EuroIntervention

Physicians, the medical device industry and the data; a healthy relationship?

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Percutaneous coronary intervention with drug eluting stents is a 'disruptive' technology. The business is now worth more than 6 billion Euros per annum, and it is estimated that 2.5 million PCI procedures will be undertaken worldwide in 2006, 75% with drug eluting stents. This explosive growth has been associated with an erosion of conventional surgical revascularisation, such that PCI:CABG rates have exceeded 4:1 in some countries. Other technologies have come and gone, for example intra-vascular brachytherapy and direct myocardial revascularisation (DMR); others continue to have a niche role, including atherectomy, thrombus extraction and protection devices, but it is drug eluting stents that predominate. The evidence base for stent use is impressive with numerous randomized controlled trials, registries and case series; much of the evidence is of high quality (Grade IA), and there are now more than 1000 published drug eluting stent papers available on Medline.

There is therefore an increasing pressure to present and publish data in this rapidly developing field. Not only does coronary intervention have widespread appeal, combining manual dexterity, patient satisfaction and apparently limitless investment from the medical device industry, but there is also a perception of interventional cardiologists having a 'high rolling' lifestyle, often the envy of medical colleagues in other specialties. Industry enthusiastically supports the KOL (Key Opinion Leader) concept with the expectation that these high profile individuals are useful to have on board, and his/her efforts are likely to spread the word and increase revenues. Furthermore, interventional cardiologists are talented individuals who often invent new devices and seek reward through intellectual property rights for the sale of their product to the medical device industry; they themselves may present data which, if favourable, will have direct financial benefit.

So far, so good, but Big Brother is watching. Never before have physicians and industry been under such close scrutiny, and it is clear that clinical and research governance is closing in, such that many research workers are increasingly frustrated at the endless wall of bureaucracy that appears purpose-made to frustrate their efforts in initiating clinical trials. This is perhaps not surprising in view of recent events; conflicts of interest, data suppression and manipulation, fabrication of results and plagiarism feature in the medical and lay press on a regular basis. In recent months there have been allegations of scientific fraud in the stem cell arena[1], suppression of data by a multinational pharmaceutical giant with implications for the Food and Drug Administration (FDA)[2,3], and pay-

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ments of 'fees' amounting to hundreds of thousands of dollars by a medical device company to surgeons in the field of spinal surgery[4]. It is 10 years since the German heart valve scandal broke new ground when 2,700 doctors from 450 hospitals were investigated for accepting bribes from the manufactures of heart valves, life support equipment, pacemakers, and artificial hip joints[5]; it was estimated that the bribes of DM100,000 cost the health insurance industry DM210 million. At the time, this was felt to be very unusual, but the present era of political correctness coupled with a media feeding frenzy makes for a daily diet of medical and scientific 'conflicts' in the press. Clearly there is a wide spectrum of deceit, much of which would be abhorrent to the average clinician or scientist.

It is clear that the noose is tightening around the relationship between the health industry and physicians. A recent paper published in JAMA[6] concluded that stringent regulation was necessary in relation to small gifts, pharmaceutical samples, continuing medical education, funds for physician travel, speakers' bureaus, ghost writing, and consulting and medical research contracts. The lead authors of this paper are employed at the Institute on Medicine as a Profession, Harvard Medical School, which was set up by the financier George Soros who gave the centre a grant of $7.5 million to study medical professionalism[7]. The pharmaceutical industry is ahead of the game; the UK Code of Practice for the Pharmaceutical Industry (2006)[8] states, "No gift, benefit in kind, or pecuniary advantage shall be offered or given to members of the health professions or to administrative staff as an inducement to prescribe, supply, administer, recommend, buy or sell, any medicine. Promotional aids must be inexpensive..." (N.B. inexpensive is defined as a cost of £6 or 8.75€ or less). There is a perception that what the pharmaceutical industry does one day, the medical device industry does the next. But where does this leave physician education? Most health economies cannot support physician registration or travel to meetings (even travelling in the economy section of the plane), and major meetings would not exist without huge sponsorship from industry. In the wider sense, 36,000 delegates travelling to Chicago for the American Heart Association Scientific Sessions has a major impact on the economy of Chicago; local hotels, restaurants, bars, shops, taxis, airlines and car hire firms benefit, to name but a few. Is this not the oil that makes the wheels go round? Would it be more appropriate for would be delegates to learn on-line, viewing presentations in the comfort of their own home, sustained by a sandwich and a glass of chardonnay? This rather purist approach would put an end to 'networking', an important part of any meeting, when colleagues share experiences (including catastrophes), data, ideas, future developments, job opportunities etc – most of which will directly benefit patient care.

There have been efforts to distance education from industry[9], and some major meetings, for example EuroPCR emphasise the importance of education under the auspices of the European Board for Accreditation in Cardiology (EBAC)[10], which provides bona fide Continuing Medical Education (CME). The often-difficult relationship between industry and education has been the subject of a number of communications[11-17].

What of clinical research? In a health economy driven by access targets and value for money, research may become a low priority. Furthermore, trainees may not view an academic career path as rewarding[18]. Even having chosen to undertake research in their given field, the labyrinthine pathway for approval of a new project through local, regional and national ethics committees has narrowed the perceived gap between a medical device company undertaking research in Europe as opposed to the US. Formerly, industry could rely on rapid access to researchers, and if necessary, patients, in Europe with a lead-time of at least two years. There have been attempts to streamline the regulatory and approval pathway at both the national[19] and European[20] level, and the development of a research governance framework will ensure that research complies with all professional, ethical, moral, legal and scientific standards, whatever the source of funding[21]. The aim should be to make the system as efficient as possible to assist researchers, whilst protecting the safety, dignity and rights of the research participants. Nevertheless, it is clear that the plurality of guidance, rules and laws within the European Union has driven companies further afield and denied the citizens of Europe innovative technology.

The results of well-constructed trials in the field of percutaneous coronary intervention have a major impact on patient care, and if a particular device is successful, sales will flourish which will increase revenues to the supplier of the product. It is therefore incumbent on the researcher, particularly the principal investigator(s) and the members of the steering committee, to maintain independence from the industry sponsor at all levels of the trial development from inception, through trial design, final protocol agreement, patient recruitment, data capture, statistical analysis, data presentation and publication. Even the choice of end-point (clinical, angiographic, intra-vascular ultrasound; single or composite) may introduce bias, and may be construed as reducing clinical relevance.

Members of the Clinical Events Committee (CEC), the Data Safety and Monitoring Board (DSMB), core laboratories, trial monitors, data management and statisticians should be independent from both the sponsor and the researchers (Figure 1). In such a small field, where

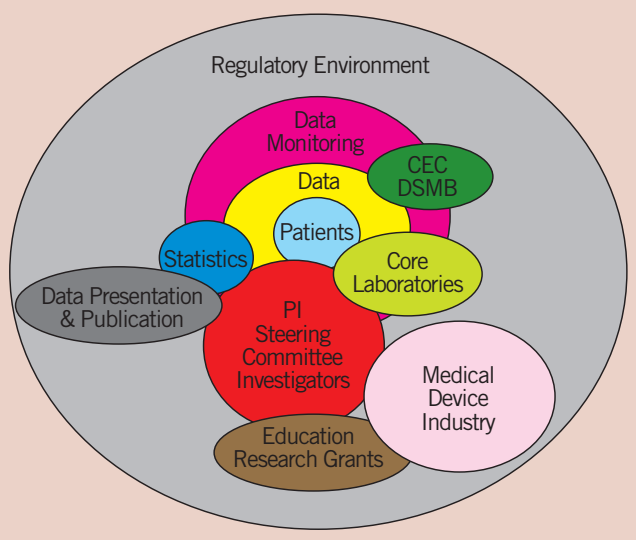

Figure 1. Suggested relationships between the key stakeholders in a typical clinical trial.

members of the various committees may themselves be conflicted, true independence may be difficult to achieve. A third party should undertake data collection and independent statistical analysis, which avoids data suppression, 'cherry picking' and publication bias. Database ownership is a current area of interest, with some advocating that databases should be in the public domain, which would allow independent analysis and comparison by other research groups. Researchers are often dependent on aid from professional statisticians to help determine both the appropriate statistical test and the significance of the results; these individuals are often funded by, or may be on the staff of the sponsor. The misuse of statistics is unethical[22], and it is frightening how statistics can distort the conclusions; according to Sackett[23], statistics may introduce bias at no less than 56 points along the path from planning to publication of a trial. The recent trend to analyse data using the non-inferiority principal has also been subject to criticism[24,25].

The presentation of the data in both scientific meetings and in press has become something of an art form. The subtleties of PowerPoint may be anathema to some researchers, but the medical device industry has whole departments devoted to media presentation, highlighting key and possibly commercial points that may influence the audience with subliminal messaging. Many companies use ghost writers for manuscript submission; the cynic would suggest that this may introduce bias ('spin'), when in reality it may merely reflect a lack of literacy on the part of the medical profession, or the tardiness of the researcher to put pen to paper. The time has come for researchers to prepare, present and write up their own data. The role of the principal investigator(s) and the steering committee should be strengthened, particularly in the areas of trial design, data analysis and data interpretation. Members of the steering committee should have unhindered access to the original data and statistical interpretation should be undertaken by an independent organisation, for example a university department, remote from the trial sponsor. Although this approach may be viewed with anxiety by the medical device industry, it is the only way for us all to maintain academic credibility in the eyes of the patients, the press, and the regulatory authorities.

Despite the rapid expansion of the drug eluting stent arena, there have been few catastrophes in the field and it is gratifying that poor results with particular devices have been published, a credit both to the investigators and the sources of funding[26,27].

Potential conflicts of interest are legion, and if physicians and the medical device industry are to maintain their scientific integrity, transparency and objectivity remains the key, although distancing oneself from the sponsor may result in financial impecunity[28] and certainly a right turn through the door of the plane may soon become the norm.

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