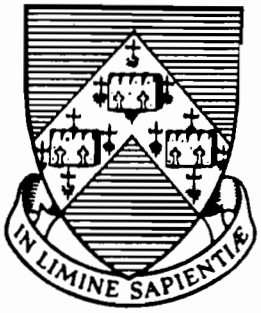

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Economic evaluation of Pharmaceuticals:

Science or marketing?

by Michael Drummond

DISCUSSION PAPER 91

University of York

Centre for Health Economics

ECONOMIC EVALUATION OF PHARMACEUTICALS: SCIENCE OR MARKETING?

by

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October 1991

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Acknowledgements

The Centre for Health Economics receives funding from the European Community for a Concerted Action on the Methodology of Economic Appraisal of Health Technology, of which Professor Drummond is Project Leader. The Centre also receives a gift from the Merck Company Foundation for exploring the methodological issues in undertaking economic evaluations alongside clinical trials. I am also grateful to Vanessa Windass for secretarial assistance.

An earlier version of this paper was presented at the Seventh Annual Meeting of the International Society of Technology Assessment in Health Care, Helsinki, June 26, 1991 and I am grateful for comments received.

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ABSTRACT

The increased pressures on health care budgets have emphasised the need to demonstrate the value for money from health technologies. Most major pharmaceutical companies have therefore commissioned cost-benefit or cost-effectiveness analysis of their products. There is an assumed analogy between clinical trials, which are required for product licensing, and economic evaluations, which would help in justifying price and securing reimbursement. In most countries it is the responsibility of the pharmaceutical companies to provide adequate data on efficacy and safety, which is monitored by government. Cost-effectiveness data is only required by government in a few countries, although in others, including the United Kingdom, the pharmaceutical industry is being encouraged to provide such data for its products. Although clinical trial data are used in the marketing of products, they are usually perceived as scientific data in support of licensed indications. It is not clear whether the same is true for economic evaluation data, which may be more open to interpretation. This paper explores the extent to which the analogy between clinical trials and economic evaluation really applies. It considers whether there is a greater potential for bias in economic evaluations, whether the use of economic evaluations for price setting raises any ethical concerns, whether clinical endpoints are any 'harder' than economic endpoints and whether there is a need to set methodological standards for economic evaluation and to develop methods for scrutinizing the results of studies. It is concluded that, in principle, there should be no more bias in a well-conducted economic evaluation than in a clinical trial. However, economists need to improve the methodological standards of economic evaluations. Priority should be given to basing studies on good medical evidence, making measurements rather than assumptions where feasible, applying conventional tests of statistical significance and improving methods of quality of life measurement. Pharmaceutical sponsors should view economic evaluations as science, although, given the increased interest in value for money, such studies will also be useful in marketing and in encouraging a rational diffusion and use of medicines.

1. INTRODUCTION

The increased pressures on health care budgets in most countries have emphasised the need to demonstrate the value for money from health technologies. As part of this general change in the environment for the provision of health care, most major pharmaceutical companies have commissioned cost-benefit or cost-effectiveness analyses of their products. There is, therefore, an assumed analogy between clinical trials, which are required for product licensing, and economic evaluations, which are perceived as being useful for securing adequate prices and reimbursement status, and for marketing of products.

However, a major distinction between clinical trials and economic evaluations is that the former provide mandatory data which are monitored by government. Cost-effectiveness data are only required in a few countries (Commonwealth of Australia, 1990), although in others, such as the UK, the pharmaceutical industry is being encouraged to provide such data for its products (DH, 1990). Although clinical trial data are used in the marketing of products, both in advertisements and in detailing prescribers, they are usually perceived as scientific data in support of licensed product indications. Indeed, in many companies the medical director has to verify the authenticity of data and criminal proceedings could follow if false declarations are made. By contrast, the same standards may not be applied to economic data, neither within the pharmaceutical industry or by government through the independent scrutiny of studies. The production and dissemination of such data are often the responsibility of the company's marketing department, which may view them in the same light as other marketing tools. On the other hand, many economic evaluations of pharmaceuticals are undertaken by independent researchers in universities or consultancy firms, and are often submitted to peer-reviewed

journals for publication.

A recent paper in the New England Journal (Hillman et al., 1991) has noted this trend and raised some concerns about potential bias in the conduct and reporting of economic evaluations sponsored by pharmaceutical companies. The authors outline an ethical protocol for economic analysis and some guidelines for study methodology. These concerns are, to some extent, echoed by those clinical researchers and individual prescribers who have been exposed to economic evaluation results. By and large, the same individuals are comfortable with the conduct and reporting of clinical trials sponsored by pharmaceutical companies. Furthermore, a recent anonymous editorial in the Lancet (1991) highlighted the increasing use of economic data in pharmaceutical company promotional material, suggesting that it may be in contravention of the Medicines Act and that, in addition, the government staff overseeing promotion may not be competent to assess claims of cost-effectiveness.

Therefore, the objective of this paper is to explore the extent to which the analogy between clinical trials really applies. Are they both legitimate methods of technology assessment, or is one science and the other more akin to marketing? The following issues are addressed:

- is there a greater potential for bias in economic evaluations than in clinical trials?

- does the use of economic evaluations for price setting and marketing of pharmaceuticals raise any ethical concerns?

- are clinical endpoints any 'harder' than economic endpoints?

- is there a need to set methodological standards for economic evaluation and to develop methods for scrutinizing the results of studies?

2. SOURCES OF BIAS IN CLINICAL TRIALS AND ECONOMIC EVALUATIONS

There are three potential sources of bias in health technology assessment; in the choice of question for study, in the analytical methods used, and in the reporting of results.

2.1 Choice of study question

In choosing the question for study, the most fundamental issue in health technology assessment is to establish whether use of the technology is better than doing nothing. Most clinical trials of pharmaceuticals address this question through placebo controlled trials, which are usually required by licensing authorities. (Where it is unethical to give a placebo the acceptable therapeutic minimum is usually given to patients in the control group.) This works well up to a point, but even here it is not usually incumbent upon pharmaceutical companies to address issues broader than those pertaining to the licensed indications for their products. For example, it was not considered relevant for the manufacturers of a medicine (misoprostol) to prevent NSAID-associated ulcers, to demonstrate that the use of the NSAIDs themselves was justifiable (Graham et al., 1988).

Also, the focus on placebo-controlled trials for licensing often means that truly relevant clinical alternatives are not always compared in the same trial. For example, until the ISIS-3 trial of thrombolytic agents and aspirin was undertaken there was no

direct comparison of the agents concerned, merely controlled trials against placebo. Furthermore, in the reporting of clinical trials, it is customary to restrict comments to the therapies actually evaluated, rather than to speculate on how other therapies might have performed.

By contrast, the methodological standards for economic evaluation (Drummond et al., 1987) state that all relevant alternatives be considered. Therefore, unlike a clinical trial where comparisons are limited to the immediate treatments under study, an economic analyst could be accused of bias if he or she omitted any relevant alternatives. These could include the 'do nothing' alternative and other therapies for the condition concerned. He or she may also be accused of bias if appropriate margins, or increments, in the level or extent of therapy, are inadequately assessed. By contrast the dose of a medicine is often set in advance of a clinical trial, although some trials investigate the therapeutic effects of different dosages (Graham et al., 1988). Therefore, if anything, the requirement for examining a wide range of alternatives is more stringent for economic evaluation: an analyst deliberately restricting the range could be accused of bias, whereas a clinical researcher could merely be accused of lack of relevance.

At this point, it is relevant to consider the role of the sponsor of economic evaluations. Sponsors normally expect to provide funding to have their own questions answered. Should pharmaceutical companies be expected to provide funding to answer the questions of their competitors or the government? The answer is not straightforward, especially when addressing a wide range of issues does not serve the sponsor's direct interest. For example, it was mentioned above that in the case of misoprostol some argued that the use of NSAIDs should be evaluated. Also, in the evaluation of new cholesterol-lowering medicines, it has been suggested that the costs of case finding should also be assessed.

These issues, although relevant, are not necessarily the responsibility of one individual industrial research sponsor. However, one important function of the economic analyst is to convince the sponsor that, in the long run, examination of a relevant range of options is both in the societal interest and the sponsor's own interest. Limited evaluations may only provoke more questions from government or health care agencies, and allow competitors to place their own interpretation on study results.

Where cost-effectiveness studies are formally required by government, guidelines for the choice of comparators have been laid down (Commonwealth of Australia, 1990). This makes sense in terms of consistency, but may have both methodological and cost consequences. Since the relevant head-to-head clinical studies are not always available, the cost-effectiveness comparisons will have to be synthesized using clinical data from a number of studies. Also, analysis of a wide range of alternatives adds to study costs.

2.2 Study methodology

Most discussion of the bias in clinical research relates to choices in study methodology. It has long been recognized that the randomized controlled clinical trial (blinded where possible) is the best form of medical evidence (Sackett et al., 1985). In addition, it is usually argued that an 'intention-to-treat' analysis should be the basis of primary reporting of results. The statistical methods of controlled clinical trials have also greatly improved over the years.

In contrast, economic evaluation is relatively young in its development, only having been extensively practised in health care for about 20 years (Warner and Luce, 1982). The methodological standards laid down for economic evaluations (Drummond et al., 1987) require that these be based on good medical evidence. However, a practical problem often

arises when reliable data are not available. Generally speaking, economic evaluations of pharmaceuticals are likely to be based on better medical evidence than evaluations of devices, procedures or organizational measures, merely because clinical trials are more often carried out.

Another major difference between clinical trials and economic evaluations is that the latter explicitly incorporate value judgements. (However, the former are not value-free. Indeed, they often incorporate value judgements without being aware of the fact. This is discussed later.) The economic analyst's defence is usually that value judgements are made explicit. Also, the better evaluations often present a sensitivity analysis, where the impact on study results of different assumptions about key study parameters is explored. However, the choice of variables and ranges for the sensitivity analysis is itself a value judgement. Also, there is the irremovable distinction (in science) between the observed event (e.g. the patient died), the assumption (e.g. patients not dying will enjoy good quality of life for the duration of therapy) and the value judgement (e.g. costs and benefits occurring in the future should be discounted at an annual real rate of 5%).

Because of its relative adolescence, economic evaluation has some catching up to do. In particular, the challenge in the future will be to make fewer assumptions about variables that are, in principle, observable. In this respect considerable effort is being devoted to resolving the methodological problems of undertaking economic evaluations alongside clinical trials (Drummond and Davies, 1991). However, it should be remembered that measurement is not a costless activity: there may be occasions where an inexpensive (but defensible) assumption is preferable to an expensive study! One implication of the increased suspicion about pharmaceutical sponsored economic evaluations is that they may have to aspire to higher standards of measurement, even when this is not strictly required for the purposes of the study.

2.3 Reporting of results

Much has been written in the clinical research field about the under-reporting of negative study results. Although there may be some active suppression of results by individuals or organizations with a particular interest, the main culprit seems to be lack of interest in negative results, both on the part of investigators and journal editors. It has to be remembered that the sponsor of evaluations also plays an important role in the reporting of results, through providing funds to organize conferences and, on some occasions, for analysis of results and production of reports.

It is understandable that sponsors, be they industry or government, are more excited by some results than others. Therefore, the reporting bias is unlikely ever to be eliminated. Whether the bias is greater for economic, as opposed to clinical results, is currently unclear. However, as Hillman et al. (1991) point out, economist researchers should consider carefully any contract that forbids publication, unless the work is being carried out on a consultancy basis for the sponsor's information only. They also argue that, when projects are commissioned on a stepwise basis, the results of one stage should not be released until publication is guaranteed and funded. Firm rules on stepwise funding may be very difficult to operate in practice. In the clinical trials field, the sponsor would obviously want to know the results of a small, exploratory trial, before going on to fund a major study. Perhaps a concern is that there may be different intentions on the part of pharmaceutical companies on receiving negative (or equivocal) results from clinical and economic studies. In the case of negative clinical findings a company may not proceed with the development of the product concerned. In the case of negative economic findings the company may decide that no-one will find out and would press on regardless.

However, in an environment where value for money is an increasing concern, there

is always the possibility that someone else may undertake the economic study, be they the government, the company's competitors, or independent researchers. One important difference between economic evaluations and clinical trials is that in the former case the data are often readily accessible. In the latter case, if the investigators do not wish to release the data, no-one else can obtain access to them. Therefore, in the long run it is not clear whether suppression of economic study results will benefit anyone.

3. ETHICAL CONCERNS IN THE USE OF STUDY RESULTS FOR PRICING AND MARKETING OF PHARMACEUTICALS

The main concerns relate to the issues of bias outlined above. Unless economic evaluations are more subject to bias than clinical studies, there should be no additional concerns in their use in decision making. It was mentioned earlier that when clinical studies are formally required for product licensing, they undergo methodological scrutiny by the licensing agency. The same surely has to be true for economic studies submitted to pricing and reimbursement authorities. Perhaps the major suggestion here is for the agencies concerned to have access to the necessary competencies to assess studies properly.

The use of economic studies in the marketing of pharmaceuticals is a more complex issue. First, it should be pointed out that an individual prescriber is highly unlikely to be influenced by a cost-effectiveness argument that flies in the face of his or her clinical intuitions. However, if economic studies are to be used in marketing more often in the future, some effort should be directed to educating prescribers and other health professionals in economic evaluation methods. This would benefit their practice more widely. Also, it has to be said that some health professionals' knowledge of clinical trial methodology is far from perfect.

One residual ethical concern that economists would do well to dispel is the notion that they, or their analyses, are any less trustworthy than clinical researchers or their studies. This would be best established through the maintenance of high methodological standards and consistent attempts to publish in peer-reviewed journals.

4. RELATIVE 'HARDNESS' OF CLINICAL AND ECONOMIC ENDPOINTS

This was mentioned earlier in the discussion of study methodology. Basically, clinical trials give the appearance of having hard endpoints, usually supported by statistical analysis. (For example, it is common to see confidence intervals given for clinical endpoints.) By contrast, many economic evaluations report point estimates for costs and cost-effectiveness ratios, although some aspects of the uncertainty in estimates are often explored through sensitivity analysis. In addition, economic evaluations often consider outcomes in terms of improvements in the quality of life of patients, which are inherently more difficult to assess.

Where economic evaluations consider variables with an observable distribution (e.g. length of inpatient stay) there is no reason why the normal statistical tests of significance should not be applied. However, as Drummond and Davies (1991) point out, statistical tests on economic variables might require larger sample sizes in some situations. Also, difficulties arise when a number of observed economic variables are combined, through the application of relative prices, to give an overall cost estimate. It is not clear whether statistical tests should be applied to the individual physical resource quantities (e.g. number of physician visits), the individual cost items (e.g. the cost of physician services), or the total costs.

With regard to quality of life measurement, Buxton and Drummond (1989) argue

that, under closer observation, the distinction between 'hard' clinical endpoints and 'soft' quality of life endpoints does not hold up. Indeed, some clinical trials report statistical analyses of the proportion of patients who 'improve' in each group. However, one study of hypertension treatment demonstrated that whether or not a given patient could be said to have improved was largely dependent on whether this was assessed by the doctor, relative or patient him or herself (Jachuck et al., 1982).

Clinical trials embody many implicit value judgements in their selection and reporting of endpoints. For example, trials that concentrate on the easily measurable endpoints, such as survival, may be missing other relevant endpoints in terms of reduced morbidity or improved quality of life. In some cases, such as chemotherapy for end-stage cancer, there may be important trade-offs between length and quality of life. Therefore, the use of apparently 'soft' endpoints is not an inherent fault of economic evaluation. Rather, it is a recognition that the most easily measurable endpoint may not be the most relevant (Drummond, Heyse, Cook and McGuire, 1991).

However, there is still considerable debate about the endpoints used in some economic evaluations, in particular the quality-adjusted life-year (QALY) (Mehrez and Gafni, 1989; Loomes and McKenzie, 1989; Drummond, 1989). Therefore, it is important that economists recognize these controversies when reporting their results.

5. METHODOLOGICAL STANDARDS AND SCRUTINY OF ECONOMIC EVALUATION RESULTS

Much of the discussion above implies that economic evaluation would benefit from explicit methodological standards, especially when applied to pharmaceuticals. As pointed out earlier, some standards already exist. In addition, projects commissioned by the

European Community (Drummond, 1989) and the World Health Organization (Drummond et al., 1991) will assist in this process. In order to guarantee that evaluations sponsored by the pharmaceutical industry are free from bias, it is important that journal referees are well aware of the existing standards. In addition, the existence of methodological standards will minimize the chances that some individuals within the pharmaceutical industry will perceive economic evaluation just as a marketing ploy rather than as scientific enquiry.

Although mandatory economic evaluations are some way away in most countries, studies submitted to decision makers (such as hospital managers, pharmacists, and formulary committees) are likely to come under greater scrutiny by an increasingly sophisticated audience. This is in addition to the scrutiny of studies by competitors (or their advisers) and journal referees.

6. CONCLUSIONS

Given the increasing concerns about the value for money from health care interventions, pharmaceutical companies are likely to continue their sponsorship of economic evaluations. Much can be learned from the largely successful industrial sponsorship of clinical trials. This paper has considered the potential sources of bias in health technology assessment and illustrated both the parallels and differences between clinical trials and economic evaluations. One message is clear. Maintenance of good methodological standards is, in the long run, the best policy both for pharmaceutical industry sponsors and economic analysts.

Economists can play their part by working to improve the methodological standards of economic evaluations of pharmaceuticals. In particular, priority should be given to

basing studies on good medical evidence, applying conventional tests of statistical significance to study results and to improving methods of quality of life measurement.

Pharmaceutical sponsors of studies should consider economic evaluations as science rather than just a marketing ploy, particularly if they wish to see their studies being published in learned journals and being taken seriously by health care decision makers. However, since economic evaluations address the important issue of value for money they are also likely to be increasingly in the marketing of pharmaceutical products and in encouraging the rational diffusion and use of medicines.

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