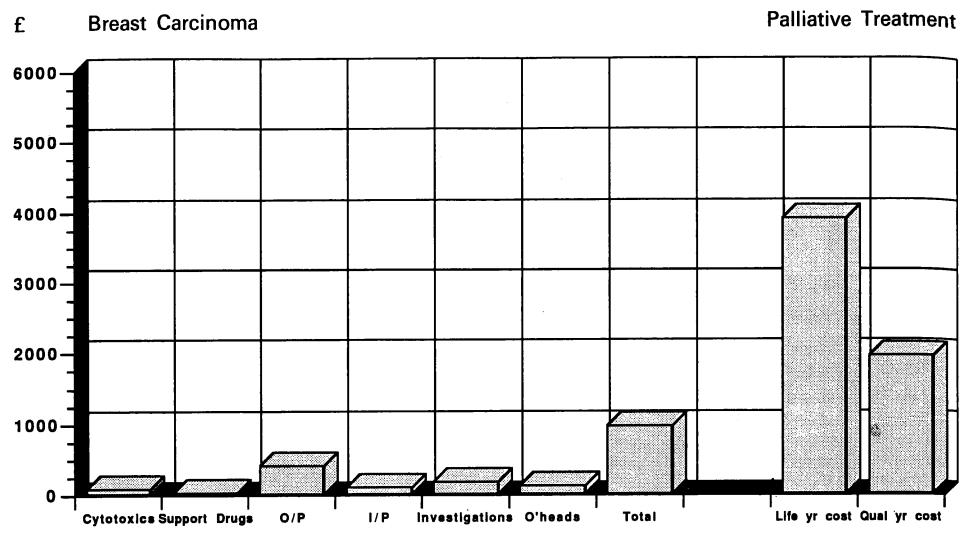

FIGURE 2

Approximate costs of 'palliative' combination chemotherapy (CMFP—cyclophosphamide, methotrexate, fluorouracil, prednisolone) for advanced breast carcinoma.
O/P out-patient attendances
I/P in-patient stays
O'heads—hospital overheads (15%)

REFERENCES

[1] NHS Management Executive. Cost for contracting. FDL (93) 59 Department of Health. 1993.
[2] Towlson KE, Leaning MS, Rubens RD. An audit of the effectiveness of cytotoxic chemotherapy in the palliative treatment of breast cancer. *Br J Cancer* 1992; **66:** Supp XVII, 11.
[3] Shibley L, Brown M, Schuttinga J, Rothenberg M, Whalen J. Cisplatin-based combination chemotherapy in the treatment of advanced stage testicular teratoma: Cost benefit analysis. *J Nat Cancer Inst* 1990; **82** (3): 186–92.
[4] Sheridan E, Hancock BW, Smith SC, Doreen MS, Neal FE, Pennington GW, Millar DR. Gestational trophoblastic disease: experience of the Sheffield (United Kingdom) Surpraregional Screening and Treatment Service. *Int J Clin Oncol* 1993; **3:** 149–55.
[5] Richards MA, Braysher S, Gregory WM, Rubens RD. Advanced breast cancer: use of resources and cost implications. *Br J Cancer* 1993; **67:** 856–60.
[6] Weeks J. Distinguishing the clinically important from the statistically significant. ASCO Educational Book, Chicago USA: Publ American Society for Clinical Oncology, 1992, 121–5.

Proc. R. Coll. Physicians Edinb. 1995; **25:** 67–75

THE COST EFFECTIVENESS OF CANCER THERAPY: THE HEALTH ECONOMIST'S VIEW*

D. K. Whynes,† Department of Economics, University of Nottingham

I am not a physician, although I spend a sizeable part of my academic life collaborating closely with physicians actively engaged in clinical research. Whilst attending to the medical needs of their patients, as their vocation demands, academic clinicians are simultaneously attempting to develop and assess new therapeutic techniques for the benefit of future generations. My role is to evaluate whether or not we, as a society, are likely to be able to afford these new techniques. Having a high regard for the talents of my clinical colleagues, I must confess that my role does occasionally give me cause for concern. After all, the simple act of healing the sick is enough to ask of anyone, without requiring that it be done economically.

My conscience notwithstanding, it is a simple fact that economic considerations have become increasingly important in health care policy in recent years. This importance was crystallised in the 1989 White Paper which pre-figured the 1990 National Health Services and Community Care Act: 'If the NHS is to provide the best service it can for its patients, it must make the best use of the resources available to it. The quest for value for money must be an essential element in its work'[1] (Section 1.15). The reasons for this strong emphasis on economics were not hard to detect. First, as the White Paper pointed out, there existed evidence of widespread variations in average inpatient costs, waiting times, drug costs and general practitioner referral rates throughout the country, evidence suggestive either of the inefficient use of resources or of inadequate provision of treatments in some regions. Second, at a national level, the health service appeared to be locked on an upward spiral, offering more and more courses of treatment each year, absorbing an ever-increasing proportion of national resources, whilst being faced with a growing waiting list for hospital admission. The overt pursuit of economic efficiency, it was felt, offered a solution to both the regional disparity and cost escalation problems.

Not surprisingly, the past few years have seen an increase in demands on the services of health economists. Their advice is sought by health care agencies when planning changes in care management, and it is increasingly difficult for clinical researchers to obtain funding unless economic evaluations are included in their protocols. Of all the techniques available to an economist, *cost-effectiveness analysis* is the one most frequently called upon. In this paper, I examine the cost-effectiveness issues in cancer therapy, which, accounts for around 7 per cent of UK health service spending.[2] We begin, with the obvious question.

WHAT IS COST-EFFECTIVENESS?

Economists consider productive systems as processes, involving the translation of

*Based upon a lecture delivered at the Symposium on *Oncology* held in the College on 13 April 1994.

†Reader in Health Economics.

inputs into outputs. Inputs are resources, for example, labour time and the services of various types of capital equipment, which are consumed during the production process. Outputs are the results of production, associated with some value or benefit. Whilst the building of aeroplanes or the construction of motorways are obvious examples of productive processes, the model can also accommodate areas of the economy such as medical care. Any medical intervention involves the consumption of resources; physician and nursing time, drugs and dressings, the use of a hospital bed and possibly an operating theatre or an intensive care unit. Every intervention produces an output, in the form of a potential change in the patient's condition. Conceptually, treating a patient is just like building a motorway.

Cost-effectiveness analysis is a way of assessing outputs relative to inputs for two or more processes and thus serves as a guide for rationing scarce resources. 'Cost' refers to the input side of the translation, that which has to be given up in order to obtain the desired outcome. For medical interventions there are three classes of costs to consider. These are, first, the direct resource costs of labour, capital, overheads, etc. incurred by the provider of care, for example, the hospital. The patient too might be partly responsible for direct costs, for example, prescription charges or travel. Second, an intervention might require that society or the patient incur indirect production costs, for example, time off work entailing a loss of production. Third, costs might be incurred by the patient in the form of, for example, pain and discomfort as a result of the intervention. It will generally be possible to express all these costs in common monetary units, 'intangible' costs such as discomfort being evaluated on the basis of the patient's expressed willingness-to-pay to avoid such events.

The 'effectiveness' part of cost-effectiveness refers to outputs, achieved as a result of surrendering the inputs. Several methods for measuring medical outcomes of alternative therapies exist. The simplest quantitative measure is survival, or expected life-year gains following intervention, and an intervention which produces more expected life-years than the alternatives is deemed the most effective. Second, one could assess outcome on the basis of changes in the patients' 'quality of life', using validated questionnaires.[3–7] Third, one could employ clinical criteria, for example, biological changes in disease progression as a result of intervention. Finally, it would be possible to attach monetary valuations to outcomes in terms of the patients' willingness to pay, were medical care to be provided on a purely private basis. The choice of outcome measure lies with the investigator, the only requirement for a comparison being that the measure is common to all the alternatives under investigation. Life-year gains can only be compared with life-year gains and not with quality of life.

Cost-effectiveness is central to the discipline of economics, which has the fundamental axiom—'more output is preferred to less, other things remaining equal'. Theoretical solutions to economic problems involve determining how to maximize output from given inputs or, alternatively, how to minimise inputs to achieve a given output. The business of economics is determining the best way of allocating or rationing scarce resources. We may state the matter more formally. Suppose there exist two alternative interventions, A and B. The former costs C_A and yields outcome gains Q_A, whilst the latter costs C_B and yields Q_B. The cost-effectiveness ratios are given as C_A/Q_A and C_B/Q_B, respectively. The intervention with the lower ratio is the more cost-effective, because its costs are lower per unit

of output gained. Put another way, if the ratio of A's to B's outputs, Q_A/Q_B exceeds the ratio of A's to B's costs, C_A/C_B, then A is the more cost-effective intervention. Expressed thus, it is clear that relatively expensive treatments may still be more cost-effective than cheaper ones, if they are capable of producing disproportionately more output.

It is important to appreciate that demonstrating one particular intervention to be more cost-effective than its alternatives does not automatically imply that it should be undertaken. Even the most cost-effective therapy still costs, and society or government might deem these costs unaffordable, irrespective of the outcomes obtained.

Although presented quite formally above, it is evident that cost-effectiveness is equivalent to the commonplace notion of 'value for money'. In exhorting the health service to offer value for money, *Working for Patients* was essentially asking health service management to be cost-effective, to obtain the best possible health outcomes from the limited budget. At a national level, this makes obvious economic sense. However, in the post-1990 world of devolved budgets and competition between providers, cost-effectiveness makes sense at the level of the individual hospital and department. Purchasers of services will themselves have an eye towards value for money when placing their contracts for care.

PROCEDURE FOR COST-EFFECTIVENESS ANALYSIS

All cost-effectiveness evaluations involve three stages. First, the investigator defines the frame of reference and, second, maps the interventions being considered as a sequence of cost and outcome events. Finally, the relevant costs and outcomes associated with these events are estimated.

Costs and outcomes are not impersonal; the former are incurred by someone and the latter accrue to someone. Defining the frame of reference involves identifying the 'someones' to include in the analysis. With the complex therapies involved in the treatment of cancer, many distinct groups have an interest. Most obviously, patients are likely to incur some costs and obtain therapeutic benefits, yet the same could well be true of informal care providers—family and friends. The formal care providers—hospitals—are likely to bear the brunt of the direct costs for most cancer therapies, yet these costs also fall eventually on taxpayers, whose contibutions fund the National Health Service. Responsible not only for health spending but for all other forms of social support, the Exchequer has a concern about the overall costs of interventions. For example, early discharge from hospital into the care of the social services might lower the therapy costs from the point of view of the hospital but raise them overall from the point of view of the Exchequer. Finally, some costs and benefits are clearly borne by society in aggregate. Early patient death, for example, impacts not only on the patient's family but on the economy as a whole, in terms of the gain in national production which that person, had he or she survived, might have contributed.

The frame of reference for a cost-effectiveness evaluation defines the parties whose costs and outcomes are deemed relevant. All such evaluations have such a frame defined, implicitly or explicitly. If, as is common, the frame of reference is that of the formal care provider, all costs incurred by other agents are ignored. In the case of an evaluation of therapy for childhood cancer, this means that we disregard all costs incurred by the patients' families, even though we know these

TABLE 1
Costs (negative) of premature mortality (£'000) from various causes

	Exchequer	*Society*
All causes, >28 days	−4.5	−521.5
All neoplasia	39.1	−540.6
Neoplasia by site: Digestive organs	84.7	−412.0
Bone, skin, breast	113.1	−423.3
Genitourinary	76.0	−390.3
Lymphatic	−185.7	−1,085.2
All other neoplasms	−44.1	−743.5
Diseases of circulatory system	89.3	−259.6
Injury and poisoning	−1,599.0	−4,572.3

to be considerable.[8–9] Moving to a broader frame of reference would require such costs to be included in our estimates.

A graphic illustration of the consequences of different frames of reference is provided by the data in the Table, which are estimates of the monetary cost of premature mortality from various diseases. To obtain the data, life-years lost as a result of death were first derived by combining age-specific mortality with normal life expectancy.[10] Society's interests are taken to be the loss of the value of production resulting from premature mortality, and the costs were obtained by combining life-years lost by age with age-specific current unemployment rates and discounted average wages. As far as the Exchequer is concerned, premature mortality means lower spending on public education (for the young), lower unemployment benefits (for the middle-aged unemployed) and a lower pensions bill (for the elderly), although taxes collected from those who would have been in work have to be foregone.[11–15] The point of these data is *not* to inform what should or not be done with respect to saving life, but simply to demonstrate that cost estimates under the two frames of reference are quite different. In general, death from any cause is much less costly to the Exchequer than it is to society, because of the net reductions in social welfare spending. Not surprisingly, the cost of premature mortality is greatest for the conditions which include a high proportion of young people, such as lymphatic cancer and injury and poisoning. On the other hand, the data suggest that curing a case of breast cancer could involve the Exchequer in considerable additional spending.

One further example of the frame of reference issue is merited. Suppose that a hospital wishes to demonstrate the cost-effectiveness of its therapies by reference to a quantitative outcome measure, such as survival gains. It accordingly confines its cost-effectiveness evaluations to this parameter. As a New England study on therapy for laryngeal cancer has demonstrated, however, patients may give priority to other outcomes.[16] In this study, patients were offered a choice between laryngectomy, with loss of normal speech, and radiation therapy, with speech preservation but much inferior life expectancy. A significant minority opted for the latter therapy. Information of this nature demonstrates that, not only might the outcome perspecitve of patients differ from that of other decision makers in the system, but that patients as a group might not hold a uniform view on the value of a particular outcome.

There is nothing wrong or right about a given frame of reference. In practice, it is likely that the frame will be chosen to represent the interests of the party

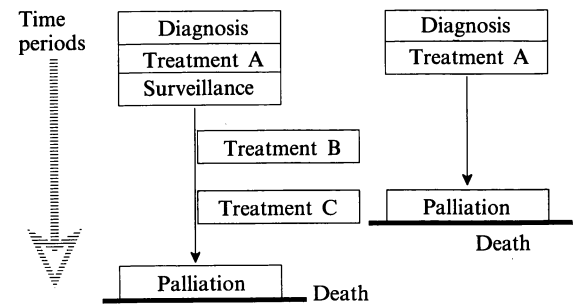

FIGURE 1
Event mapping for two alternative interventions.

who is requesting the evaluation. The crucial point to bear in mind is that the results of an evaluation only have meaning within the pre-specified frame of reference; what is cost-effective under one frame might well be cost-ineffective under another.

The second stage in cost-effectiveness analysis involves mapping the cost and outcome events over time, for individual patients or for groups of patients if an homogeneous group can be defined. The Figure presents such a mapping for two hypothetical courses of action. One entails more treatment episodes with a longer life expectancy. Mapping essentially tells us what happens during the intervention and when it happens, and is essential in auditing the events with which costs and benefits must be associated. The time framework provides the structure for the discounting of future costs to present values.

SOME EXAMPLES

To illuminate the points made above, I shall describe some examples of cost-effectiveness from the recent medical literature. A useful starting point is the comparison of bone marrow transplantation with conventional chemotherapy in the treatment of acute nonlymphatic leukemia.[17] The frame of reference for this study was the one most widely used in cost-effectiveness, namely, hospital costs and patient survival benefits. The former comprised the costs of routine ward care, laboratory tests, radiological procedures, and the use of intensive care and operating theatre facilities. Mappings of the two interventions revealed that the chemotherapy group of patients had more hospitalisations over five years, but spent less time on average in intensive care. Five-year average costs for the transplantation group were 42 per cent higher than for the chemotherapy group ($193,000 and $136,000, respectively), virtually all of the cost difference occurring within the first six months of therapy. However, after five years, the average costs per life-year saved of the two interventions were virtually equal ($62,500 and $64,000, respectively), owing to the superior rate of disease-free survival in the transplantation group. Transplantation is thus revealed as a therapy significantly more costly, but no less cost-effective, than chemotherapy.

A comparison of the use of interferon (IFN) alfa-2b with chlorambucil in the treatment of hairy cell leukemia[18] reveals that the use of expensive drugs need not imply expensive treatments from the provider's point of view. Courses of the former drug were estimated to be over eight times more costly than those of the

latter, per patient per year ($3,364 and $414, respectively). However, the use of IFN, as opposed to chlorambucil, was found to significantly reduce the requirement for (and thus the costs of) transfusions, inpatient and outpatient antibiotic treatments and splenectomy. Taking these additional direct costs into account, IFN therapy was discovered to be considerably cheaper, per patient per year, than therapy using chlorambucil ($5,027 and $14,046, respectively). Additionally, the IFN-treated patients exhibited greatly-increased survival expectancies, implying that such patients generated lower social costs in terms of losses of future production owing to premature mortality. In fact, the disparity between such indirect costs was even more marked than that between direct costs (at $4,771 and $63,507, per patient per year, respectively). On the basis of the published evidence, IFN is revealed as a particularly cost-effective therapy.

Finally, a Canadian study of appropriate strategy of diagnosis for tumour site[19] illuminates an important concept in economic valuation, namely, incremental or marginal cost. Traditionally, when a patient presents with a carcinoma of unknown primary origin, a comprehensive series of investigations is carried out to locate the primary site. Many of these, it is argued, are painful or distressing to the patient, costly and have a low success rate. Moreover, whilst tumours in some sites can be treated successfully with systemic therapy, those in others are typically unresponsive. In the event of the site not being found after comprehensive investigation, the available therapy options are broad-spectrum chemotherapy or symptomatic care. As an alternative to this comprehensive investigation scenario, the authors proposed a more limited regimen, whereby the physician only attempts to locate and identify those primary tumours for which relatively successful systemic therapy exists. In the event of failure to detect using the limited investigation, the patient is then allocated to broad-spectrum chemotherapy or symptomatic care, as before.

The study was a meta-analysis for a nominal 1000 patients, using literature results for site distribution and patient survival. The authors concluded that, using limited investigation followed by symptomatic therapy when the site is not found, 110 patient-years would be gained at an annual cost of $761,000. On the other hand, 115 patient-years would result from comprehensive investigation followed by broad-based chemotherapy when the site is not found, at a cost of approximately $8·6 million. The second scenario thus provides five additional patient-years at an additional cost approaching $8 million, i.e. a marginal cost per patient per year of approximately $1·5 million. It is not, of course, the economists's function to determine whether such a cost should be afforded in creating life-year gains. The point is to alert clinicians and medical managers to the economic implications of their decisions. In this case, the additional life-years would be purchased at a particularly high rate, and there exist many other interventions offering equivalent gains at considerably lower cost.[20]

MORAL OF THE TALE

As stated in the opening section of this paper, cost-effectiveness analysis has come to play an important role in clinical research. In the future, its role will increase, as health agencies wrestle with the problems of cost-containment, resource rationing and priority-setting. Accordingly, I conclude this paper with four general points, part-summary and part-warning.

First, the health economist has on occasion been portrayed as the enemy of the clinician, by those who are concerned that economic considerations will come to take precedence over clinical matters in choice of therapy. This criticism is only partly justified. There is no question of the usurping of roles through cost-effectiveness analysis. Having no specific expertise in medicine, economists require the medical parameters of all interventions under investigation to be laid out by clinical specialists. Mappings such as those of Figure 1 are derived from observation of practice and medical advice; they are only 'economic' in the sense of having measured costs and outcomes associated with them. Good cost-effectiveness analysis is therefore obliged to work within a framework established by clinicians and, indeed, the best cost-effectiveness studies invariably result from strong economist/physician collaboration at all stages of the research programme. This having been said, it is possible for the economist to conclude that a particular form of therapy favoured by the clinician is not cost-effective, and this information might be employed by management to attempt to constrain clinical freedom. Whether or not this represents a source for concern depends upon our criteria for rationing resources, a point we shall return to shortly.

Second, cost-effectiveness evaluations always have a specific frame of reference and it does not follow that cost-effectiveness under one frame of reference equates with cost-effectiveness under another. Most importantly, for a given health outcome, it is inevitably more cost-effective from the point of view of one agent, if someone else foots the bill. As budgets within the NHS are developed, issues of this nature will become increasingly significant. Patients with chronic diseases will encounter multiple care providers, for example, the family, the general practitioner, the hospital, hospice and local authority social services. The global optimum might involve one agency bearing the lion's share of costs. It is clear that the evaluation of global cost-effectiveness will require the broadest frame of reference.

The development of good cost-effectiveness evaluations on the basis of collaboration between economists and clinicians is of paramount importance. It this task is not undertaken, it is likely that planning decisions will be made on the basis of cost alone and there are good grounds for believing that low cost treatments *per se* are not necessarily the most cost-effective. The interferon example is a case in point, but further examples are commonplace. In a study of 99 Illinois hospitals,[21] the researchers detected a significant negative association between the stage of breast cancer at time of diagnosis and oncology charges in each hospital. Specifically, hospitals charging less for oncology services typically detected cancers at a later stage. Given that cancer staging at detection is a predictor of survival outcome, it is evident that, across these hospitals, higher price generally meant higher effectiveness. In a study of lumpectomy *vs* mastectomy for breast cancer,[22] the direct treatment costs of the latter were revealed to be significantly lower than those of the former. The authors express concern that, as, in their clinical view, mastectomy is far less satisfactory for many patients, purely-financial considerations could require that patients receive the inferior therapy.

Finally, it is pertinent to state that, health economics is, like medicine, only a partially-exact science. Both the medical and the economics professions suffer at the hands of outsiders, intent on picking holes in their procedures. Just as medicine has failed to come up with the definitive therapy for the majority of complaints, so the majority of cost-effectiveness evaluations embody assumptions

or conjectures which make them less than perfect. The remedy in both cases, however, is the same; not to abandon the exercise on the grounds that it fails to produce perfect results, but simply to try harder. The question to ask of health care resource allocation of the basis of the cost-effectiveness criterion is not: 'In what respects is this particular method less than perfect?' but, rather, 'Would *any other* criterion for resource allocation produce better solutions than those resulting from the use of cost-effectiveness analysis?' 'Better' is, of course, a subjective notion and all evaluation criteria (cost-effectiveness included) are essentially subjective. Other possible criteria for the rationing of health care resources are:

1) allow potential patients to form a queue, and then treat first those who have waited the longest, irrespective of costs or potential outcomes of treatment;
2) as above, except that those who recklessly disregard their own health, such as cigarette smokers, drug addicts or alcoholics, are placed automatically at the end of the queue;
3) organise a lottery, with the lucky ones being treated and the unfortunate ones being sent home untreated;
4) NHS resources flow to those areas in reciept of the strongest attention in the mass media;
5) clinicians discriminate against less productive members of society and restrict care to those deemed socially-useful;
6) society is stratified into age/sex/ethnic/etc. cohorts and each cohort gets a share on NHS resources, irrespective of disease, treatment costs or outcomes;
7) replace the NHS by fully-private medicine and ration health care by ability to pay.

I leave it to the reader's judgement as to whether such rationing criteria represent an improvement on cost-effectiveness.

REFERENCES

[1] CM 555. Working for Patients. London: HMSO, 1989.
[2] CM 1523. The Health of the Nation. London: HMSO, 1991.
[3] Aaronson NK, Ahmedzai S, Bergman B *et al.* The European Organisation for Research and Treatment of Cancer QLQ-30: a quality-of-life instrument for use in international clinical trials in oncology. *J Int Cancer Inst* 1993; **85** (5): 365–76.
[4] Clark A, Fallowfield LJ. Quality of life measurements in patients with malignant disease: a review. *J R Soc Med* 1986; **79:** 165–9.
[5] De Haes JCJM, Van Knippenberg FCE. The quality of life of cancer patients: a review of the literature. *Soc Sci Med* 1985; **20:** 809–17.
[6] Selby P. Measurement of the quality of life: the particular problems of cancer patients. In: Hopkins A, ed. Measures of the quality of life. London: Royal College of Physicians of London, 1992: 91–104.
[7] Walker SR, Rosser RM, ed. Quality of life assessment: key issues in the 1990s. Dordrecht: Kluwer Academic Publishers, 1993.
[8] Lansky SB, Cairns NU, Clark GM, Lowman J, *et al.* Childhood cancer: nonmedical costs of an illness. *Cancer* 1979; **43:** 403–8.
[9] Bodkin CM, Pigott TJ, Mann JR. Financial burden of childhood cancer. *Br Med J* 1982; **284:** 1542.
[10] Office of Population Censuses and Surveys. Mortality Statistics: Cause, England and Wales, Series DH2, No. 19. London: HMSO, 1993.
[11] Employment Gazette 1993; **100** (11): S54.
[12] Chartered Institute of Public Finance and Accountancy. Education Statistics, 1992–93 Estimates. London: CIPFA, 1992.

[13] Department of Social Security. Social Security Statistics. London: HMSO, 1993.
[14] Office of Population Censuses and Suveys. Labour Force Survey, 1990 and 1991, Series LFS No. 9. London: HMSO, 1992.
[15] Whynes DK. Welfare State Economics. London: Heinemann Educational, 1992.
[16] McNeil BJ, Weichselbaum R, Pauker SG. Speech and survival: tradeoffs between quality and quantity of life in laryngeal cancer. *N Engl J Med* 1981; **305:** 982–7.
[17] Welch HG, Larson EB. Cost effectiveness of bone marrow transplantation in acute nonlymphocytic leukemia. *N Engl J Med* 1989; **321:** 807–12.
[18] Ozer H, Golumb HM, Zimmerman H, Spiegel RJ. Cost-benefit analysis of inerferon alfa-2b in treatment of hairy cell leukemia. *J Int Cancer Inst* 1989; **81:** 594–602.
[19] Levine MN, Drummond MF, Labelle RJ. Cost-effectiveness in the diagnosis and treatment of carcinoma of unknown primary origin. *Can Med Assoc J* 1985; **133:** 977–87.
[20] Jennett B, Buxton M. When is treatment for cancer economically justified? *J R Soc Med* 1990; **83:** 25–8.
[21] Hand R, Sener S, Imperato J, Chmiel JS, *et al.* Hospital variables associated with quality of care for breast cancer patients. *Journal of the Am Med Assoc* 1991; **266:** 3429–32.
[22] Munoz E, Shamash F, Friedman M, Teicher I, Wise L. Lumpectomy *vs* mastectomy: the costs of breast preservation for cancer. *Arch Surg* 1986; **121:** 1297–1301.