Anti-Cancer Drugs, **4(Supplement 3)** pp. 13–20

Clinical studies to assess the economic impact of new therapies: pragmatic approaches to measuring costs

Volker Kirchner
Clinique de Médecine, Hôpital Cantonale Universitaire de Genève, Switzerland.

Pragmatic clinical trials using unselected patients in normal clinical situations are more appropriate for the economic assessment of new drugs. However, standard clinical studies that do not reflect current practice are useful and at present the only source of information. Anti-emetic drug studies using granisetron and ondansetron have demonstrated that the overall economic impact of these drugs is equivalent to standard therapies such as metoclopramide. Thus, an efficient anti-emetic drug with less frequent dosing, using a simplified dosage regimen and producing a reduction in anticipatory nausea and vomiting and in nursing time, may result in an overall reduction in cost. Decisions made purely on the basis of drug costs may be misleading and promote inefficient use of health resources.

Key words: Anti-emetics, chemotherapy-induced vomiting, cost–effectiveness, cost analysis, serotonin-receptor antagonists.

Introduction

Therapeutic innovations inevitably have an impact on treatment budgets. Since the introduction of 5-HT_3 receptor antagonists, the anti-emetic drugs budget has increased eight-fold from 1990 to 1992, which corresponds with an increase of 8–30% of the drug costs of one hospital pharmacy.[1] This suggests the need for economic analyses, especially as health care resources are limited and hospital policy makers have to make difficult choices in a climate of cost containment. Cost is not merely a currency transaction but the consumption of a resource that could otherwise be used for another purpose.

Before any economic evaluation can be conducted, three questions need to be addressed: (i) what kind of study should be chosen to conduct a clinical economic evaluation?, (ii) at what point should an economic analysis be done?, and (iii) do the costs incurred have a wider implication for medical research?

Correspondence to V Kirchner, Division of Signal Transduction, Harvard Medical School, Alpert Building, First Floor, 200 Longwood Avenue, Boston, MA 02115, USA. Fax: (+1) 617 278 3131.

This paper will concentrate mainly on the first question.

Clinical economic evaluation

Undertaking economic analysis alongside clinical trials has never been clear cut.[2–5] Clinical trials are recognized as the best source of data for efficacy, but the care given during the trial may be so atypical that it is perhaps unwise to extrapolate these data to evaluate the economic impact of a new drug in normal practice.[6] Thus, standard clinical trial design results in substantial interference with the normal pattern of patient management. This is essential if clinical trials are to answer therapeutic questions in a scientific manner, but limits their usefulness in assessing the costs and benefits of therapy under conditions of normal use. However, an assessment of the price and recommended usage of an innovation can give an indication of the potential cost of a compound. In practice, if there is a wide range of recommended usage or if an innovation is used indiscriminately, the costs can be substantially greater than estimates based upon recommended usage. Pragmatic clinical studies that assess the impact of therapy in a cohort of patients while keeping protocol-driven interference to a minimum could provide an alternative to measuring cost effectiveness of new therapies.

Pragmatic clinical studies *vs* standard clinical trials

Two broad questions are useful in interpreting the results of a trial: can the treatment work under ideal circumstances, and does it work in ordinary settings? In this context, the distinction between efficacy and effectiveness needs to be outlined.

Efficacy is established by restricting patients in a study to those who will co-operate fully with medical advice. It is an evaluation of a treatment under

ideal conditions. These are 'equalized', 'optimal' or 'laboratory' conditions for a standard clinical trial, an explanatory or an intention-to-treat trial. It could be a randomized or a cohort study. The aim here is to acquire information.

Effectiveness is established by offering a treatment or programme to patients under 'ordinary' or 'normal' conditions and is called a pragmatic trial. It is a management trial and could be used to study cost effectiveness. The aim here is to make a decision.[7-11]

It is interesting to examine some differences between common practice and clinical trials. A major concern of common practice trials is external validity or generalizability and the resolution of symptoms, whereas a clinical efficacy study is concerned with the internal validity of the clinical endpoint. The objective of the two kinds of trials are quite different. Common practice requires a realistic estimate of drug impact, whereas clinical trials require control of the confounding variable or the 'drug effect'. The study design for these two situations is quite different, as discussed above. The comparisons made will also be quite different. In trials of common practice, a comparison is inevitably made with current practice, whereas in clinical trials the comparison is usually with placebo or therapeutic gold standards. The patients entered in these trials are also quite different. In common practice, comparisons are made with 'everyday patients', whereas in clinical trials they are made with a highly selected group. In terms of evaluation, data are thought to be 'soft' in common practice trials because symptom relief and quality of life are being evaluated, and 'hard' in clinical trials, because a well-defined endpoint like survival is the key goal.

The various theoretical requirements explain some biases of standard clinical trials and may contribute to some differences with pragmatic trials.[12-16] In any clinical trial, a clinician first selects a sample of people at risk, which is then randomized. The sample is then exposed (or not) to a drug and the outcome is measured. In this process it is possible to introduce bias in sampling, selection and measurement (Figure 1).

Data from the Coronary Artery Surgery Study (CASS) exemplify the problem clearly.[17] This study was a randomized trial comparing clinical *vs* medical treatment in patients with stable coronary artery disease. Initially 16 626 patients were potentially eligible for study. After all of the normal exclusion criteria had been applied, only 12.7% of patients were suitable for entry to the study. When the inclusion/exclusion criteria, as specified in the study protocol, were applied, only 4.7% of patients were eligible for randomization.[17,18]

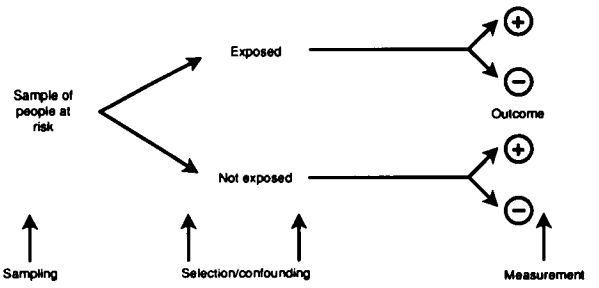

Figure 1. Clinical trials *vs* common practice: potential biases. (Adapted from Feltcher *et al.*[7])

A clinician usually makes a diagnosis at the appearance of the first significant symptom for the patient. When conducting a trial, the clinician makes regular evaluations which will allow the detection of symptoms to be made early on and to be treated quite differently, especially when the clinical outcome is favorable, in marked contrast to common practice (Figure 2).[19]

In the case of adverse-event analysis, it is known that liver enzyme abnormalities, for example, are an adverse event which has been associated with 5-HT_3 receptor antagonists and chemotherapy.[20-22] This is only detected via blood sampling and has no clinical relevance, its detection serves only to increase the indirect costs of the treatment.[23,24]

Cost studies

In order to assess the economic efficiency of a particular treatment, it is necessary to examine the

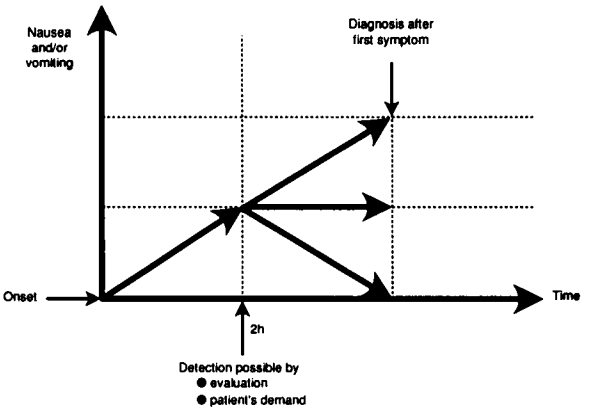

Figure 2. Clinical trials *vs* common practice: length/time bias (active/passive case finding).

effect of new treatment in three areas. Firstly, the impact on health service resources (hospital and ambulatory cost, pharmacist, medical and nursing time, equipment, drugs, etc). Secondly, one should examine the impact on other community resources (input from patients and families, patient's ability to work). Finally, one needs to examine the impact of the new therapy on health status by evaluating improvements in health *per se* and in terms of other effects including money, health effects such as lives saved, or health 'utilities' such as quality-adjusted life years.[25]

An economic analysis can be represented in three dimensions (Figure 3).[26–34] Firstly, it is necessary to consider the types of analysis: cost identification (enumeration of costs involved in medical care ignoring the outcome of treatment); cost benefit (comparison of the management strategies in which the costs and benefits are both expressed in the same terms); and cost effectiveness (comparison of management strategies in terms of their cost per unit of output, where output is an outcome such as additional years of life, utilities, or additional cases of newly detected disease). Secondly, it is important to consider from which point of view the conclusions will be drawn, i.e. the patient, the payer, the provider or society. Thirdly, the type of costs must be considered and it is important to ensure that all have been taken into account:

— Direct costs: resources required to produce a service. These stem from transactions for goods or services, and include physician, drug and direct non-medical costs such as those payed for by patients and their families. These costs can be fixed or variable, increasing with increasing volume of activity.
— Indirect costs: those which do not stem from transactions for goods or services. Costs of mortality and morbidity.
— Intangible costs: those of pain, suffering, and grief. These are usually extremely difficult to measure and often omitted in clinical economic research.

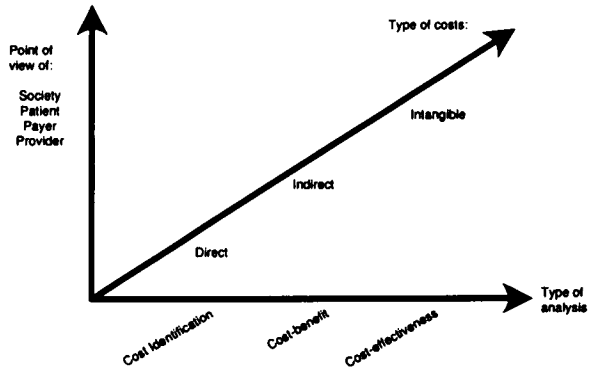

Figure 3. Economic analysis: a three-dimensional aspect. (Adapted from Bombardier C, Eisenberg J. Looking into the crystal ball: can we estimate the lifetime cost of rheumatoid arthritis. *J Rheumatol* 1985; **12**: 201, and from reference 26.)

Anti-emetic cost studies

Anti-emetic cost studies have been carried out using highly emetogenic chemotherapy regimens in an inpatient setting (Table 1). An exception is the study by Cox,[35] which is a retrospective analysis in an outpatient setting using cyclophosphamide-based chemotherapy. All the trials so far are retrospective cost analyses, involving small numbers of patients. All ondansetron trials used high-dose ondansetron (24–32 mg given as three or four divided doses, intravenously)[35–37] apart from the study by Sands *et al.*[36] In comparative studies using granisetron, however, up to 80% of patients were treated with a single daily dose of 3 mg.[38,39] This simplified treament regimen with granisetron reduced direct costs of anti-emetic therapy associated with drug cost acquisition, nursing time and materials necessary for the drug's administration, all elements which have been discussed as relevant in these types of analysis.[40,41] A sensitivity analysis has only been done for two studies[35,42] with an analysis based on a decision-analytic framework. The type

Table 1. Clinical economic anti-emetic trials (5-HT_3 receptor antagonists)

Methodolgy	Results	Reference no.
Cost effectiveness	OND > MTC	37
	GRAN > MTC/DEX	38
	OND/DEX > MTC/DEX/LOR	36
	OND/DEX > MTC/DEX	35
Cost benefit	OND > MTC/LOR	54
Cost identification	GRAN > standard anti-emetic treatment	39
Decision making	5-HT_3 RA: +3–10% total cost	58

OND, ondansetron; DEX, dexamethasone; GRAN, granisetron; LOR, lorazepam; MTC, metoclopramide; 5-HT_3 RA, 5-HT_3 receptor antagonist.

of costs considered and the perspectives taken are not the same in these studies. Costs presented are based on the UK health care system (ondansetron-based studies) or the Swiss health care system (granisetron-based studies), and may vary between countries. The costs of non-proprietary brands of standard drugs may affect their acquisition cost, although in the UK the costs of parenteral generic brands are the same as that of the proprietary brands. Some of the non-drug costs associated with the two anti-emetics (such as in-patient stays, staff time costs of administering the drugs and the numerous tests associated with cytotoxic treatment) will fall on other budgets in varying amounts, as has been already demonstrated. The time spent by a nurse or a physician may diminish with the use of more efficient anti-emetic drugs, but the staff costs will remain the same, as they are fixed.[43–49] Labor, materials and hospital stay can vary between institutions. In addition, since these data have been published, the costs of 5-HT_3 receptor antagonist drugs have been significantly reduced. All these changes can affect an economic evaluation and should be kept in mind.[50] In general, these studies highlight the fact that decisions made purely on the narrow basis of drug costs may mislead decision makers and promote inefficient use of health resources.[51]

Ondansetron vs metoclopramide in acute emesis

The study by Cunningham *et al.*[37] was an open, multicenter, randomized, parallel group, unblinded study involving two centers. Thirty-two patients were randomized to receive either ondansetron (8 mg i.v. every 4 h for three doses) or metoclopramide (3 mg/kg body weight i.v. loading dose, followed by 0.5 mg/kg/h, i.v., for 8 h). Nursing staff recorded the number of emetic episodes, details of adverse events, and specific data related to direct costs of anti-emetic treatment such as all materials used in the administration of the anti-emetic and time spent caring for the patient. No significant emesis was defined as no or one emetic episode during the 24 h period following chemotherapy with no adverse events. Drugs costs were derived from the *Monthly Index of Medical Specialities* (February 1991) and the *British National Formulary No. 19* (April 1990). Average staff wages were determined using data from the Department of Health, and material costs were based on Health Service Costing Returns 1986/89. Successful treatment, as defined, was achieved in 50% of ondansetron-treated patients (seven out of 14) and in 22% of the metoclopramide-treated patients (four out of 18). The drug cost of ondansetron in the first 24 h after chemotherapy was approximately four times higher than that of metoclopramide (£44.57 *vs* £11.91 per patient). The mean utilization cost (considering the direct cost) was 2.5-fold higher for ondansetron than for metoclopramide (£47.60 *vs* £20.28). The cost per successfully treated patient (by dividing the mean overall utilization cost per patient by the probability of being successfully treated) was £95.20 for ondansetron and £92.18 for metoclopramide. These results suggest that ondansetron is nearly as effective as metoclopramide in this setting. However, the number of patients was small and a sensitivity analysis was not provided. Corticosteroids were allowed if they were part of the chemotherapy regimen or for physiological supplementation, and it is not known whether this treatment was balanced in the two groups of patients.

In a second study,[42] a pre-marketing economic evaluation combined secondary analysis of data from a large clinical trial[52] with estimates of emesis management costs in a UK hospital setting in order to assess the cost effectiveness of ondansetron (8 mg i.v. leading dose, followed by 1 mg/h i.v. for 24 h) compared with metoclopramide (3 mg/kg i.v. leading dose, followed by 0.5 mg/kg/h for 8 h) in highly emetogenic chemotherapy treated patients. Results of the cost analysis (original patient specific data from the clinical trial were used to construct a probability tree for each treatment group) showed that the two anti-emetic regimens would have equivalent treatment costs if ondansetron were priced 2.3 times (1.6–3.5, using a sensitivity analysis) higher than the £10.00 acquisition of metoclopramide. The cost-effectiveness analysis showed the same trend. However, in this study therapeutic success was defined as two or less emetic episodes during the 24 h after chemotherapy. Extended hospitalization costs were also considered, but anti-emetic administration costs (i.e. alcohol, swabs, needles, etc.) were not. It should be noted that the probability of extended hospitalization may depend on the availability of hospital beds, the attending physician and other factors, and these costs may vary between institutions.[53]

In a cost-benefit study by Tanneberger *et al.*,[54] it was estimated that an ondansetron regimen, using total doses of 24–32 mg for the prophylaxis of acute emesis due to highly emetogenic chemotherapy, would increase the cost of chemotherapy cycles by no more than 6%, compared with a regimen using metoclopramide 10 mg/kg i.v. plus loraze-

pam. By means of the real cost–benefit index, the ondansetron regimen was found to be favorable.

Ondansetron in combination

Sands *et al.*[36] carried out a cost-effectiveness evaluation of ondansetron (8 mg i.v., single dose) plus dexamethasone (8 mg i.v., every 8 h, in two doses) compared with that of combination therapy with metoclopramide (3 mg/kg i.v. loading dose, followed by 8 mg/kg i.v. over 8 h), dexamethasone (8 mg i.v.) plus lorazepam (1–1.5 mg i.v.). The economic analysis was carried out using the clinical data from two studies. In one study, 13 patients received the ondansetron combination during 31 chemotherapy cycles; the complete remission rate was 93%. In the second study, 54 metoclopramide recipients achieved a complete response of 76% (41 out of 54). The authors concluded that the cost per effective treatment (calculated by dividing the cost of the local hospital-discounted drug by complete response rate) was lower for the ondansetron combination (£16.27) than for the metoclopramide regimen (£17.35). As these data were collected from two studies, they require confirmation in a larger, randomized, double-blind clinical trial. In addition, adverse events, nursing time, consumption of disposable items and the cost of 'rescue' anti-emetics were not included as part of the analysis.

A cost-effectiveness analysis by Cox[35] using a decision-analytic framework (costs associated with anti-emetic regimens, management of vomiting and retching and significant anti-emetic-related adverse events, were combined with the differential probabilities resulting from the trial) was carried out using data from 70 patients randomized to ondansetron (8 mg i.v. loading dose followed by 8 mg three times a day during the 5-day period following chemotherapy) compared with 80 patients randomized to metoclopramide (60 mg i.v. loading dose followed by 20 mg three times a day during the 5-day period following chemotherapy) both in combination with dexamethasone. Patients included women with breast cancer receiving their first cyclophosphamide-based ($\geq$500 mg/m^2) chemotherapy on day 1. The cost per successfully treated patient (cost per patient divided by the probability of a patient being successfully treated) was £184.00 for ondansetron and £160.00 for metoclopramide. Based on a study by Dicato,[55] showing that ondansetron given orally twice a day was as effective as three times daily dosing in patients receiving cyclophosphamide ($\geq$500 mg/m^2), the costs per successfully treated patient for ondansetron (£133.00) were lower than for metoclopramide (£160.00).

Granisetron

A retrospective cost–effectiveness study of 22 Swiss patients treated for malignant disease and naive to chemotherapy, who received cisplatin (>15 mg/m^2 per day, i.v.) or etoposide (120 mg/m^2 per day for 5 consecutive days) as hospital in-patients, were randomized to receive either granisetron 40 μg/kg body weight (with an optional two additional daily doses of 40 μg/kg i.v. upon the emergence of symptoms), or the combination of metoclopramide (3 mg/kg i.v. loading dose, days 1–2, with an optional dose reduction to 2 mg/kg i.v. on days 3–5, followed by 3 mg/kg i.v., infused over 8 h) plus dexamethasone (12 mg i.v. daily).[38] Drug prices were derived from published Swiss prices (1991) with 33% discount to obtain hospital prices. A methodological model was used for cost assessment based on assessment of routine practice in oncology clinics in the Geneva area. The study shows that although acquisitional drug costs of metoclopramide plus dexamethasone (54.94 SFr) was less expensive than granisetron (80 SFr), the total costs were comparable (metoclopramide plus dexamethasone = 95.77 SFr, granisetron = 97.20 SFr). As metoclopramide plus dexamethasone was less effective as an anti-emetic and associated with more adverse events than granisetron, total costs (metoclopramide plus dexamethasone = 118.81 SFr, granisetron = 113.73 SFr), cost efficacy ratio (efficacy ratio divided by total cost; efficacy ratio = total number of patient days with complete remission divided by the total number of treatment days; complete remission was defined as no vomiting, or no or only mild nausea per day; metoclopramide plus dexamethasone = 0.42/118.81 = 1:283; granisetron = 0.67/113.73 = 1:170) and the incremental cost–effectiveness ratio (total costs of granisetron minus total cost of metoclopramide plus dexamethasone, divided by the percentage efficacy of granisetron minus the percentage efficacy of metoclopramide plus dexamethasone = 5.02/25) were in favor of granisetron.

A second study[39] was a retrospective anti-emetic cost identification of 12 consecutive patients presenting with anticipatory nausea and vomiting during consecutive chemotherapy cycles with moderate to severe emetogenic potential. The anti-emetic regimen used were classical regimen: diphenhy-dramine 12.5 mg plus prednisolone

25 mg plus dehyrobenzoperidol 1.25 mg i.v., up to three times/day; metoclopramide 2 or 3 mg/kg i.v. loading dose, followed by 3 or 4 mg/kg infused i.v. over 8 h plus dexamethasone 20 mg i.v.; others (in various combinations): midazolam 5 mg i.v.; domperidone 10 mg orally three times/day; alizapride 50 mg i.v.; metoclopramide 10 mg i.v.; haloperidol 2.5 mg i.v.; thiethylperazine 6.5 mg i.v.; chlorpromazine 25 mg orally three times daily; and 5-HT_3 receptor antagonists: granisetron 3 mg i.v. up to three times/day; ondansetron 8 mg i.v. three times/day; dolasetron mesilate 10-50 mg i.v. The methodology used was as follows: calculation of costs: (a) drugs costs: anti-emetic drug + prophy-lactic agents; (b) added costs: materials + pharmacy costs + nursing costs; (c) direct costs: a + b; (d) adverse event/failure of treatment costs: additional drugs + materials + nursing, behavioral therapy and pharmacy costs; and (e) total costs: c + d. The results show that the total drug costs of the 12 evaluated patients range from 37.30 to 318.70 SFr (mean SFr 143.05). It is known that the incidence of anticipatory nausea and vomiting is about 24%.[56] However, recent data[57] have shown that in patients treated with granisetron the incidence of anticipatory nausea and vomiting is significantly lower (4.6%) during consecutive chemotherapy cycles. The conclusion was that granisetron used as a first-line anti-emetic in new patients scheduled for consecutive chemotherapy cycles may reduce the incidence of anticipatory nausea and vomiting and result in long-term economic savings.

Decision-making analysis

Jones *et al.*[58] constructed a treatment model which represents a baseline of efficacy and the costs of treating a cohort of patients with conventional anti-emetics. Groups of patients who would be expected to receive the most benefit from 5-HT_3 receptor antagonists were identified and then the effect upon costs of using these compounds in a consecutively larger proportion of selected patients was calculated. On the basis of illustrative costs from the Cookridge Hospital in the UK, it was concluded that the new anti-emetics can be used in acute emesis with substantial clinical benefit with an increase of 3–10% in the total treatment costs. For delayed emesis these compounds have not yet shown a clinical advantage, and the increase in total costs of 12–34% is not justified.

Conclusions

Clinical trials are not the best way to conduct a clinical economic evaluation. However, they are all that is available at present. Clinical trials do not necessarily need to address the problem of cost evaluation, but when cost considerations are foremost, it becomes essential to determine the cost of a clinical trial at an early stage. The methodology for economic evaluations should be standardized. Clinical economic analyses will change opinions in conducting research studies, in the same way that statistical analysis has done in the past.

References

1. Buri A. Geneva University Hospital pharmacy. Mühlebachs. Aarau Hospital pharmacy, personal communication.
2. Drummond MF, Davis L. Economic analysis alongside clinical trials: revisiting the methodological issues. *Int J Technol Assess Health Care* 1991; **7**: 561–73.
3. Hillman AL, Eisenberg JM, Pauly MV, *et al.* Sounding board: avoiding bias in the conduct and reporting of cost-effectiveness research sponsored by pharmaceutical companies. *N Engl J Med* 1991; **324**: 1362–5.
4. Editorial. Farewell to promising goodbuys? *Lancet* 1991; **338**: 416–7.
5. Miller JP. Use of cost-benefit analysis in promotional material. *Lancet* 1991; 338: 823–4.
6. Evans RG, Robinson BC. Surgical day care: measurements of the economic payoff. *Can Med Ass J* 1980; **123**: 873–80.
7. Fletcher RH, Fletcher SW, Wagner EH. *Clinical epidemiology. The essentials.* 2nd Edn. Baltimore, USA: Williams and Wilkins, 1988: 129–56.
8. Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. *J Chron Dis* 1967: **20**: 637–48.
9. Lurie A, de Lauture D, Sancho-Garnier H, *et al.* Towards pragmatic trials in asthma? *Eur Respir Rev* 1991; **1**: 57–61.
10. Drummond MF, Stoddart GL. Economic analysis and clinical trials. *Controlled Clin Trials* 1984; **5**: 115–28.
11. Feinstein AR. An additional basic science for clinical medicine: II. The limitations of randomized trials. *Ann Intern Med* 1983; **99**: 544–50.
12. Sackett DL, Gent M. Controversy in counting and attributing events in clinical trials. *N Engl J Med* 1979; **26**: 1410–2.
13. Peto R, Pike MC, Armitage P, *et al.* Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. *Br J Cancer* 1976; **34**: 585–612.
14. Glatstein E, Makuch RW. Illusion and reality: practical pitfalls in interpreting clinical trials. *J Clin Oncol* 1984; **2**: 488–97.
15. Easterbrook PJ, Berlin JA, Gopalan R, *et al.* Publication bias in clinical research. *Lancet* 1991; **337**: 867–72.
16. Baar J, Tannock I. Analysing the same data in two ways: a

demonstration model to illustrate the reporting and misreporting of clinical trials. *J Clin Oncol* 1989; **7**: 969–78.
17. CASS Principal Investigators and Their Associates. Coronary artery surgery study (CASS): a randomized trial of coronary artery bypass surgery. Survival data. *Circulation* 1983; **68**: 939–50.
18. Antman K, Amato D, Wood W, *et al.* Selection bias in clinical trials. *J Clin Oncol* 1985; **3**: 1142-47.
19. Mittra I. Axillary lymph node metastasis in breast cancer: prognostic indicator or lead-time bias? *Eur J Cancer* 1993; **29**: 300–302.
20. Hesketh PJ, Twadell R, Finn A. A possible role for cisplatin in the transient hepatic enzyme elevation after ondansetron administration. Abstract 1250. *Proc Am Soc Clin Oncol* 1990; **9**: 323.
21. Clark RA, Kris MG, Gralla JR, *et al.* Serotonin antagonists demonstrate antiemetic effectiveness without extrapyramidal symptoms: analysis of studies with 3 new agents in 155 patients. Abstract 1246. *Proc Am Soc of Clin Oncol* 1990; **9**: 322.
22. Smith RN. Safety of ondansetron. *Eur J Cancer Clin Oncol* 1989; **25**: 547-50.
23. Moertel CG, Hanley JA. The effect of measuring error on the results of therapeutic trials in advanced cancer. *Cancer* 1976; **38**: 388–94.
24. Warr D, McKinney S, Tannock I. Influence of measurement error on assessment of response to anticancer chemotherapy: proposal for new criteria of tumor response. *J Clin Oncol* 1984; **2**: 1040–6.
25. Drummond MF, Stoddart GL, Torrance GW. *Methods for the economic evaluation of health care programmes.* Oxford: Oxford Medical Publications, 1987.
26. Eisenberg J, Glick H, Koffer H. Pharmacoeconomics: Economic evaluation of pharmaceuticals. In: Strom BL. *Pharmacoepidemiology.* New York: Churchill Livingstone 1990: 325–50.
27. Sox HC, Blatt MA, Higgins MC, *et al. Medical decision making.* Boston: Butterworth Heinemann 1988: 317–35.
28. Weinstein MC, Stason WB. Foundations of cost-effectiveness analysis for health and medical practices. *N Engl J Med* 1977; **296**: 716–21.
29. Stoddart GL, Drummond MF. How to read clinical journals: VII. To understand an economic evaluation (part A). *Can Med Ass J* 1984; **130**: 1428–34.
30. Stoddart GL, Drummond MF. How to read clinical journals: VII. To understand an economic evaluation (part B). *Can Med Ass J* 1984; **130**: 1542–9.
31. Drummond M, Stoddart G, Labelle R, *et al.* Health economics: an introduction for clinicians. *Ann Intern Med* 1987; **107**: 88-92.
32. Eisenberg JM. Clinical economics: a guide to economic analysis of clinical practice. *J Am Med Ass* 1989; **262**: 2879–86.
33. Detsky AS, Naglie IG. A clinician's guide to cost-effectiveness analysis. *Ann Intern Med* 1990; **113**: 147–54.
34. Udvarhelyi IS, Colditz GA, Rai A, *et al.* Cost-effectiveness and cost-benefit analyses in the medical literature: are the methods being used correctly. *Ann Intern Med* 1992; **116**: 238–44.
35. Cox F. Ondansetron — a cost–effective advance in antiemetic therapy. Presented at the XVIIth Congress of the European Society for Medical Oncology, Lyon, France, 8 November 1992.
36. Sands R, Roberts JT, Marsh M, *et al.* Low dose ondansetron and dexamethasone: a cost effective alternative to high dose metoclopramide/dexamethasone/lorazepam in the prevention of acute cisplatin induced emesis. Correspondence. *Clin Oncol* 1992; **4**: 67–8.
37. Cunningham D, Gore M, Davidson N, *et al.* The real costs of emesis — an economic analysis of ondansetron vs. metoclopramide in controlling emesis in patients receiving chemotherapy for cancer. *Eur J Cancer* 1993; **29A**: 303–6.
38. Kirchner V, Aapro M, Alberto P, *et al.* The cost-effectiveness of granisetron compared with metoclopramide plus dexamethasone. *Proc Am Soc Clin Oncol*, 1992; **11**: 379.
39. Kirchner V, Aapro M, Terrey JP. Antiemetic treatment costs in chemotherapy: the economic evaluation of granisetron. *Ann Oncol* 1992; **3(suppl 5)**: 185.
40. Parker SE, Davey PG. Pharmacoeconomics of intravenous drug administration. *Pharmacoeconomics* 1992; **1**: 103–15.
41. Freund DA, Dittus RS. Principles of pharmacoeconomic analysis of drug therapy. *Pharmacoeconomics* 1992; **1**: 20–32.
42. Buxton MJ, O'Brien BJ. Economic evaluation of ondansetron: preliminary analysis using clinical trial data prior to price setting. *Br J Cancer* 1992; **66**: S64-7.
43. Rees G. Cost–effectivness in oncology. *Lancet* 1985; **ii**: 1405–28.
44. Thimothy A. Report of a conference: cost versus benefit in non-surgical management of patients with cancer. *Br Med J* 1988; **297**: 471–2.
45. Jenett B, Buxton M. When is treatment for cancer economically justified? *J Roy Soc Med* 1990; **83**: 25–8.
46. Calman K, McVie J, Soukop M, *et al.* Cost of outpatient chemotherapy. *Br J Med* 1978; **1**: 493–4.
47. Wodinsky H, DeAnglis C, Rusthoven J, *et al.* Reevaluating the cost of outpatient cancer chemotherapy. *Can Med Ass J* 1987; **137**: 903-6.
48. Goodwin P, Feld R, Ward P, *et al.* The cost of cancer therapy. *Eur J Cancer* 1990; **26**: 223–5.
49. Miles D, Richards M, Reubens R. Cost-effectiveness of cancer chemotherapy. *Cancer Topics* 1990; **7**: 141–2.
50. Goddard M. The real costs of emesis. *Eur J Cancer* 1993; **29A**: 297–8.
51. Tigh M, Goodman S. Carboplatin versus cisplatin. *Lancet* 1988; **ii**: 1372–3.
52. Marty M, Pouillart P, School S, *et al.* Comparison of the 5-hydroxytryptamine, (serotonin) antagonist ondansetron (GR38032F) with high-dose metoclopramide in the control of cisplatin-induced emesis. *N Engl J Med* 1990; **322**: 816-21.
53. Plosker GL, Richard JM. Ondansetron: a pharmacoeconomic and quality-of-life evaluation of its antiemetic activity in patients receiving cancer chemotherapy. *Pharmacoeconomics* 1992; **2**: 285–304.
54. Tanneberger ST, Lelli G, Martoni A, *et al.* The antiemetic efficacy and the cost–benefit ratio of ondansetron calculated with a new approach of health technology assessment (real cost-benefit-index). *J Chemother* 1992; **4**: 326–331.
55. Dicato MA. Oral treatment with ondansetron in an outpatient setting. *Eur J Cancer* 1991; **27** (Suppl 1): S18–19.
56. Morrow GR. Prevalence and correlates of anticipatory nausea and vomiting in chemotherapy patients. *JNCI* 1982; **68**: 585–8.

57. Aapro MS, Kirchner V, Terry JP. Is anticipatory nausea and vomiting a thing of the past? *Proc Am Soc Clin Oncol* 1992; **11**: 394.
58. Jones AL, Lee GJ, Bosanquet N. The budgetary impact of 5-HT_3 receptor antagonists in the management of chemotherapy-induced emesis. *Eur J Cancer* 1992; **29A**: 51–6.

Appendix—Discussion

C Courtois (Belgium): We already have what we call good clinical practice in the general practice setting, but we should also have good clinical practice enabling us to carry out pragmatic clinical studies. It is very difficult at the moment to promote these studies to the health authorities, because of the direct and indirect costs. Their idea of the importance of cost is sometimes very different to our own. It is important to address the guidelines within the short term if we want to be credible to the health care authority.

V Kirchner (Switzerland): The health care authority may be very interested in this approach using pragmatic clinical studies, but for the FDA this is not a major aspect for consideration. There may be problems with the study if the interest is not stated, i.e. where there is tremendous input from the health authority or from the pharmaceutical companies. We have to be aware of this and stress this is in our publications. In conclusion there are some trials of decision-making analyses which are quite useful in this kind of setting such as the study by Jones *et al.*[1]

C Latour (France): I agree with you when you say that common clinical practice is very different from clinical trials. Our experience is that clinical trials involve procedures with an informed consent using a product with a number code. When Zofran became generally available patients and nurses believed that the drug was less effective than when it was on clinical trial, because they could see the normal packaging for the drug.

V Kirchner (Switzerland): This is a well-known example of the placebo effect, and you have to take into account the placebo effect in clinical trials. This is quite different from the placebo effect you could expect in common practice, which depends on the medical and paramedical staff.

MS Aapro (Switzerland): When a compound acts on well-known receptors we know something of its physiology, but where the brain has a major impact there is no doubt that a placebo effect exists. A placebo effect may exist in clinical trials because the patient thinks that he or she is getting something which is new and better than existing therapies.

Reference

1. Jones AL, Hill AS, Soukop M, *et al.* Comparison of dexamethasone and ondansetron in the prophylaxis of emesis induced by moderately emetogenic chemotherapy. *Lancet* 1991; **338**: 483–7.