

## COMMENTARY

# Keeping faith with trial volunteers

How best to serve patients' interests in large clinical trials? Martine Piccart, Aron Goldhirsch and their colleagues argue that maintaining academic independence is essential to early breast cancer trials.

How do patients who sign up for clinical trials know that the right questions are being asked and that the data support the reported answers to these questions? For many patient groups, transparency in study design, data collection and analysis, and full publication of results are issues of paramount importance. Concerns have been raised in recent years about the misreporting of trial results and we note a push by pharmaceutical companies for greater control of clinical trials and data, outside the framework of academia. In our view, a more equal partnership between academic researchers and the pharmaceutical industry is better for patients, especially those in early stages of disease for whom over-treatment and adverse side effects are important considerations.

The substantial progress in treatment of early breast cancer, reflected in falling mortality rates in many countries, is the direct result of more than half a century of sustained commitment to randomized clinical trials<sup>1</sup>. The implicit ethical contract between the investigators and the many patients who participate in trials has made this progress possible. The prime objective of clinical trials is to improve the outcomes for patients with the disease, and no consideration of commercial or academic advantage should cloud the collection or interpretation of data from such trials.

## Conflicts of interest

Modern clinical trials often seek subtle but important improvements in outcomes, for example with adjuvant therapies the intended outcome is to keep cancer from recurring. Trials are also necessary to define the frequency and severity of any adverse reactions to treatment, which affect the patient's quality of life and influence future treatment decisions. Moreover, trials increasingly tailor treatment questions to specific subpopulations as investigators learn more about tumour biology or patient drug tolerance. For example, one trial may be designed to test adjuvant chemotherapy in patients older than 70, and another the adequacy of endocrine treatment in a specific biologically defined target group<sup>2,3</sup>. Assessing the effectiveness of such therapies requires trials, usually multicentered and multinational, with very large numbers of participants (several thousands or more).

**"Trials designed and controlled purely by drug companies may fail the best interests of patients."**



Who should collect, control and analyse clinical-trial data: academic investigators or drug companies?

Trials of adjuvant therapies in early breast cancer involve treating patients whose disease has not relapsed following local treatment with surgery, or in some cases radiotherapy, and therefore individuals have no evident disease that can be assessed. Instead, group comparisons after an adequate period of follow-up — usually in the range of 2 to 5 years — are needed to assess average outcomes, and to explore patient or tumour differences that may influence treatment benefit<sup>4</sup>.

Typical agents used in adjuvant treatments include hormonal therapies such as tamoxifen, or chemotherapy alongside newer targeted agents such as trastuzumab. Without the clinical trial process it is impossible to determine the benefits of experimental treatments for individual patients. Trial analyses will ultimately feed into individual patients' informed decisions on future treatments.

Such large modern trials need financial resources that currently exceed those available to academic researchers from governments and philanthropy alone. Partnership with pharmaceutical industry, often for the supply of the drug, is usually essential. But how should such partnerships work? Contrary to the interests of academics, and we believe to

those of patients, pharmaceutical companies are increasingly attempting to recruit academic investigators to conduct adjuvant trials in which the data will be controlled by the company outside the framework of a research cooperative group or a network of academic centres<sup>5</sup>.

It is important to understand the conflicts of interest inherent in the clinical trials process. At times the interests of the pharmaceutical industry and those of academic investigators overlap, and at other times they diverge, although both are legitimate. For example, the pharmaceutical partner might wish to establish or extend regulatory approval for a commercial version of the tested product; whereas the academic researchers might be interested in the publication of the trial results, which help to advance their careers.

In some cases, academics will wish to explore trial results in detail to derive hypotheses that may eventually lead to even more precisely tailored treatments for future patients. Such efforts often require translational research investment and prolonged follow up, beyond that needed for commercial drug registration. So, views on funding levels and trial length may differ between the partners<sup>6</sup>. However, all parties are interested in the success of the experiment.



**A partnership with the pharmaceutical industry is essential for the supply of drugs to be tested in clinical trials.**

No one should forget that commercial success of trials is necessary to ongoing pharmaceutical research investment. But we believe trials designed and controlled purely by pharmaceutical companies, particularly relating to new and highly expensive pharmaceutical agents, may fail the best interests of patients in several ways. We call upon academic investigators recruited for such trials to consider the following issues carefully before they agree to participate.

### Data control

First, if a trial is focused on answering a purely commercial question, vital opportunities to answer other important questions related to the care of patients and to biological understanding may be lost. Second, trial design can be distorted by commercial interest, for example, requiring an arbitrary duration of treatment, rather than focusing on the optimal treatment duration for patient benefit. We note an increasing tendency, especially in pharmaceutically controlled trials, to withdraw funding or cease follow-up studies after commercial endpoints have been satisfied.

Regrettably, cases have been recorded in which data held by the pharmaceutical industry have allegedly been withheld for commercial reasons<sup>7</sup>. Data control entirely within a commercial organization may enhance the temptation to delay or suppress unwelcome findings. For example, large trials designed to define a subset of the patient population that benefit most from a treatment can run counter to the interests of a drug company wishing to maximize the number of potential patients for a new treatment. In such cases, control of data by the drug company would not be in the best interests of patients. When such activities

become public they affect the credibility of all clinical trials as well as that of the commercial organizations involved<sup>8</sup>. In the long run, concerns about the control and reporting of data may deter eligible patients from participating in future trials.

Indeed, by seeking to control clinical trial data, the pharmaceutical industry is ignoring moves towards greater data transparency, as increasingly demanded by institutional review boards (IRBs) and informed consumers. We support calls by the World Medical Association<sup>9</sup> and others to expand disclosure of funding sources and financial conflicts of interest to potential trial participants. We also welcome the possibility that in the near future consumers and IRBs may insist on full disclosure of who collects, controls and analyses trial data. It is essential that the data to explore and report all possible findings from clinical trials are transparent and available to the academic investigators and thus ultimately to consumers.

### Win-win situation

We believe that undesirable outcomes can be avoided by pursuing a better partnership between academia and industry. We note several recent examples of such successful partnerships in large-scale breast cancer adjuvant trials, including MA.17, HERA, BIG 1-98 and IES<sup>10-13</sup>. In these trials the clinical trial database was held by academic researchers who limited industry's access until the trial outcomes were reached. All relevant parties had access to safety data (adverse events and so on), but outcome data were analysed by an independent statistician, and while the trial was ongoing, shown only to an independent data monitoring committee (IDMC), which had the task of ensuring patient safety and the timely release of positive

or negative outcomes. The IDMC members for these trials were independent from industry, usually involving academic researchers knowledgeable about clinical trials, but not involved in the specific trials concerned, plus a consumer representative and at least one statistician.

In each case, once the primary endpoints of the trial have been reached, the database is transferred to the pharmaceutical company for commercial registration purposes. This model reduces commercial bias and conflicts of interest between the parties involved, while ensuring the protection of patients. In our view, it yields a win-win situation resulting in commercial registration of products, academic publications, and last but not least, hopefully better outcomes for patient treatments.

We firmly believe that such a model provides the best basis of fruitful current and future collaboration between academia and industry. Simultaneously, it maintains sacrosanct the overriding interests of the participating patients and those who will follow them. Only by ensuring untrammelled access to long-term information, both the good and the bad, can we conduct clinical trials in a credible manner. This access will ensure that those patients who consent to participate in them maintain faith in the clinical trial process. ■

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1. Early Breast Cancer Trialists' Collaborative Group *Lancet* **365**, 1687-717 (2005).
2. Giordano, S. H., Duan, Z., Kuo, Y. F., Hortobagyi, G. N. & Goodwin, J. S. *J. Clin. Oncol.* **18**, 2750-2756 (2006).
3. Regan, M. M. & Gelber, R. D. *Breast* **14**, 582-593 (2005).
4. NIH *Adjuvant Therapy for Breast Cancer* available at <http://consensus.nih.gov/2000/2000AdjuvantTherapyBreastCancer114html.htm> (2000).
5. Mello, M. M., Clarridge, B. R. & Studdert, D. M. *N. Engl. J. Med.* **352**, 2202-2210 (2005).
6. Gilpin, K. N. *New York Times* (2 June 2004).
7. Angell, M. *The New York Review of Books* **53**(10), (2006).
8. Drazen, J. M. *N. Engl. J. Med.* **347**, 1362-1363 (2002).
9. World Medical Association *Declaration of Helsinki* ([www.wma.net/e/policy/b3.htm](http://www.wma.net/e/policy/b3.htm)).
10. Goss, P. E. *et al. N. Engl. J. Med.* **349**, 1793-1802 (2003).
11. Piccart-Gebhart, M. J. *et al. N. Engl. J. Med.* **353**, 1659-1672 (2005).
12. Thürlimann, B. *et al. N. Engl. J. Med.* **353**, 2747-2757 (2005).
13. Coombes, R. C. *et al. N. Engl. J. Med.* **350**, 1081-1092 (2004).