

Corporate influence over planning and presentation of clinical trials: beauty and the beast

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Flávio Danni Fuchs

*Serviço de Cardiologia,
Hospital de Clínicas de
Porto Alegre, Ramiro
Barcelos 2350,
90035-903, Porto Alegre,
RS, Brazil
Tel.: +55 513 359 8420
Fax: +55 513 359 8420
ffuchs@hcpa.ufrgs.br*

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Currently, cardiovascular therapy is almost exclusively driven by the results of randomized clinical trials, and most of them have been funded by pharmaceutical companies. Commercial interests have sometimes subtly prevailed over science, leading to guidelines and choices that are not based on the best clinical evidence. An academia that is more independent from the pharmaceutical industry is warranted in order to set research agenda.

A notion prevails that the common grounds underlying the relationship between doctors, drug corporations and patients results in more-effective therapies to mitigate human suffering and, hence, there is an almost unlimited willingness to pay for new therapies. Profits of the pharmaceutical industry are, therefore, among the largest in business worldwide. The promotion of drug sales by pharmaceutical companies has been based on many strategies, such as direct advertising to physicians and patients, and financial support to many areas of medical education. Occasionally, misconduct has been seen in this scenario, and this is probably as common as it is in other legal business. The evaluation of the utility of drugs hardly can be carried out by consumers/patients. Physicians are in-between decision-makers but are also limited in identifying the utility of therapies. The intrinsic effect of drugs is hardly isolated given the many factors that influence the effect of therapies.

The first efficacious drugs had their efficacy identified in either a series of patients or in only one patient, for example, the

Scotland Yard officer with infective endocarditis who was treated with G penicillin. The necessity to identify the efficacy of treatments in controlled studies, particularly with the random allocation of patients (i.e., randomized, controlled trials [RCTs]), became evident in the following years. The spectacular efficacy of streptomycin in the management of tuberculosis was first demonstrated in a RCT [1]. This trial was honored, together with 11 other trials, in a tribute to the 50th anniversary of its publication [2]. These studies are major examples of the influence of RCTs over the way that we practice medicine.

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Penicillin and the first antimicrobial drugs were left free of patent for humanitarian reasons, and were produced and sold by many companies worldwide. Newer medicines, however, were put under patent protection, with variable regulations among countries, which led to the current and almost universal rules of commercial protection.

Six out of 12 classic trials were conducted with cardiovascular drugs [2]. The trial that identified the efficacy of benzathine penicillin to prevent rheumatic fever recurrence [3], and the International Study of Infarct Survival (ISIS)-2 trial [4], which identified a 40% reduction in mortality in patients with acute myocardial infarction

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treated with aspirin and streptoquinase, were funded by pharmaceutical companies. As such, these studies can be recognized as major examples of 'the beauty' in the association between pharmaceutical corporations and academic institutions to promote the advancement of knowledge.

The history of RCTs in hypertension started with another classic study, the Veterans Hypertension Trial [5]. This study demonstrated that treating only three patients with severe hypertension for 2 years prevented a major adverse outcome in patients with severe hypertension. Thereafter, a series of studies controlled by placebo or no treatment showed the efficacy of diuretics and β -blockers to prevent cardiovascular events in patients with a wide range of blood pressure and at various ages. The high prevalence of hypertension worldwide, as well as the evidence that its treatment is highly advisable, motivated pharmaceutical companies to explore this new huge market. National drug agencies made requests for comparative, drug-controlled trials to demonstrate the presumed advantage of new agents. Drug companies were also interested to performing such trials, which were part of their commercial strategies. In an *Expert Review of Cardiovascular Therapy* article published a few years ago [6] and updated recently [7], I concluded that these trials did not demonstrate the superiority of new agents over diuretics. Law *et al.*, reviewing almost all trials that had compared blood pressure agents among themselves and with placebo, concluded that they all have a similar efficacy for a given reduction in blood pressure, so excluding material pleiotropic effects [8].

This substantial evidence is not corroborated by the preference of physicians in the prescription of blood pressure-lowering agents. The worldwide leading brands are angiotensin receptor blockers (ARBs), despite the fact they are considered to be mere substitutes of angiotensin converting-enzyme (ACE) inhibitors. Commercial strategies have been based on the results of RCTs sponsored by drug companies. Most of these presented distortions in their planning, presentation or interpretation that favored the drugs from the sponsor, the corporate bias [9]. This influence is a major example of 'the beast' in the association of pharmaceutical corporations and clinical investigators to conduct RCTs. In letters and commentaries, I and others have identified many examples of this corporate bias. For example, several trials employed atenolol as comparator drugs in elderly patients, ignoring the results of the multicenter RCT with elderly participants, which showed that atenolol was inert as a first option in this age group [10]. The Losartan Intervention for Endpoint (LIFE) trial was among them, and it has been the basis of a massive strategy for the commercial promotion of losartan [11]. There are more than 130 publications with 'LIFE trial' or 'LIFE study' in the title, a volume never seen before for one study. In a report of the Intervention as a Goal in Hypertension Treatment (INSIGHT) trial, restricted to patients with diabetes, the INSIGHT investigators used ill-defined outcomes, leading one to presume that they had counted the deaths twice [12].

Most international guidelines for hypertension management have absorbed the corporate bias of the original studies because they have been written by the same authors as the original studies.

For instance, the 2007 European Society of Hypertension guideline recommended diuretics for Black and elderly patients, and ARBs or ACE inhibitors for a long series of clinical conditions [13]. These recommendations were based on the results of the biased studies or even in the absolute absence of evidence, such as in atrial fibrillation, and against the evidence, such as in metabolic syndrome [14].

In trials published recently, the corporate influence has gone too far, as they are still comparing blood pressure agents with placebo in patients at higher risk of presenting cardiovascular events. This beast-like action of the association between pharmaceutical corporations and investigators is threatening the ethics of science. The Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation (ADVANCE) trial is a major example of such unethical studies [15]. It compared a fixed association of perindopril and indapamide with their placebos in patients with Type 2 diabetes and cardiovascular disease or major cardiovascular risk factors. Participants of the placebo group were not allowed to be treated with diuretics or full doses of ACE inhibitors, despite the fact that these agents were already ruled as the first option to treat patients with diabetes and hypertension by guidelines that were in effect at the time of the trial planning. As a result of this major deviation of good research practices, participants allocated to the placebo group had a mortality rate 14% higher than those treated effectively, as a result of the higher blood pressure during the trial after having their effective treatments withdrawn [16].

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The ADVANCE trial was sponsored by the same corporation and carried out by almost by the same investigators as two other trials that can be regarded as prime examples of 'the beauty' in corporate-sponsored RCTs. The Preventing Strokes by Lowering Blood Pressure in Patients With Cerebral Ischemia (PROGRESS) trial showed the impressive benefit of using blood pressure-lowering agents in patients who had suffered a stroke, irrespective of their blood pressure [17]. The Hypertension in the Very Elderly (HTVET) trial settled the controversy about treating very elderly patients with hypertension, showing that a diuretic, whether accompanied or not by an ACE inhibitor, was able to reduce their mortality [18]. These trials were absolutely ethical when they were planned.

Other pharmaceutical companies have funded irreprehensible RCTs. For instance, the benefit of ARB agents in the prevention of recurrence of atrial fibrillation, which was already an indication of guidelines [13], was almost exclusively based on *post hoc* analyses of the LIFE trial [11]. The makers of valsartan contracted the investigators of the Italian Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI [Italian Group For The Study Of The Survival Of Myocardial Infarction]) group to investigate its efficacy, and the trial demonstrated that valsartan

is absolutely inert in the prevention of recurrence of atrial fibrillation [19]. Another recommendation from the guidelines – to prefer ARBs or ACE inhibitors to treat patients with diabetes in order to prevent the development of renal damage – was challenged by a recent NIH- and corporate-funded RCT [20]. Patients treated with losartan had a higher incidence of microalbuminuria than patients treated with placebo or enalapril.

What direction are we going in now? Pessimists believe that doctors will be always surfing on the wave of the interests of large pharmaceutical companies. Pragmatic individuals believe that the world will move on and that the truth will always emerge. As an affiliate of this interpretation, I believe that a clear separation of the objectives of researchers from those of the pharmaceutical companies, is a welcome initiative. The collaboration between

scientists from universities and from the pharmaceutical industry is welcome for the joint development of science and technology but a higher independence of academia from the pharmaceutical industry to set the research agenda in the planning and presentation of randomized clinical trials is warranted.

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