increasing profits, while operating under the rules of a free market economy. These rules include free competition with other firms, in a manner in which there is no fraud or deceit. Although more recent writings in the field of business ethics acknowledge that corporations, like individuals, have moral status and consequent ethical obligations that go well beyond the rules of the market [27-31], ethical arguments do not have strong persuasive force with corporate leaders in the absence of some incen-

tive or enforcement mechanism that encourages compliance. Therefore, as a matter of first principle, information restrictions need to be examined as an aspect of market failure, in order to craft effective solutions.

Economists explain that even a perfectly competitive market often does not generate important consumer information due to what economists refer to as a "public goods" or "collective action" problem [32,33]. When many of the costs or benefits of safety information extend far beyond the parties to an immediate transaction, the information will tend to be generated at suboptimal levels, since the incentives affecting individual manufacturers and consumers are poorly matched to broader social welfare. The costs of obtaining and disseminating drug safety and effectiveness information are certainly not trivial, but they could be recouped from sales revenues, just as are research and development costs. More significant, however, are manufacturers' willingness to bear the reputational costs of supplying this information when it is not favorable. The absence of any market mechanism for compensating manufacturers for this cost, or for inducing them to absorb it, is a collective action problem. Thus, even if the industry as a whole agreed that there is a collective need for more extensive drug safety information, no single manufacturer is likely to view it as an advantage to its competitive stance to be the first to disseminate bad news about its products. If other manufacturers are not disclosing such information, and patients and physicians do not expect it or demand it, then competition or reputational rivalry does not compel manufacturers to do so.

Possible solutions

In our society, the public expects to be informed about inferior products, whether they be drugs, tires, or automobiles. The ideal solution discussed above places a significant degree of trust in the pharmaceutical industry to protect public interests by providing not only favorable but also unfavorable information about its products. A voluntary effort to improve the dissemination of unfavorable trials results would be desirable. All parties would need to work together to establish and maintain trust and to develop a system that protects the public's interest. Pharmaceutical companies could benefit from an improved public image and reputation and greater confidence in the veracity of publications emanating from industry-sponsored studies. Patients could benefit by getting better care, and society would consequently benefit from reduced utilization of health care services.

However, there is considerable debate in the business literature regarding the wisdom of a voluntary approach. The "accountability theory" speaks to situations in which there is an asymmetry of power and information between the firm (the pharmaceutical company) and the stakeholders (in our case the public, health care professionals, and the health care system) (Swift 2001). Rather than assuming any degree of trust between the firm and its stakeholders, the accountability theory assumes that firms cannot be trusted to act in the best interests of society when there is a conflict between the two (e.g., when provision of information to stakeholders results in adverse economic consequences to the firm.) Under this theory, formal agreements and structural controls are substitutes for trust, and shortfallings are addressed by regulation or legislation to prevent them from occurring again [34].

Another solution would be an act of Congress to compel pharmaceutical companies to report all material results from clinical trials. An independent office would be needed to systematically review the findings, to determine which are clinically relevant and to assure timely and effective communication of these. Other functions would include monitoring industry's compliance with the regulations and enforcing penalties for violations so that the rights and interests of the public are protected. In the current political climate, it is not likely that this degree of industry oversight would be enacted, but that should not deter leaders in the medical, public health, and public policy fields from developing such a proposal and fleshing out the details necessary to make this possibility more concrete and visible.

A more market-oriented solution, similar to that used for the quality of health plans, could be used. Each pharmaceutical firm could be rated by a government agency according to how well it informs physicians and the public about drug safety problems with its products. A visible and meaningful rating system might effectively compel the industry to improve its performance, without the government having to mandate or conduct the particular aspects of performance. Or, more aggressively, the government could give such a rating system more teeth by using its purchasing power under Medicare, the Veteran's Health Administration, and other government insurance and health care programs to refuse to purchase or pay for non-essential drugs from companies that perform poorly under such a rating system. How these various alternatives would actually function, and how well they would likely address the problems, requires additional detailed analysis.

Conclusions

The current system for timely, complete and unbiased dissemination of unfavorable trial results fails, to a large extent, to protect public interests. Pharmaceutical companies do not serve social welfare as well as they could. Various strategies may be used to withhold critical drug information from health care providers and patients. For research findings that are likely to reduce drug sales,

efforts may be made to delay their publication [1], to suppress their release [2-4] or to give trial results a more positive "spin" [6,7].

An ideal solution to the problem would be a voluntary joint effort by all parties to improve the dissemination process. This would require major trust in the pharmaceutical industry, which currently controls what, when and how unfavorable research findings are communicated to health care providers and the public. A disincentive to industry would be reduced sales of inferior, less safe and inadequately tested drugs. Therefore, a more realistic approach is legislative or regulatory action to compel timely, complete and unbiased reporting of vital clinical trial results, or at least to call the public's and medical profession's attention to each pharmaceutical firm that fails to do so voluntarily.

Competing Interests

None declared.

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