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European Journal of Cancer 41 (2005) 2237–2240

European Journal of Cancer

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Disclosure of competing financial interests and role of sponsors in phase III cancer trials

Jean-Jacques Tuech [a,b,*], Grégoire Moutel [a], Patrick Pessaux [c], Véronique Thoma [d], Simon Schraub [a,d], Christian Herve [a]

[a] *Laboratoire d'Ethique Médicale et Médecine Légale, Faculté de Médecine de Paris 5, 45 rue des Saints-Pères, 75006 Paris, France*
[b] *Department of Digestive Surgery, CHU Rouen, 1 rue de Germont, 76031 Rouen Cedex, France*
[c] *Département de Statistiques Bio-médicales, CHU Angers, 4 rue Larrey, 49000 Angers, France*
[d] *CRLCC Paul Strauss, 3 rue de la Porte de l'Hôpital, BP 42, 67 065 Strasbourg Cedex, France*

Received 13 December 2004; accepted 13 December 2004
Available online 14 April 2005

Abstract

Financial relationships between industry, researchers and academic institutions are becoming increasingly complex, raising concern about sponsors' involvement in the conduct of biomedical research. A review of published randomised trials (RCTs) in cancer research was performed to assess adherence to the 1997 disclosure requirements and to document the nature of the disclosed interests. Source(s) of study support, author–sponsor relationships and the role of the study sponsor were assessed for all RCTs published between 1999 and 2003 in 12 international journals. A total of 655 cancer RCTs were identified. Of these, 516 (78.8%) disclosed the source of sponsorship. The nature of the relationship between the authors and the study sponsor was included in 219 of the 227 industry-sponsored studies. The most commonly cited relationships were (131 studies had multiple relations): grants (93.6%); employment (39.2%); consultant/honorarium (12.7%) and stock ownership and participation in a speaker's bureau (12, 5.5% each). Only 41 (18%) of the 227 industry-sponsored RCTs reported the role of the sponsor. Of these, 20 explicitly stated that the sponsor had no role in the study. Twenty-one papers described the sponsor's role, the degree of sponsor involvement was variable and usually described vaguely. Among these papers, four stated that researchers had full access to all data, one that the researchers had no limits on publication and one that 'the decision to submit the paper for publication was determined by the study sponsor'. In conclusion, no researcher should be expected to produce 'findings' without full access to the data, freedom from interference in analysis and interpretation and liberty to publish all results, however disappointing to the stakeholder they may be. In the meantime, researchers do well to arm themselves with the rules for research partnerships and editors to take on the role of watchdog.

1. Introduction

Conflict of interest has been defined as a set of conditions in which professional judgement concerning a primary interest (such as patient welfare or the validity of research) can be influenced by a secondary interest (such as financial gain) [1].

Financial relationships between industry, researchers and academic institutions are growing increasingly complex, raising concern about sponsors' considerable, and perhaps inappropriate, involvement in the conduct of biomedical research [2,3].

Editors have been concerned about this for a long time. In 1985, the International Committee of Medical Journals Editors produced a statement on conflicts of interest [4]. The 1997 Uniform Requirements for Manuscripts to Biomedical Journals [5] recommend that all published studies should include information on sources

* Corresponding author. Tel.: +33 2 32 88 81 42; fax: +33 2 32 88 84 16.
E-mail address: jean-jacques.tuech@chu-rouen.fr (J.-J. Tuech).

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doi:10.1016/j.ejca.2004.12.036

of funding, financial conflicts of interest of the authors, and specific descriptions of 'the type and degree of involvement of the supporting agency'. For industry support, authors are asked to describe the sponsor's role in the design, analysis and reporting of the study data [5]. If there has been no such involvement, the manuscript is expected explicitly to state this fact [5]. More than 500 journals subscribe to these requirements.

Previous work has shown that many published papers do not contain statements of financial competing interest [6]. However, little is known about authors' adherence. It is not known whether these findings apply to cancer randomised controlled trials (RCTs).

2. Methods

All phase III cancer RCTs trials published in the following journals: New England Journal of Medicine, Lancet, British Medical Journal, Journal of the American Medical Association, British Journal of Cancer, Journal of Clinical Oncology, Lung Cancer, Annals of Oncology, European Journal of Cancer, Clinical Cancer Research, Cancer and Journal of National Cancer Institute from January 1999 to December 2003 were identified. To identify eligible articles, all issues of these journals were hand-searched.

Every publication of phase III cancer trials was included. The exclusion criteria were: (i) trials published as letters to the editor, abstracts or short articles, (ii) randomised phase II cancer trials, (iii) non-experimental (observational) studies, (iv) non-cancer trials, and (v) trials which referred to a previous publication as the source of detailed description of the trial methods. An abstractor used explicit abstraction to record source(s) of study support, author–sponsor relationships and the role of the study sponsor. Disclosed author–sponsor relationships were coded as follows: advisory board, consultant/honoraria, educational activities/speakers bureau, employment, grants, patent/licences, and stock. Study authors who had an industry address were categorised as employees.

2.1. {bh} Ethical aspects

Our study was not approved by a research ethics committee, nor did we request informed consent from the authors of the articles, because our research did not involved an experimental design using people. No financial support was received for this study.

3. Results

We identified 655 cancer RCTs: 280 (9.2%) in Journal of Clinical Oncology 72 (11%) in Cancer 60 (9.2%) in Annals of Oncology, 52 (8%) in Journal of National Cancer Institute, 48 (7.3%) in New England Journal of Medicine, 42 (6.4%) in Lancet, 38 (5.8%) in British Journal of Cancer, 28 (4.3%) in European Journal of Cancer, 16 (2.4%) in Lung Cancer, 12 (1.8%) in Clinical Cancer Research, 5 (0.8%) in Journal of the American Medical Association, and 2 (0.3%) in British Medical Journal. Of these, 516 (78.8%) disclosed the source of the study sponsor (Table 1).

The nature of the relationship between the authors and the study sponsor was included in 219 of the 227 industry-sponsored studies. When the authors provided this information, the most commonly cited relationships were: grants (205/219, 93.6%); employment (86, 39.2%); consultant/honorarium (28, 12.7%) and stock ownership and participation in a speaker's bureau (12, 5.5% each).

The 86 papers that were co-authored by employees of the industry sponsor represented 37.8% of published industry-sponsored studies and 13% of all RCTs in our study.

Only 41 (18%) of the 227 industry-sponsored RCTs reported the role of the study sponsor as recommended by the uniform requirement. Of these studies, 20 papers explicitly stated that the sponsor had no role in the study (i.e. 'the sponsor of the study had no role in study design, data collection, analysis, interpretation, or writing of the report') and, of these, four stated that the sponsor had no role in the decision to publish the report.

Twenty-one papers described the sponsor's role, the degree of sponsor involvement was variable and usually described with vague wording (Table 2). Among these

Table 1
Compliance with requirement for disclosure of financial competing interests in cancer randomised trials published between January 1999 and December 2003

Requirements	Disclosure
Source of study sponsorship	
Overall	516/655
Industry-sponsored	159
Non-industry-sponsored	288
Association of industry and non-industry sponsored (mixed funding)	68
No financial support	1
Not disclosed	139
Author–sponsor relationship[a]	
Overall	219/227
Employment	86[b]
Consultant/honorarium	28[b]
Grants	205[b]
Educational/speakers bureau	12[b]
Stock ownership	12[b]
Advisory board	8[b]
Role of study sponsor	40/227

[a] Disclosure of author–sponsor relationship and role of study sponsor applicable to only 227 studies with industry support.

[b] Out of the 219 studies that disclosed author–sponsor relationship, total number of studies is greater than 219 because 131 studies had multiple relations.

Table 2
Disclosure of the sponsor's role in 21 papers

Ref.	Design	Data collection	Data analysis	Data interpretation	Writing the report	Acknowledged role of sponsor
Icon [7]	Mixed	Ind	Ind	Ind	Ind	
Langman [8]	NA	NA	NA	NA	NA	Sponsor only knew the allocated treatment
Bramhall [9]	NA	NA	NA	NA	NA	Treatment assignments were kept in sealed envelopes by the sponsor
Rosell [10]	NA	NA	NA	NA	NA	Randomisation was performed centrally by the sponsor
Littlewood [11]	Mixed	Mixed	NA	NA	NA	'We thank' the sponsor 'for his extensive participation in the design and analysis of this study'
Kurie [12]	NA	NA	NA	NA	NA	Sponsor approved the final draft of the article
Rothenberg [13]	NA	NA	NA	NA	NA	'We thank' the sponsor 'for superb study management'
Faiss [14]	Mixed	Mixed	Ind	Ind	NA	Sponsor and authors agreed at the outset to publish the results at the earliest opportunity
Schouten [15]	Ind	Mixed	Ind	Ind	NA	
Cardenal [16]	NA	NA	NA	NA	NA	'We thank' the sponsor 'for technical assistance'
Nabholtz [17]	NA	NA	NA	NA	NA	Randomisation was performed centrally by the sponsor
Agarwala [18]	NA	NA	NA	NA	NA	'We thank' the sponsor 'who managed this trial'
Cummings [19]	Ind	Mixed	Mixed	Ind	Mixed	The submitted manuscript was approved by the sponsor
Sjöström [20]	NA	NA	NA	NA	NA	The source data verification was performed by the sponsor
Mouridsen [21]	NA	Mixed	NA	NA	NA	Internal sponsor data evaluation committee reviewed in a blinded all tumour assessment and overall response data
FASG [22]	NA	NA	Mixed	NA	NA	
Kantarrjian [23]	Mixed	Mixed	Mixed	Mixed	Mixed	
Demetri [24]	Mixed	Mixed	Mixed	NA	Mixed	
Smith [25]	NA	Mixed	Mixed	NA	NA	
O'Brien [26]	Mixed	Mixed	Mixed	Mixed	Mixed	
Punt [27]	Mixed	Mixed	Sponsor	Mixed	Mixed	The decision to submit the paper for publication was determined by the study sponsor and was made in collaboration with principal researchers

NA, not available; Ind, independently (only by researcher); Mixed, performed by researcher and sponsor.

papers, four [23–26] stated that researchers had full access to all data, one [25] specified that researchers had no limitation on publication and one [27] specified that 'the decision to submit the paper for publication was determined by the study sponsor'.

4. Discussion

Financial and other competing interests have recently received increasing attention [28]. This concern has coincided with the reduced availability of public research funding, which has, in turn, resulted in scientist's increasing reliance on industry support.

The costs of medical research have increased to levels that even the wealthiest university or co-operative group can no longer afford. Public funds cannot do the job; partnerships with industry are mandatory, but we have to manage them better [29]. Lewis and colleagues [30] expressed it well when they said that, in the context of rules for governing the university–industry relationship: 'Some bargains are Faustian, and some horses are Trojan. Dance carefully with the porcupine, and know in advance the price of intimacy'. By all means, dance with the porcupine, but read and understand the contract first. A recent survey of 108 medical schools in the United States of America (USA) reveals that very few agreements between academic medical research sites and their industrial sponsors adequately protect researcher independence [31]. Median scores for compliance with such essential items as ensuring that researchers had access to the data in multi-centre trial were astounding. Only 1% of the site researchers surveyed had access to all data in the trials and only 40% had control over publication of their findings.

Recently, editors of prominent medical journals have moved beyond disclosure as a mechanism for managing competing interests. Editors will ask authors to document that they had access to the data and were able to make independent decisions about publication [32]. Poor adherence to the existing uniform requirements raises the question of the degree to which journals adhere to these more stringent requirements.

No researcher should be expected to produce 'findings' without full access to the data, freedom from interference in analysis and interpretation, and the liberty to publish all results, however disappointing to the stakeholder they may be. In the meantime, researchers do well to arm themselves with the rules for research partnerships and editors to take on the role of watchdog.

Conflict of interest statement

None declared.

References

1. Thompson DF. Understanding financial conflicts of interest. *N Engl J Med* 1993, **329**(8), 573–576.
2. Blumenthal D. Ethics issues in academic industry relationships in the life science. *Acad Med* 1996, **71**, 1291–1296.
3. Bodenheimer T. Uneasy alliance – clinical investigators and the pharmaceutical industry. *N Engl J Med* 2000, **342**, 1621–1626.
4. International Committee of Medical Journal Editors. Conflict of interest. *Lancet* 1993, **341**, 742–743.
5. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. *Ann Intern Med* 1997, **126**, 36–47.
6. Hussain A, Smith R. Declaring financial competing interests: survey of five general medical journals. *BMJ* 2001, **323**, 263–264.
7. The International Collaborative Ovarian Neoplasm (ICON) Group. Paclitaxel plus carboplatin *versus* standard chemotherapy with either single-agent carboplatin or cyclophosphamide, doxorubicin, and cisplatin in women with ovarian cancer: the ICON3 randomised trial. *Lancet* 2002, **360**, 505–515.
8. Langman MJ, Dunn JA, Whiting JL, *et al*. Prospective, double-blind, placebo-controlled randomized trial of cimetidine in gastric cancer. British Stomach Cancer Group. *Brit J Cancer* 1999, **81**, 1356–1362.
9. Bramhall SR, Hallissey MT, Whiting J, *et al*. Marimastat as maintenance therapy for patients with advanced gastric cancer: a randomised trial. *Brit J Cancer* 2002, **86**, 1864–1870.
10. Rosell R, Gatzemeier U, Betticher DC, *et al*. Phase III randomised trial comparing paclitaxel/carboplatin with paclitaxel/cisplatin in patients with advanced non-small-cell lung cancer: a cooperative multinational trial. *Ann Oncol* 2002, **13**, 1539–1549.
11. Littlewood TJ, Bajetta E, Nortier JW, *et al*. Epoetin Alfa Study Group. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a randomized, double-blind, placebo-controlled trial. *J Clin Oncol* 2001, **19**, 2865–2874.
12. Kurie JM, Lotan R, Lee JJ, *et al*. Treatment of former smokers with 9-*cis*-retinoic acid reverses loss of retinoic acid receptor-beta expression in the bronchial epithelium: results from a randomized placebo-controlled trial. *J Natl Cancer Inst* 2003, **95**, 206–214.
13. Rothenberg ML, Oza AM, Bigelow RH, *et al*. Superiority of oxaliplatin and fluorouracil–leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil–leucovorin: interim results of a phase III trial. *J Clin Oncol* 2003, **21**, 2059–2069.
14. Faiss S, Pape UF, Bohmig M, *et al*. Prospective, randomized, multicenter trial on the antiproliferative effect of lanreotide, interferon alfa, and their combination for therapy of metastatic neuroendocrine gastroenteropancreatic tumors – the International Lanreotide and Interferon Alfa Study Group. *J Clin Oncol* 2003, **21**, 2689–2696.
15. Schouten HC, Qian W, Kvaloy S, *et al*. High-dose therapy improves progression-free survival and survival in relapsed follicular non-Hodgkin's lymphoma: results from the randomized European CUP trial. *J Clin Oncol* 2003, **21**, 3918–3927.
16. Cardenal F, Lopez-Cabrerizo MP, Anton A, *et al*. Randomized phase III study of gemcitabine–cisplatin *versus* etoposide–cisplatin in the treatment of locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* 1999, **17**, 12–18.
17. Nabholtz JM, Senn HJ, Bezwoda WR, *et al*. Prospective randomized trial of docetaxel *versus* mitomycin plus vinblastine in patients with metastatic breast cancer progressing despite previous anthracycline-containing chemotherapy. *J Clin Oncol* 1999, **17**, 1413–1424.
18. Agarwala SS, Glaspy J, O'Day SJ, *et al*. Results from a randomized phase III study comparing combined treatment with histamine dihydrochloride plus interleukin-2 *versus* interleukin-2 alone in patients with metastatic melanoma. *J Clin Oncol* 2002, **20**(1), 125–133.
19. Cummings SR, Duong T, Kenyon E, *et al*. Multiple Outcomes of Raloxifene Evaluation (MORE) Trial. Serum estradiol level and risk of breast cancer during treatment with raloxifene. *JAMA* 2002, **287**, 216–220.
20. Sjostrom J, Blomqvist C, Mouridsen H, *et al*. Docetaxel compared with sequential methotrexate and 5-fluorouracil in patients with advanced breast cancer after anthracycline failure: a randomised phase III study with crossover on progression by the Scandinavian Breast Group. *Eur J Cancer* 1999, **35**, 1194–1201.
21. Mouridsen H, Gershanovich M, Sun Y, *et al*. Superior efficacy of letrozole *versus* tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group. *J Clin Oncol* 2001, **19**, 2596–2606.
22. French Adjuvant Study Group. Benefit of a high-dose epirubicin regimen in adjuvant chemotherapy for node-positive breast cancer patients with poor prognostic factors: 5-year follow-up results of French Adjuvant Study Group05 randomized trial. *J Clin Oncol* 2001, **19**, 602–611.
23. Kantarjian H, Sawyers C, Hochhaus A, *et al*. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. *N Engl J Med* 2002, **346**, 645–652.
24. Demetri GD, von Mehren M, Blanke CD, *et al*. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med* 2002, **347**, 472–480.
25. Smith TJ, Staats PS, Deer T, *et al*. Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: impact on pain, drug-related toxicity, and survival. *J Clin Oncol* 2002, **20**, 4040–4049.
26. O'Brien SG, Guilhot F, Larson RA, *et al*. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med* 2003, **348**, 994–1004.
27. Punt CJ, Nagy A, Douillard JY, *et al*. Edrecolomab alone or in combination with fluorouracil and folinic acid in the adjuvant treatment of stage III colon cancer: a randomised study. *Lancet* 2002, **360**, 671–677.
28. Smith R. Beyond conflict of interest. Transparency is the key. *BMJ* 1998, **317**, 291–292.
29. Moses 3rd H, Braunwald E, Martin JB, *et al*. Collaborating with industry – choices for the academic medical center. *N Engl J Med* 2002, **347**, 1371–1375.
30. Lewis S, Baird P, Evans RG, *et al*. Dancing with the porcupine: rules for governing the university–industry relationship. *CMAJ* 2001, **165**, 783–785.
31. Schulman KA, Seils DM, Timbie JW, *et al*. A national survey of provisions in clinical-trial agreements between medical schools and industry sponsors. *N Engl J Med* 2002, **347**, 1335–1341.
32. Davidoff F, DeAngelis CD, Drazen JM, *et al*. Sponsorship, authorship, and accountability. *Lancet* 2001, **358**, 854–856.