

GUIDELINES FOR THE ECONOMIC EVALUATION OF PHARMACEUTICALS:

Can the UK learn from Australia and Canada?



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Foreword

Adrian Towse

Getting value for money from the use of pharmaceuticals is crucial for the NHS. This publication explores the role for guidelines in generating good quality value for money information examining the experience of Australia, Canada and the UK – the first three health care systems to introduce national guidelines for economic assessments.

Some commentators^{1,2} have argued that the UK is lagging behind Australia and Canada by linking guidelines to a voluntary approach to the supply of economic information, rather than introducing rigorous guidelines and (in Australia and Ontario) a formal requirement for studies to assess the cost effectiveness of new medicines. A number of issues arise for the UK. Some relate to whether differences between health care systems require different approaches, notably whether:

- the lack of NHS policies on rationing mean that it is better to concentrate on other means of getting value for money from pharmaceuticals;
- the decentralised nature of NHS decision making requires a less prescriptive approach to guideline content and study requirements;
- given this decentralised approach, enough high quality economic information on pharmaceuticals is being supplied and used in the NHS?

Others relate to the content and process of developing guidelines. In particular whether:

- more detailed guidelines are needed to enable comparisons between study results to be made;
- the process by which guidelines are drawn up is important to their effectiveness.

The publication examines the workings and impact of the Australian and Canadian Guidelines. The key elements of the UK prescribing environment are then examined, including existing value for money arrangements, the role of the UK Guidance, the way in which the UK promotional code of practice polices economic information, the methodological issues involved in complying with the UK Guidance, and the role of the UK NHS CRD in reviewing economic evaluations. An overview concludes that, in relation to system design:

1 Freemantle, et al. Promoting cost effective prescribing. Britain lags behind. *BMJ*, 1995; 310:955-6.

2 Ferner R E, Newly Licensed drugs. Should be put on probation until their value is demonstrated. Editorial. *BMJ*, 1996; 313:1157-8.

- economic evaluations are having much more impact on prescribing expenditure in Australia and Canada;
- the NHS, however, has much better arrangements for getting value for money from medicines;
- lack of explicit rationing criteria limit the use of economic evaluations in all three countries, but much more so in the NHS;
- barriers to moving funds between health care budgets, rather than lack of information, are seen by NHS decision makers as the major obstacle to greater NHS use of economic evidence;
- the credibility of studies remains an issue although the NHS has put in place arrangements, including the NHS CRD database and the ABPI/ Government guidance, to raise quality.

In relation to the content of guidelines and the process of development;

- guidelines can only be more prescriptive if decision makers are clear about the information they want, and the perspective they intend to take;
- methodological issues remain unresolved which will mean continued debate on choice of design, outcome measures and sources of evidence.

Perhaps the most important message is that there should be more use of information from economic studies in the UK, but the experiences of Australia and Canada do not suggest that there is an easy route to achieve this. We do not know how cost-effective the approaches of the three countries are. We do know that changing the culture of a health care system takes time. Guidelines can play an important part in stimulating change.

In the UK there is some way to go. The NHS and the pharmaceutical industry need to review progress. To the extent, however, that public and medical attitudes to rationing are reflected in the government's policy that patients continue to receive all medicines they clinically require, the role for economic evaluation may be limited. Value for money may be more effectively sought through other routes. Continued financial constraints, however, together with the growing role for GPs in purchasing, may lead to greater use of clinical and prescribing guidelines and of research into local outcomes. Economic evaluation may be more readily accepted when contributing to these activities.

1 THE AUSTRALIAN COST-EFFECTIVENESS GUIDELINES: AN UPDATE

Michael Drummond and Michael Aristides

INTRODUCTION

6 In January 1993 the Commonwealth government of Australia became the first jurisdiction to require the submission of economic data in support of requests for reimbursement (public subsidy) of pharmaceutical products. The submission of data must be in accordance with guidelines that were first issued in draft form in August 1990 and subsequently revised in August 1992 and November 1995^{1, 2}. The guidelines give detailed specifications for the types of clinical and economic data required, the analysis of such data and the presentation of results. The contents page and main requirements are set out in the appendix to this chapter. They are supplemented by the production (by the Commonwealth government) of standard cost data to be used in the calculations. In making the submission the applicant company has to state what price it feels the product should have and to make its economic calculations accordingly.

Under the guidelines, submissions are made to the Pharmaceutical Benefits Advisory Committee (PBAC) and are evaluated by government officials in the Pharmaceutical Evaluation Section. The PBAC recommends that the Minister (of Health and Family Services) either does or does not list the product on the Pharmaceutical Benefits Schedule (PBS). (The PBS is a positive list of around 1,200 drug items approved for reimbursement for community use. It includes around 530 distinct chemical entities.) The PBAC also determines the indications for use on the PBS of a given product and can restrict the indication(s) for public funding within the approved indications for marketing in Australia. Further, the PBAC will advise whether the drug is cost-effective or not at the submitted price and may advise a range within which the drug would be cost-effective. This advice is provided to a separate body that advises the Minister on price, the Pharmaceutical Benefits Pricing Authority.

In essence the Australian guidelines represent the first case of the 'fourth hurdle', whereby economic data are required in addition to those of efficacy, safety and quality of manufacture. Whilst issues of reimbursement are kept separate from those of

licensing (which are dealt with by a separate committee), public subsidy is an essential requirement for the successful marketing of most products. Therefore, the Australian guidelines are important since they may provide a template for other countries (or jurisdictions) considering similar measures.

The existence of methodological controversies in economic evaluation has led to a debate about whether these analytical approaches are sufficiently well-developed to be useful in decision making³. In the case of the Australian guidelines it has to be remembered that listing decisions were made prior to their existence. Therefore in one sense the guidelines merely represent a formalisation and a clarification of a procedure that was already in place. However, in another sense, the guidelines represent a shift to an 'evidence-based' model of decision-making, from one that could be described as opinion-based. Now clinical and economic claims are critically assessed in the light of the evidence presented.

Despite its problems, economic evaluation is the only way of assessing the relative value for money from health care interventions and it is likely that, in listing drugs on formularies, all committees go through such a process, albeit informally. Thus the key question is whether the more formal process embodied in the guidelines offers the potential to make more informed listing decisions than was previously the case.

HOW DOES THE PROCESS WORK?

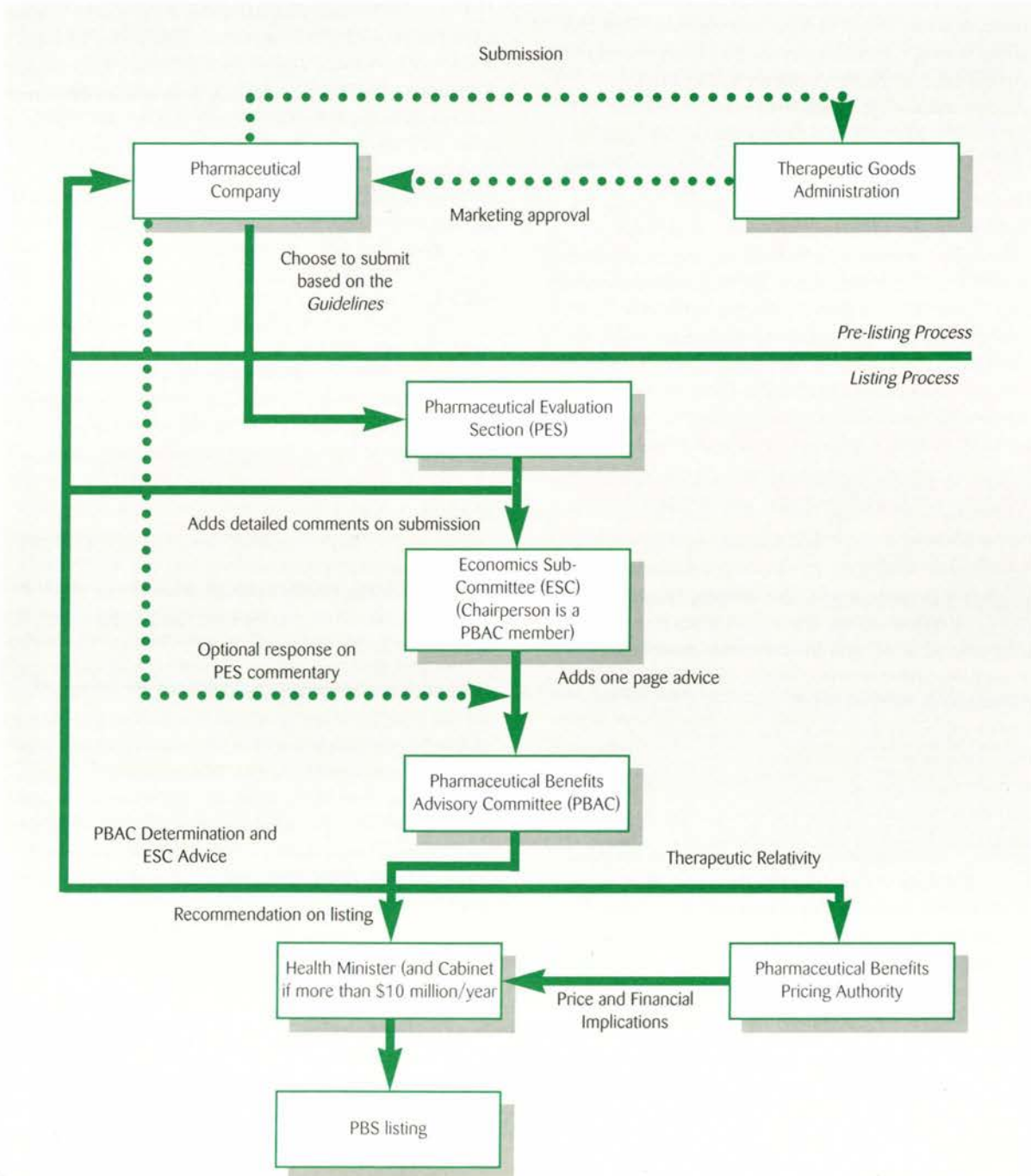
The process of making and considering a submission is outlined in Figure 1. There are currently four submission deadlines per year. Unlike licence applications, the time taken to process PBAC submissions is not open-ended, since the Committee guarantees that any submission made by a given deadline will be considered at the next PBAC meeting (usually around 11 weeks from submission). This is important since the addition of a 'fourth hurdle' should not be seen to add significantly to the 'drug lag'. Of course, the fact that a submission will be considered at the next meeting does not guarantee

a resolution of the application for reimbursement. It is common for submissions to be deferred, or referred back to the company for more information.

Technical criticism of submissions is provided by or through government officials in the Pharmaceutical Evaluation Section. These comments, along with the manufacturer's submission is reviewed by the

Economics Sub-Committee of the PBAC. The sub-committee's membership comprises academics in health economics, clinical epidemiology and biostatistics and includes three members of the parent committee (one of whom is the chairperson of the Sub-Committee), as well as an industry nominee. The Sub-Committee advises the PBAC on each

Figure 1 Submission and review process under the Australian guidelines (Glasziou and Mitchell, 1996)



submission in terms of the clinical comparisons, the quality of the data/analysis and the appropriateness of assumptions and models used.

To date, submissions have been prepared by companies in-house, or with help from academic researchers and other consultants. The PBAC takes no view on the method of preparing submissions and bases its judgement solely on the quality of the submission itself. Given the new challenges posed by the guidelines, companies are able to seek advice from the Pharmaceutical Evaluation Section on the structure and content of their submissions. This advice is made available on the condition that it is non-binding. If the PES's advice is disputed, companies may approach the PBAC for advice, particularly in the choice of comparator drug to be used in the analysis. This advice is also non-binding.

The fact that advice is non-binding could be problematic if a company were to make a major investment, perhaps in a clinical trial with economic endpoints, for the purposes of a PBAC submission, only to find that the PBAC subsequently ruled that the wrong approach had been used, or that new information had made the approach obsolete. In all major submissions since 1991 the PBAC disagreed with the comparator nominated on 31 out of 241 occasions. Of these 31 disagreements, the company had not sought advice on 29 occasions, and on the other 2 the company had not followed the advice given.

Up until the end of 1994 there had been 133 submissions under the guidelines, including the voluntary period. Nearly half of these (44 per cent) were cost-effectiveness analyses. Just over a quarter (28 per cent) were cost-minimisation analyses; in these cases there was no clinical difference to justify a difference in price. A small proportion (2 per cent) were cost-utility analyses. The remaining submissions were qualitative rather than quantitative in nature and included incompletely constructed cost-effectiveness analyses and requests for price premiums based on theoretical clinical advantages⁴.

The popularity of cost-minimisation or cost-effectiveness analysis may reflect either the lack of data or the lack of expertise to undertake cost-utility or cost-benefit analysis. For example, if only short-term efficacy data are available, or if no quality of life data were collected alongside clinical trials of the product, analyses will be limited accordingly. Therefore it will be interesting to see whether the relative balance of types of analysis changes in the future, now that companies know what is required and have the opportunity to collect relevant data alongside their clinical trials. On the other hand, companies may be responding to the fact that the PBAC discourages cost-benefit analyses and studies that make large numbers of assumptions beyond the available data.

WHAT ISSUES HAVE ARISEN?

Practical issues for industry

The guidelines have had a number of practical implications for industry. First, the selection of the appropriate comparator therapy, to the drug of interest, has not proved straightforward in all cases. The guidelines state that a comparison should be made with the therapy that the new drug is most likely to replace. This was intended to be a pragmatic request to reveal the main impact of the applicant drug on the cost-effectiveness of treatment and to discourage overly complex submissions with multiple evaluations using multiple comparators¹. However, in some cases more than one commonly used treatment may be replaced and the selection of one that is marginally more common can be misleading. In other cases therapeutic practices may be changing over time, owing to the development of new therapies.

Therefore the company needs to decide whether to compare its drug with the most widely used therapy today, or with the one that it thinks might be the therapy of choice in three years' time when its new drug will be launched. This decision is potentially flexible if the economic evaluation is to be undertaken by synthesising evidence from a number of sources, including existing clinical trials (i.e. a modelling study). That is, new comparators can be added or substituted if the situation changes late in the development process. However, if a trial-based economic evaluation is to be conducted, the final selection of the comparator may need to be made well in advance.

Although head-to-head comparisons are preferred, the revised guidelines suggest an analysis of two sets of head-to-head trials with a common reference (such as placebo) to assess incremental outcomes². This data can be used in the absence of conventional head-to-head data or as a supplement, where, for example, head-to-head trials lack statistical power. However, claims of superiority using this approach are less likely to gain acceptance.

Secondly, existing clinical evidence may not form a suitable basis for the economic evaluation. For example, the drug may not have been compared, in head-to-head studies, with the relevant alternative. Also, comparisons may be hard to interpret if existing trials of the relevant drugs have been performed on different patient populations, or using different treatment protocols, or with measurements of different endpoints.

Furthermore, even if the relevant comparisons have been made, the clinical trials may be of short duration or only have measurements of surrogate

endpoints. As more experience is gained with applying the guidelines it is becoming increasingly apparent that the standards sought in the clinical data required for economic evaluation are often more exacting than those required for licensing decisions. This is because value for money assessments are always *comparative* and because assessments require information about *final endpoints*. Comparative assessment requires a relatively precise measure of the size of the differences between treatments, rather than merely whether one is superior to another. This in turn requires greater statistical power (for narrower confidence intervals) and a greater need for head-to-head studies. Final endpoints are often harder to measure, or practically impossible to measure, because of other potential confounding factors and the need for long-term follow-up.

In addition, since many clinical trials are performed under atypical conditions, the data may not be easily used for economic evaluations without adjustment. The alternative, of performing more 'naturalistic' trials, where the protocol more closely reflects regular practice, may be time-consuming and costly.

Thirdly, some possible economic advantages of a new drug may be difficult to demonstrate to the standards required by the PBAC. Items in this category include improved productivity (at work) and the benefits of improved compliance.

Practical issues for government

An obvious difficulty for government has been the resource commitment required to evaluate submissions satisfactorily. The Pharmaceutical Evaluation Section has expanded and, in addition, the time spent by members of the Economics Subcommittee and PBAC itself is not inconsiderable. Therefore ways have been sought to streamline the process.

Another issue facing government has been the demand for increased transparency in the decision making process. This was always likely to be a consequence of the guidelines⁵ and it has now been agreed that applicant companies will receive a copy of the Pharmaceutical Evaluation Section commentary on their submissions. In addition, the PBAC now has to give a formal reason for its recommendations in writing within 15 working days of the meeting. Also, the secretary of the committee and members of the Pharmaceutical Evaluation Section are available to expand on this written feedback. However, in spite of this, the industry maintains that the reasons for many decisions remain obscure.

Revision of the guidelines

From the outset there was a commitment to revise the guidelines according to experience by the end of Autumn 1995. This review is now complete and several changes have been made². Although there are no changes to the underlying principles, the government's view is that the revision of the guidelines better reflects the PBAC's information needs and provides further clarification.

The main emphasis of the revision is on measurement, with more attention being paid to evidence from randomised controlled clinical trials (preferably head-to-head) and less attention being paid to observational studies and expert opinion. In practice, this change applies mainly to the clinical component of the submission, but increasingly could apply to the resource data now that more of such data are being gathered alongside clinical trials.

The main reason for the change is that, over time, the PBAC has become increasingly concerned about the bias inherent in observational studies and the difficulties of judging submissions that are heavily reliant on clinical opinion or assumptions. Therefore a particular proposal is that companies should present, in their submission, a preliminary economic evaluation based on randomised trial evidence alone.

This proposal has been controversial since, at the time of product launch, few data will be available on long term outcomes and the trials performed at that stage of product development may not reflect normal clinical practice. In addition, if cost data were collected alongside such trials, many items of resource use may have been driven by the protocol.

The debate about 'trial-based' economic evaluations versus 'modelling' studies is not confined to Australia⁶ and can be viewed as a trade-off between internal validity (minimisation of bias) and external validity (broader relevance). In addition, Drummond⁷ has pointed out that two main conditions need to hold for the incremental difference, in cost-effectiveness, in the trial-based analysis to be a good predictor of the difference in the long term. These are that; (i) the difference in short-term outcome is indicative of the difference in long-term outcome; and (ii) the difference in outcome does not lead to any significant cost consequences beyond those measured in the trial-based analysis.

Nevertheless, the PBAC's current position is that such a preliminary analysis is a good starting point for further consideration of the value for money of a given drug. If value for money is clear after the preliminary analysis, less reliance on models and assumptions is needed. Also, the proposed revisions to the guidelines do recognise a place for subsequent

modelling, in order to extrapolate from intermediate to final outcomes, to relate to a target patient population with different characteristics, or to adjust for the differences between the trial situation and normal practice².

HOW COULD THE OUTCOME OF THE GUIDELINES BE ASSESSED?

Possibilities for policy evaluation

Those wishing to evaluate the impact of the guidelines face two difficulties. First, the outcome of particular submissions is not publicly available, owing to the general secrecy provisions of the legislation that established the PBAC. Secondly, although the guidelines are a relatively new development, the process of listing by the PBAC has been in operation for a number of years. Therefore, whilst they have attracted worldwide attention, the guidelines merely represent a clarification of a process that was already in place prior to 1993.

However, it is interesting to speculate on what the likely outcomes of the guidelines could be and how such outcomes could be assessed. There appear to be three possible outcomes. First, one might expect that, because of the guidelines, certain medicines may not be listed on the PBS. That is, because of the opportunity in Australia to consider formally whether an individual medicine should attract public subsidy, some drugs would be refused on the grounds that their incremental benefit over existing therapy is marginal in relation to their additional cost.

Secondly, one might expect that certain medicines may be listed, but with fairly restrictive indications for use. As in licensing, the indications are a key feature of the reimbursement process. Under the Australian system drugs can be placed on 'restricted benefit', which means that they can only be given to a limited group of patients, or 'on authority', which means that the prescribing doctor needs to give (in addition) an assurance (usually by telephone) that the medicine is being used within the approved indications. In general, companies tend to resist such restrictions.

Thirdly, one might expect that the prices of new medicines in Australia would be lower than those of the same, or equivalent, drugs in other developed countries. This could be because, under the listing process, value for money comparisons are often made with older existing drugs, many of which have historically lower prices. Alternatively, companies preparing submissions may reach the conclusion that their proposed price is hard to justify on the grounds

of value for money and may revise their expectations downwards.

Of course Australia is not the only country to have administered drug prices. The difference is that when the first drug in a new class is launched, an explicit consideration is made of its incremental benefits over existing therapies. In other countries drugs in a new class are not explicitly compared, in value for money terms, with existing therapies and usually a higher price is given. However, once the benchmark price for a new class is established, similar products are likely to attract a similar price, in Australia as elsewhere.

This contrasts with markets that are more price driven, where 'me-too' drugs may be offered at lower prices to gain market share. In Australia, me-too drugs on the PBS tend to compete on a non-price basis only. However, on occasions a new manufacturer entering the market may offer its product at a lower price than equivalent products already on the PBS. If this happens the government may approach the companies concerned to see whether they will drop their prices accordingly, or face possible de-listing.

The other area where differences may be observed is in line extensions or new formulations. In many countries these are used by companies to maintain or increase price in situations where a given medicine has been on the market for a number of years and where generic competition is present, or on the horizon. However, the advantages of new formulations are sometimes modest and it would be interesting to see whether, under the Australian system, the price differences are correspondingly modest, when compared with other countries.

Preliminary evidence

In order to demonstrate how some of the outcomes of the guidelines might be evaluated, preliminary evidence is presented below. However, this is illustrative only and does not constitute a thorough examination of the outcome of the guidelines.

In the examples below the United Kingdom is selected as the reference country, on the grounds that whilst it is similar to Australia in many ways, it differs greatly in the process of drug pricing and reimbursement, with most licensed drugs being automatically reimbursed and the pricing decisions on individual products being left to the companies themselves, within the overall constraints placed upon them by the Pharmaceutical Price Regulation Scheme and the wider efforts within the NHS to encourage cost-effective prescribing (e.g. the Indicative Prescribing Scheme and budgets for GP Fund holders).

Considering first the issue of the availability of drugs under the public health system, it is interesting to examine whether there are any notable absentees from the PBS, compared with the UK. For example, neither finasteride, the first of a new class of drugs for benign prostatic hyperplasia, nor sumatriptan, a new medicine for migraine, are listed in Australia, despite having approval to market. On the other hand, both are available under the NHS in the UK.

Whilst this may give an indication of the impact of the Australian guidelines, we must not fall into the trap of thinking that listing is the sole determinant of the availability of a drug. Under the NHS it may be that actual availability of the medicines in question is limited by the natural conservatism of some prescribers, or by budgetary constraints. The Australian guidelines, and the PPRS, need to be viewed in the context of the overall set of checks and balances on prescribing in the health care system as a whole.

We should also not fall into the trap of picking examples to prove a particular point. The examples given above were selected because they are innovative products that have caused considerable debate and interest in the UK. On the other hand, another innovative product that has also generated debate in the UK, risperidone for treatment of schizophrenia, *is* listed on the PBS. So is dornase; a new biotechnology product for people with cystic fibrosis although this was initially rejected. Nevertheless it is clear that a number of 'high profile' new products have had a tougher time in Australia than in the UK, owing to the existence of the formal listing process. The latest case is interferon beta-1b for multiple sclerosis.

The second issue concerns the restriction of indications that might be placed on a given product. An example here is that of the granulocyte colony stimulating factors (G-CSFs). In the United Kingdom the indications for use are quite general, being 'for reduction in duration of neutropenia and incidence of febrile neutropenia in cytotoxic chemotherapy of non-myeloid malignancy and reduction in duration of neutropenia (and associated sequelae) in myeloablative therapy followed by bone-marrow transplantation'. However, in Australia these drugs are listed for more specific indications. These are for (i) patients with non-myeloid malignancies receiving marrow-ablative chemotherapy and subsequent bone marrow transplantation; (ii) patients being treated with aggressive chemotherapy *with the intention of achieving a cure or substantial remission* (emphasis added) in seven specific conditions (which are named) or (iii) patients with severe congenital neutropenia, severe chronic neutropenia, or chronic cyclic neutropenia (the definitions of which are quite

precise). In the latter case patients must have had 'an absolute neutrophil count of less than 0.5×10^9 cells per litre, lasting for three days per cycle, measured over three separate cycles of chemotherapy and (emphasis added) evidence of serious or recurring infections'.

Similarly, in the United Kingdom the indications for proton-pump inhibitors are fairly broad, including oesophageal reflux disease, reflux oesophagitis, long-term management of acid-reflux disease, and duodenal and benign gastric ulcers including those complicating NSAID therapy. In Australia the listing is more specific, being 'for severe refractory ulcerating oesophagitis, scleroderma oesophagus proven by endoscopy and unresponsive to other measures and refractory duodenal or refractory gastric ulcer, with proven failure to heal despite eight weeks of continuous therapy with other 'ulcer healing' drugs'. Furthermore, the prescription for a proton-pump inhibitor for refractory ulcer by the physician, under the authority system, must include the date of the final assessment (e.g. X-ray, endoscopy or surgery).

Again we should be cautious, in that some of the additional restrictions on indications in Australia may merely flow from the licensing procedure, which itself may be more restrictive than in the UK. Also, both the licensed indications and the criteria for listing, change over time, and there could be a lag before they are fully harmonised. However, it would be particularly instructive to consider cases where the restrictions imposed in listing by the PBAC are clearly more stringent than the licensed indications. Also, in the United Kingdom restrictions on the indications for use might be imposed elsewhere in the healthcare system, through formulary decisions or the adoption of local treatment protocols (e.g. for when and how to use G-CSF in chemotherapy).

However, the greater specificity of the indications for listing and the authority system must send signals to the prescriber about the use of certain medicines in Australia. Also, due to doctors' well-known aversions to bureaucracy, the authority system may deter some use of the more expensive medicines.

The third issue, of price comparisons, is more complex and has bedeviled researchers for a number of years. In particular currency conversions need to be made by purchasing power parities rather than exchange rates. However, it is well known that, for new medicines, companies are attempting to set a World price. It would be interesting to assess how often this is achieved in Australia, as compared with other countries. Within each country it would also be interesting to see whether line extensions or new formulations attract a premium and whether there are fewer of them listed in Australia than elsewhere.

Proposals for future evaluation

The evidence presented above is highly selective and partly anecdotal. However, fuller evaluation of the outcomes of Australian guidelines should be undertaken. At the outset it should be recognised that there are different perspectives for such an evaluation; those of industry, government or the society at large. The main perspectives of industry (profitability) and government (budgetary control) are fairly well understood. The perspective of society at large is the most relevant, but possibly the most difficult to comprehend. Certainly society has an interest, shared by government, in knowing whether the resources devoted to the development and maintenance of the guidelines give good value for money. It probably also has an interest in equity, in particular whether any disadvantaged groups of patients are denied subsidised medicines that are freely available in other countries.

The economic evaluation of the guidelines would first have to consider the cost of the guidelines process, including the opportunity cost of the time of unpaid (or underpaid!) academic advisors. In order to assess the benefits one would first have to undertake a more rigorous assessment of the differences, between Australia and elsewhere, in the listing of medicines (in terms of the range of products available and their indications for use).

Where differences are observed, as in the few cases identified above, an assessment should be made of whether any additional restrictions imposed in Australia are likely to lead to more cost-effective care or not. For example, are there fewer cases in Australia of price premiums for medicines offering only modest advantages (e.g. sustained release formulations)? In situations where medicine use is restricted, is this backed up by cost-effectiveness evidence? Are there examples in Australia where innovative new medicines, offering considerable benefits to patients, are unlisted, or are only listed after considerable delay? Where restrictions on expensive medicines are in place in Australia, does this have 'knock-on' effects on other health care costs?

CONCLUSIONS

The Australian cost-effectiveness guidelines provide an interesting insight into the use of economic evaluation for decision making about health technologies. Over the first two years of the formal scheme much has been learned but the guidelines themselves have survived despite extensive scrutiny.

The proposed revisions raise interesting questions about the strengths and weaknesses of 'trial-based'

and 'modelling' approaches to economic evaluation. Both approaches have a place and more debate is required before the final balance between them is struck.

Satisfaction with the process of evaluating submissions is still much higher in government circles than within the industry. Because of the confidential nature of the process, the scope for evaluation is reduced, but the examples given here suggest that some assessment of the outcome of the guidelines can and should be made.

ACKNOWLEDGEMENTS

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Appendix 1

EXTRACTS FROM THE GUIDELINES FOR THE PHARMACEUTICAL INDUSTRY ON PREPARATION OF SUBMISSIONS TO THE PHARMACEUTICAL BENEFITS ADVISORY COMMITTEE

1 Summary of contents

- Part I Roles and responsibilities for the PBAC
- Part II Basic information on preparing a submission to the PBAC
- Part III Guidelines for preparing the main body of a major submission
 1. Details of the proposed drug and its proposed use on the PBS
 2. Data from comparative randomised trials for main indication
 3. Modelled economic evaluation for main indication
 4. Estimated extent of use and financial implications

Appendices

- A. Description of the search of the published literature
- B. Measures taken by investigators to minimise bias in each trial listed
- C. Characteristics of each trial listed
- D. Analysis of the outcomes of each trial listed
- E. Measurement of quality of life and utility; estimation of quality-adjusted life-years
- F. Identifying and defining economic inputs and outcomes
- G. Use of meta-analysis
- H. Types of economic evaluation
- I. Estimating the present value of costs and health outcomes
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- M. Presenting non-randomised studies
- N. Measures taken by the investigators to minimise bias in non-randomised studies
- O. Expert opinion
- Part IV About the guidelines

2 Key questions to help determine the acceptability of a major submission

In addition to the main body of the submission, other material has to be provided including 'Answers to key questions to help determine the acceptability of the submission'. The advice for the completion of this is as follows.

'Answer the following questions concisely. This will help the PBAC Secretariat and the Pharmaceutical Evaluation Section determine the acceptability of the submission.

- a) Are the indication(s) proposed for PBS listing with the TGA-approved indications (or, if necessary, the ADEC-recommended indications)?
- b) When was the proposed drug recommended by the ADEC (or if not considered by the ADEC, give the date of registration and indicate whether a TGA evaluation report is available)?
- c) Is the comparator justified according to the criteria given in Section 1.5? Give the page number of the submission where the choice of comparator is justified.
- d) Has a thorough search for relevant comparative randomised trials been conducted? Give the page number of the submission where the search strategy is presented.
- e) Does the key clinical evidence in the submission relate to the proposed main indication for PBS listing?
- f) Have the measures taken by the investigators to minimise bias in the key clinical evidence been assessed? Give the page number of the submission where the assessments are presented.
- g) Have the outcomes of the studies been clearly defined? Give the page number of the submission where these definitions are presented.
- h) Has a meta-analysis been conducted? Give the page number of the submission where the methods of the meta-analysis are presented.
- i) Where section 2.8 and/or Section 3 has been completed, are the cost components tabulated according to the approach given in Appendix I? Give the page number of the submission where the table is presented.'

3 Extracts from guidelines for preparing the main body of a major submission

Reproduced below are the questions and data requirements set out in Part III of the Guidelines in red type. The relevant guidance and advice set out in Part III and elaborated in the Appendices is not included.

1 Details of the Proposed Drug and Its Proposed use on the PBS

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1.1 Pharmacological class and action

Give the brand name, Australian approved name and therapeutic class for the proposed drug. What is its principal pharmacological action? What pharmaceutical formulation(s) (ampoule, vial, sustained release tablet etc.), strength(s) and pack size(s) is proposed for PBS listing?

1.2 Indications

State the indication(s) approved by the TGA (or recommended by the ADEC). Then state the indication(s) proposed for PBS listing. If a restricted listing is sought, suggest a wording for the proposed restriction. If a general listing is sought, identify the main indication(s).

If the indication is likely to be unfamiliar to the members of the Economics Sub-Committee or the PBAC, it may be helpful to provide a summary of the disease suitable for an informed layman. If so, take no more than two pages to describe the relevant characteristics and the likely impact of the disease, and of its current and proposed management.

1.3 Treatment details

What is the proposed course of treatment?

1.4 Co-administered and substituted therapies

What other therapies, if any, are likely to be prescribed with the proposed drug as part of a course of treatment?

If the proposed drug is listed, what therapies, if any, are likely to be prescribed less for the target patient population:

- for the therapeutic indication; or
- for the treatment of side-effects of current therapies?

1.5 Main comparator

Of the substituted therapies, identify the main comparator(s) and justify the selection.

1.6 Differences between the proposed drug and the main comparator

What are the main differences in the indications, contra-indications, cautions, warnings and adverse effects between the proposed drug and the main comparator?

2. Data from Comparative Randomised Trials for Main Indication

2.1 Description of search strategies for relevant data

Describe the search strategies used to retrieve relevant clinical and economic data both from the published literature and from unpublished data held by the company.

2.2 Listing of all comparative randomised trials

List citation details of all randomised trials that compare the proposed drug directly with the main comparator for the main indication ('head-to-head' trials). If there is none, state this and then list citation details of all randomised trials comparing the proposed drug with other therapies, including placebo, for the main indication. Provide the same reference treatments for the main indication. If there are no randomised trials of either the proposed drug or the main comparator, state this and then list all relevant non-randomised studies that are relevant to the main indication.

2.3 Assessment of the measures taken by investigators to minimise bias in the comparative randomised trials

Provide information on the measures taken to minimise bias in each of the randomised trials listed in response to section 2.2.

2.4 Characteristics of the comparative randomised trials

Provide information on other characteristics of each of the randomised trials listed in response to Section 2.2.

2.5 Analysis of the comparative randomised trials

State how the outcomes of each of the randomised trials listed in response to Section 2.2 were analysed.

2.6 Results of the comparative randomised trials

Present the results of each type of patient-relevant outcome of each trial (or meta-analysis) separately as the extent of any differences in outcomes between the proposed drug and the main comparator in terms of their natural units.

2.7 Interpretation of the results of the comparative randomised trials

Based on the results of the trials presented in Section 2.6, state the category which best describes the proposed drug.

- a) The proposed drug has significant clinical advantages over the main comparator:
 - i) it has significant advantages in effectiveness over the main comparator and is associated with similar or less toxicity; OR
 - ii) it has similar effectiveness to existing therapies but has less toxicity; OR
 - iii) it has significant advantages in effectiveness over existing therapies but is associated with more toxicity.
- b) The proposed drug is no worse than the comparator in terms of effectiveness and toxicity.
- c) The proposed drug is less effective than the main comparator, but is associated with less toxicity.

State which type of economic evaluation has been conducted.

2.8 Preliminary economic evaluation based on the evidence from the comparative randomised trials

Provide a preliminary economic evaluation of substituting the proposed drug for the main comparator based on the results of the randomised trials presented in Section 2.6.

3 Modelled Economic Evaluation for Main Indication

3.1 Need for a modelled evaluation

Justify the decision as to whether or not to present a modelled economic evaluation.

3.2 Approach used in the modelled evaluation

Describe the type of economic evaluation that was modelled (see Appendix H) and the approach used.

3.3 Population in the modelled evaluation

What population has been used as a basis for the calculation of costs and outcomes?

3.4 Resource inputs and outcomes in the modelled evaluation

For the population described in Section 3.3, list, define and justify:

- a) the relevant types of resource inputs;
- b) the final outcomes of treatment (and, if different, the outcomes modelled); and
- c) the appropriate time horizon for follow-up.

For each item listed in a) and b) above, indicate whether it differs from the evidence previously presented in Section 2.6. For each item which is different, also supply the following in a technical document or an attachment to the submission:

- a) state the source of the information; and
- b) explain and justify the modelling of the resource use estimates and the linking of short-term and/or surrogate outcomes to the final outcomes (including a justification for how these are quantified over time).

3.5 Results of the modelled evaluation for each alternative

Present, separately for each alternative, the results of the modelled evaluation:

- a) for each type of resource and outcome measure in natural units;
- b) for each type of resource valued in dollar terms;
- c) for resources appropriately aggregated and discounted; and
- d) for outcomes appropriately aggregated and discounted.

For assistance in calculating b) see Appendix I.

If the submission includes a claim for indirect benefits in c), present the results both with and without these included (see Appendix I for rationale).

3.6 Results of the incremental analysis from the modelled evaluation

Provide the incremental cost of achieving each additional unit of outcome with the proposed drug when substituted for the main comparator.

3.7 Sensitivity analysis of the modelled evaluation

On what basis were the sensitivity analyses performed?

4 Estimated extent of use and financial implications

4.1 Estimated extent of use of the proposed drug

Estimate the likely prescription volume of the proposed drug on the PBS for at least each of the first two full years from the date that it is listed on the Schedule.

4.2 Estimated extent of substitution of other drugs

Estimate the change in the extent of use of other drugs using the information provided in Sections 1.4 and 4.1.

4.3 Estimated financial implications for the PBS

The implications for PBS expenditure are:

$$(d \cdot s_d) - (\sum c_i \cdot s_i) + (\sum e_j \cdot s_j) - (\sum f_k \cdot s_k)$$

where:

d = expected sales (quantity) of the proposed drug;

s_d = the PBS unit subsidy on drug d ;

c_i = the reduction in the quantity of competing PBS subsidised drug i resulting from a successful submission;

s_i = the PBS unit subsidy on this drug;

e_j = the quantity of PBS subsidised drug j co-prescribed with d ;

s_j = the PBS unit subsidy on this drug;

f_k = the reduction in the quantity of PBS subsidised drug k used to treat side effects of the i drugs; and

s_k = the PBS unit subsidy on this drug.

4.4 Estimated financial implications for government health budgets

Estimate the financial implications by adding the following calculations to the costs estimated in the previous equation:

- a) the medical costs of treating side effects to drug that would be met by Commonwealth or State governments (e.g. doctor visits, hospital stays, procedures);
- minus b) savings in the same type of medical costs from treating fewer side effects of competing drugs;
- minus c) savings in medical costs met by Commonwealth or State governments from fewer competing procedures (e.g. drug d substitutes for an operation);
- minus d) savings in medical costs met by Commonwealth or State governments because drug d reduces the burden of illness (e.g. anti-hypertensives reduce strokes).

2 THE CANADIAN EXPERIENCE: STEP CHANGE OR GRADUAL EVOLUTION?

Martin Buxton

INTRODUCTION

In September 1994, the Canadian Province of Ontario followed the Australian lead in issuing guidelines for the economic evaluation of drugs¹, and, since September 1995, submissions for listing of new drugs on the Ontario provincial formulary have been deemed to be incomplete, if they do not contain an economic analysis or justify its absence. These Ontario guidelines were shortly followed, in November 1994, by a national set of guidelines (issued under the auspices of the Canadian Coordinating Office for Health Technology Assessment – CCOHTA)^{2,3}. It was proposed that the CCOHTA guidelines would provide a common framework for adoption in all Canadian provinces.

Like the earlier developments in Australia, these Canadian developments have been watched with an interest that goes far beyond their local market importance. The impression, in the wider community concerned with economic evaluation, is that these two sets of guidelines from Canada together represent a further major step towards a situation where internationally the cost-effectiveness of new drugs will become a major factor in accepting new pharmaceutical products for inclusion on reimbursement formularies, and perhaps for pricing. It can be seen as a very positive step for economic evaluation, that Canada now has formal guidance that attempts to identify preferred methodology and to establish common standards for the submission of economic evidence to Ontario and to provincial authorities more generally.

However the emergence within Canada of two sets of similar, but nevertheless different, guidelines in Canada, which together are clearly in turn different from the earlier Australian Guidelines, is seen by some observers as a threatening indication that the international pharmaceutical industry may well face the development of a multiplicity of locally varying requirements. The worry is that quite distinct and separate economic analyses may be required for each of many jurisdictions.

This paper draws out from the emerging Canadian situation a number of issues of particular relevance

outside Canada. The first two broad areas relate to the guidelines themselves: their substantive content and the processes of their development. The third relates to their application, and the extent to which the interest in economic evidence represents the introduction of a new hurdle or merely the clearer signposting of an obstacle that has been in existence for some time. The fourth, and final, issue is in many ways the most important. It concerns the effect of the guidelines. Is there any evidence that they have begun to make a difference and if so in what way? Whilst they are certainly of academic interest they are intended to be functional, and should primarily be judged by their impact.

THE CONTENT OF THE GUIDELINES

The impression as to whether there are predominantly similarities or differences between the two sets of guidelines probably lies in the eyes of the commentator. Certainly at first sight, the overall *appearance* of the Ontario and CCOHTA guidelines is rather different. Table 1 summarises their rather different structure, contents and length. There are clear differences in the amount of detail provided. Overall, because of their greater brevity, the Ontario Guidelines *appear* somewhat less directive: they go into less detail about methodology and provide fewer judgements about 'the state of the art'. By contrast, the 'technical appendix' in the CCOHTA guidelines provides a little more guidance on methodology and is more suggestive as to the preferred approaches.

Table 1 Content and format of Canadian Guidelines

Ontario	CCOHTA
Text (11 pages)	Summary (4 pages) 16 item 'Reporting Structure'
Worksheet of 18 Questions	Worksheet of 18 Questions Glossary Technical Appendix (19 pages)
References	References

Fuller point by point comparisons of their methodological positions have already been published⁴. It is clear that the guidelines agree on a number of key points. Both suggest that the comparators should be the most commonly used and least expensive strategies used to treat the same condition. They both focus on a social perspective, including both direct and indirect costs, but recommend that the data are presented in a way that permits disaggregation to more partial perspectives of, for example, the health care system. Neither offers much specific detail on the 'nuts and bolts' of costing; but both emphasise that costs need to be locally appropriate to Canada. The CCOHTA guidelines looks further forward and propose the development of a standard glossary of cost terminology and a manual of standard cost values for resource items.

Not surprisingly given the state of the wider debate about methods of economic evaluation, both guidelines deal at greater length with issues of appropriately measuring outcomes than with measurement of costs. Both, with appropriate reservations, recommend the use of QALYs, but the Ontario guidelines appear to give a stronger emphasis to the potential value of cost per QALY comparisons to illuminate resource allocation choices between quite different disease groups and different health-care sectors. Both sets of guidelines 'encourage' those submitting studies to try the use of the less well-developed approach of willingness to pay; but CCOHTA emphasises the methodological benefits of gaining more experience, whilst Ontario implies a greater immediate usefulness of the results.

The key distinguishing factor between the two is not one of small differences of content, or the precise position adopted on the familiar debates still surrounding economic evaluation. The key difference is the specificity of the context in which it is proposed that the evidence be used. The Ontario guidelines have the distinct advantage of being quite specific to a particular decision context and reimbursement agency. The guidelines relate to information to be provided to the Drug Quality and Therapeutics Committee (DQTC) which advises the Ontario Minister of Health about public funding of pharmaceutical products. The aim is to ensure that the DQTC is provided 'with better information to enable its members to judge "the value for money" associated with each product under review'. The guidelines are directed to manufacturers who will be making submissions with respect to the listing of new drugs. The implicit message is: 'this is the evidence that we want you to provide if you want us to reimburse your drug'.

The CCOHTA guidelines are necessarily less context specific, and attempt to identify methodology

appropriate to a variety of possible decision-making users and contexts, including within – firm decisions about R&D priorities, pricing decisions including the Federal Patented Medicine Prices Review Board, formulary decisions at provincial, hospital or insurer level, those developing clinical guidelines relating to prescribing, and those concerned with post-marketing surveillance of actual utilisation. The guidelines are seen as more broadly educational, 'providing guidance both to doers and users.' The resultant lack of a particular contextual focus, and the potential breadth of their relevance, makes it much more difficult to prescribe a single preferred approach. The guidelines have necessarily to be more like a textbook of the state of the art, rather than an instruction guide as to how to do economic evaluation to meet specific requirements. The message in this case is less precise: 'this is the evidence that we think a variety of other bodies ought to find useful in making the various decisions they make'.

But despite these differences the two are essentially compatible and conceptually consistent: moreover the Ontario guidelines specifically foresaw the publication of the national document and announced that, whilst they did not expect there to be any substantial differences in recommended methodologies, they would review any differences, for example, of format and inform manufacturers about the relationship between the two. The common element is the Checklist of questions (originally from the Ontario document but included by CCOHTA and reproduced here as Table 2). It is suggested that these questions will be in the minds of those reviewing submissions and therefore need to be clearly addressed in the economic report. The CCOHTA document helpfully adds a proposed standardised reporting structure (reproduced here as Table 3). A significant inclusion in each (Question 17 in the checklist, and Section 13 of the reporting structure) is the 'Disclosure of Relationships'. This topic reflects an explicitly shared concern about the need to avoid possible biases in cost-effectiveness research. Whilst neither guideline precludes evidence produced from within the company or resulting from other relationships, the preference in each is for the economic analysis to be undertaken by third-party independent investigators with free rights of publication. This concern is not particular to Canada and mirrors the concerns of Hillman and colleagues⁵: and the presumption that the likelihood of bias depends upon the analyst's employer and contractual relationships: the position now adopted by the *New England Journal of Medicine*⁶.

Table 2 Checklist

<p>Q1 What was the question being asked in the report? What type of economic analysis was performed to answer the question?</p> <p>A. Cost comparison B. Cost consequence analysis C. Cost-effectiveness analysis D. Cost-utility analysis E. Cost-benefit analysis</p>	<p>Q10 How was health-related quality of life measured?</p>
<p>Q2 Did the study involve a comparison of alternate treatments for patients with the same clinical condition? Were those alternatives explicitly stated? Was the analysis an incremental analysis?</p>	<p>Q11 What equity assumptions were made in the analysis? For example, are QALYs gained by any individual considered equal?</p>
<p>Q3 Was the viewpoint or perspective for the analysis stated clearly? Is it a societal perspective, third-party payer perspective, or patient perspective? Is the analysis presented in a disaggregated fashion showing these perspectives separately?</p>	<p>Q12 If some variables were difficult to measure, how did the analysts handle this difficulty? Did they slant the analysis all in favour of one intervention in order to bias the analysis against the expected result?</p>
<p>Q4 Was the evidence of the product's efficacy established through randomised trials? Was this evidence of efficacy supplemented by evidence of effectiveness applicable to the patient population or subgroups considered in the study (see Executive Summary: Summary of Guidelines, point 6). Was the latter evidence derived from studies documenting routine use in clinical practice? Have all relevant and significant variations in effectiveness for different subgroups been identified and reported?</p>	<p>Q13 Were extensive sensitivity analyses performed? What were the ranges of values for variables in the sensitivity analyses?</p>
<p>Q5 Were the methods and analysis displayed in a clear and transparent manner? Were the components of the numerator (cost of each alternative) and denominator (clinical outcomes of each alternative) displayed? Were clinical outcomes expressed first in natural units and then translated into alternate units such as benefits or utility?</p>	<p>Q14 Is health-related quality of life an important component of an economic analysis of this question? How sensitive is the estimate of cost-utility to variations in health-related quality of life?</p>
<p>Q6 Were all important and relevant costs and consequences (outcomes) including adverse effects for each alternative identified?</p>	<p>Q15 Is there an estimate of the aggregate incremental expenditure required for the provinces or other decision makers to whom the study is addressed to provide this product to patients covered by their programmes? What is the estimate of aggregate incremental costs? Does this estimate cover all of the major indications for use of the product?</p>
<p>Q7 Were costs and consequences modelled as in a decision tree with information derived from a variety of sources or estimated directly from a specific patient populations?</p>	<p>Q16 Has the incremental cost-effectiveness ratio been estimated for a specific clinical indication that represents the majority of its expected use by those covered under the programmes operated by the decision makers to whom the report is addressed? Do these other indications involve a large amount of utilization for which the ratio may be very different?</p>
<p>Q8 Were capital costs and overhead costs included as well as operating costs? How were they measured?</p>	<p>Q17 Who performed the analysis? Did the authors of the report sign a letter indicating their agreement with the entire document presented? Does the report indicate that the authors had independent control over the methods and right to publish the analysis regardless of its results?</p>
<p>Q9 How were indirect costs identified and estimated?</p>	<p>Q18 What is the 'bottom line' result of the analysis in quantitative terms? The answer to this question will be statements like the following: a) The cost per QALY gained for using this product compared to the alternative is \$X or ranges from \$Y to \$Z; b) The use of this product compared to the stated alternative will result in expected incremental expenditure of \$X per patient treated with a net reduction of Y major adverse clinical events (e.g. cardiac deaths) and Z minor clinical events (e.g. side-effects).</p>

Source: Adapted from the Ontario draft guidelines for economic analysis of pharmaceutical products¹.

Table 3 CCOHTA reporting structure

<p>1 Product description</p> <ul style="list-style-type: none"> - Therapeutic classification, brand and generic names, dosage form, route - Approved indications - Clinical efficacy results - [Checklist Q4] <p>2 Target audience</p> <ul style="list-style-type: none"> - Target audiences (decision makers) for the study (e.g. formulary decision makers, patient purchasers, prescribers) <p>3 Viewpoint</p> <ul style="list-style-type: none"> - Viewpoints selected and reasons (e.g. societal, Ministry of Health) - [Checklist Q3] <p>4 Treatment comparator</p> <ul style="list-style-type: none"> - Comparators selected and reasons (e.g. no treatment, drug, surgery) - [Checklist Q2] <p>5 Type of analysis</p> <ul style="list-style-type: none"> - Prospective, retrospective, modelling, or mixture of methods - Analytic techniques used and reasons (e.g. cost-minimisation analysis, cost-consequence analysis, cost-effectiveness analysis, cost-utility analysis, cost-benefit analysis) - [Checklist Q1, Q15] <p>6 Related studies</p> <ul style="list-style-type: none"> - Systematic review of previous analyses that concern the same or similar problems or the same or similar treatments <p>7 Cost measurement</p> <ul style="list-style-type: none"> - Cost items included and how measured (e.g. direct costs, costs of lost time, spillover costs on other sectors, spillover costs on other individuals) - How were prices determined? (e.g. were standard costs used?) - [Checklist Q5, Q6, Q7, Q8, Q9] <p>8 Outcome measurement</p> <ul style="list-style-type: none"> - Clinical outcomes included and how measured (e.g. adverse events, morbidity, mortality) - Health-related quality of life instruments included (e.g. disease-specific instrument, generic HRQOL profile, preference-based measure) - [Checklist Q5, Q6, Q7, Q10, Q14] 	<p>9 Analysis and results</p> <ul style="list-style-type: none"> - Presentation of all analyses in a clear, step by step fashion so readers can replicate the calculations if interested - Display any models used, and the assumptions - Presentation of results in detail first, with aggregations and the use of value judgements (e.g. preference scores) introduced into the presentation as late as possible - Interpret results in the context of all reasonable alternative therapies - [Checklist Q5, Q7, Q12] <p>10 Uncertainty</p> <ul style="list-style-type: none"> - Sampling error, range of plausible assumptions, sensitivity analysis - [Checklist Q13, Q14] <p>11 Sub-group analyses</p> <ul style="list-style-type: none"> - Are there identifiable subgroups with differential results (e.g. effectiveness subgroups, preference subgroups, cost subgroups, cost-effectiveness subgroups) - [Checklist Q16] <p>12 Equity</p> <ul style="list-style-type: none"> - Equity assumptions (e.g. a QALY is equal for all) - Distributional considerations (e.g. who gains, who loses) - [Checklist Q11] <p>13 Disclosure of relationships</p> <ul style="list-style-type: none"> - Funding and reporting relationships, contractual arrangements - Investigators' autonomy and publication rights - [Checklist Q17] <p>14 Executive summary</p> <ul style="list-style-type: none"> - Summary of study and bottom line result - Interpretation in the context of all reasonable alternative therapies - Recommendations, if appropriate - [Checklist Q18] <p>15 References</p> <p>16 Appendices</p> <ul style="list-style-type: none"> - Detailed tables of data - Step by step details of analyses - Intermediate results - Copies of data collection forms, questionnaires, instruments, etc.
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Source: CCOHTA².

THE PROCESS OF CREATING THE GUIDELINES

It is hardly surprising that the substance of the two sets of guidelines is so similar. Both Canadian guidelines are products of quite extensive consultation and discussion, and they share a complex and interrelated development process. In October 1991, the Pharmaceutical Manufacturers Association of Canada (PMAC) established a health economics committee, one of whose objectives was to cooperate in the development of 'guidelines for the conduct and use of evaluations which determine the impact of pharmaceutical products on the economics of the health care systems.' Very shortly after this, the province of Ontario widely distributed for comment draft guidelines⁷, produced for its scientific advisory committee on Drug Quality and Therapeutics Committee by Allan Detsky, a physician/health economist and committee member. These draft guidelines, and reactions to them, were the focus of discussions amongst the various stakeholders at a national, as well as provincial level. It was felt that it would be useful to develop a set of Canadian Guidelines, that each Province could adopt, with or without modifications, as they saw fit. This consultation process eventually culminated in the Canadian Collaborative Workshop on Pharmacoeconomics held at Sainte-Adèle, Quebec in June 1993⁸⁻¹⁰. Contributions to that workshop illustrate the interest of both provincial and federal governments' in guidelines as a means of providing additional support to cost-containment policies^{11,12} and the industry's concern that economic evaluation needs to be used within an overall policy framework¹³.

Following this workshop, a steering committee with academic, governmental and industry representatives, with Professor George Torrance as lead writer produced draft guidelines which were eventually published by CCOHTA in November 1994². It appears that it was mainly frustration with the speed of this process¹⁴, rather than a desire to express a different position, that lead Ontario to publish its own guidelines in September 1994¹ without waiting for the final CCOHTA document. But, in December 1994, the Deputy Ministers of Health of all Provinces endorsed the CCOHTA Guidelines. Subsequently Ontario has formally stated that it sees the two sets of guidelines as consistent, but it requires that submissions to the DQTC adopt the reporting format (reproduced here as Table 2) which appears in both documents but is described by CCOHTA as a check on content rather than a required format.

The Sainte-Adèle workshop, and the wider debate, was clearly enlivened by the strong and rival local academic interests in economic evaluation and their

interactions with the wider international academic community. Needless to say academics are not impartial observers of methodology: the strength of academic preferences for particular methodologies usually bears a relationship to vested academic interests in their development and use, and academic concerns about niceties of emphasis may get out of all proportion to their practical importance. As a result the guidelines must be viewed in part as a reflection of the academic inputs rather than a clearly different interpretation by the decision-makers of the evidence to justify different methodologies.

The process of guideline development continues. In May 1996, CCOHTA distributed a questionnaire to 'users, doers and methodologists' seeking views as part of a process of reviewing the guidelines in the light of the first year's experience¹⁵. The intention is that the review committee will suggest proposed changes in the Autumn of 1996.

THE APPLICATION AND CONTEXT OF THE GUIDELINES

In Canada in the late 1980s, the context for the decisions about spending on pharmaceuticals was one of concern about overall rising health care costs, with a number of official enquiries established at federal and provincial levels. Controlling drug expenditure, and achieving more cost-effective prescribing was a particular focus of attention¹⁶, particularly as public expenditure on pharmaceuticals was rising at a faster rate than expenditure on other sectors of health care. The absence of a particularly strong local pharmaceutical industry, in terms of local investment and employment in research and development or manufacturing, may have contributed to the pressures on pharmaceutical spending.

In British Columbia, for example, the provincial program funding drug benefits doubled in cost in the five years to 1995. In many provinces, arbitrary cuts are being sought from drug budgets: in Alberta, for example, a saving of CDN \$50 million is sought in 1996 from the drug budget.

In Ontario at the time of the introduction of the guidelines, the position was one of particularly strong pressures on the drugs budget. For example, the introduction of a new drug onto the provincial formulary required the company to identify (from expenditure on other of their drugs) 'cost-offsets' from within the formulary budget to balance the costs of the new drug and to make its introduction budget neutral. Critics noted that a budgetary control of this sort potentially could negate the logic of the cost-effectiveness evidence, although the Director of

the Drug Programmes Branch of the Ministry of Health publicly justified the two separate and sequential initiatives¹⁴. The concern was that a new drug might be shown to add to the costs of the drugs budget, but offsetting savings from a resultant reduced need for hospitalisation would not be taken into account. Alternatively, even where the additional costs of a new drug might lead to compensating offsets within the drugs budget, those offsets might well be from reduced use of drugs produced by other companies. One of the reasons for the industry's active support for the economic guidelines was a hope that this move would make undefendable (and hence unsustainable), the arbitrary requirements of new introductions to the formulary being budget neutral in terms of the drugs budget alone. Officials certainly recognised that if this 'temporary requirement' to keep the drugs bill unchanged remained in place, the logic of the guidelines would be diminished. With a change in the Ontarian Provincial government in mid-1995, the specific policy of 'cost-offsets' was dropped. Nevertheless, in Ontario as in other provinces, the budgetary system still focuses on the drugs budget and does not facilitate the acceptance of cost-effective increases in drugs expenditure that could be, for example, be offset by savings in other health care budgets. This represents a major potential limitation to the likelihood that economic arguments for 'more expensive' new drugs will be accepted, even where economic evaluation shows that they offer savings elsewhere in the system.

The two sides foresaw other potential illogicalities in the proposed system. The logic of the economic case for listing a new drug might well be that an older existing comparator drug is now relatively less cost-effective and should be delisted from the formulary. The industry resists this idea and Government seems to view it as too sensitive. In a few cases, whole therapeutic areas have now been reviewed and some products have been delisted, but only after considerable consultation and negotiation. Amongst these in Ontario are some of the more expensive formulations of drugs: such as long-acting, sustained-relief and those delivered through 'patches'.

This growing interest in reviewing whole areas of prescribing, changes the emphasis from a situation in which the entire onus is, as in Australia, on the sponsoring company to prove cost-effectiveness as it initiates the submission for new listing, to one where publicly funded studies will need to be undertaken to review products listed earlier, perhaps at a time when there was no specific consideration of cost-effectiveness. In Canada, the original proposal had been that the role of a separate agency to evaluate cost-effectiveness and, if necessary, to commission

Table 4 List of CCOHTA pharmaceutical studies

rhDNase for cystic fibrosis
Finasteride
Pharmaceutical management of peptic ulcer disease
Pharmaceutical management of gastroesophageal reflux disease
Interferon beta-1b in multiple sclerosis
Filgrastim use in lung cancer
Comparison of nitrate formulations in angina
Sumatriptan in migraine
HMG-CoA reductase inhibitors (statins) in hyperlipoproteinemias
Fluroquinolones in three different infectious disease processes
Risperidone/dozaril in schizophrenia
Riluzole in ALS
SSRIs in depression
Macrolide antibiotics
Tacrine in Alzheimers disease

Source: CCOHTA Update Issue 25

studies and reviews, should be undertaken by the Canadian Agency for Pharmaceutical Information Assessment, but in the end this responsibility was given as an additional role to an expanded and now permanent CCOHTA funded by federal, provincial and territorial governments. (CCOHTA had been set up originally for a three-year trial period and during that period had worked mainly on non-pharmaceutical technologies.) In relation to pharmacoeconomics, CCOHTA both undertakes reviews internally and manages the process of commissioning reviews from mainly academic groups. A committee consisting of provincial, federal and territorial drug managers (the Pharmaceutical Policy Committee) establishes the priorities: CCOHTA's work and agenda is thus driven by the collective needs of the potential users of its reports. By June 1996, after the first eighteen months of its role, it had externally commissioned 12 pharmaceutical studies, following invitations to submit proposals, and is undertaking three studies internally. Table 4 lists the topics of these first 15 studies. All tend to be secondary analyses or syntheses of existing data, undertaken over a period of just a few months, rather than primary research. By June 1996, the first studies had been published (on rhDNase, interferon beta-1b, filgrastim, finasteride and the pharmaceutical management of peptic ulcer disease and gastroesophageal reflux disease [GERD]).

Each of these studies had been undertaken by a different Canadian university-based team, and after review and acceptance by CCOHTA's Scientific Advisory Panel and its consideration of comments received from relevant manufacturers, their reports are available in full. In addition, CCOHTA publishes a brief overview of each which 'attempts to put the economic findings into a broader clinical perspective'. This overview provides an opportunity for CCOHTA to highlight what it sees as the strengths and weaknesses of the independent reports, noting for example, in the overview of the study of the management of GERD, that the study uses data on comparative clinical efficacy from RCTs supplemented with expert opinion on the resources used to treat recurrence, rather than effectiveness studies of actual clinical practice and emphasising that the study takes only a health care perspective rather than a full societal perspective of costs^{17,18}. More generally, CCOHTA has commissioned the work on standard methods of costing and will undertake an annual process to evaluate the guidelines and provide a forum for stakeholder input.

THE IMPACT OF THE GUIDELINES

The key question has to be: what is the impact of the guidelines in practice? The concept that cost as well as effect should be considered in making formulary decisions predates them. Equally their introduction does not require authorities to list according to some cost-effectiveness criterion. Has their introduction in Canada marked a step change in the way decisions are made, or is it simply part of an evolving process of politically juggling a whole range of considerations of which cost-effectiveness is one small part?

The first point to make is that the picture varies from province to province and is changing all the time. Formally, whilst the Guidelines have been endorsed by all the Provincial Ministers of Health, economic evidence is not yet a requirement in all Provinces. But even where there is not a formal requirement, the absence of economic evidence can delay formulary listing. The shared expectation is that economic evidence will be provided, but each province insists on its right to make its own particular rules. The PMAC would like CCOHTA to broker the review process to ensure a greater consistency between the 10 Canadian provinces. But tensions between national and provincial initiatives remain strong in Canada. British Columbia, for example, announced in 1995 that it would set up a programme of its own to evaluate the cost-effectiveness of new drugs. Asserting a degree of provincial independence, the initiative will include work on 'streamlining of

national cost-effectiveness guidelines to fit British Columbia's drug plan and develop guidelines for drug manufacturers on what they must include in their submissions for Pharmacare (the provincial drug formulary) approval of new drugs.

The provincial variability of the situation is made all the greater by the fact that the coverage of the provincial drug formularies varies. Provincial drug plans cover between 40 and 100 per cent of residents under a variety of reimbursement formats. Typically, provinces pay for drugs for the elderly, those on low incomes receiving social security support and particular groups of patients with chronic drug needs. Typically, those working and their dependents are not covered. The latter group must pay out of their own pocket for prescription medications, unless they have private insurance cover. Thus formulary decisions only have a direct impact on a proportion of the market, but they may have a further indirect effect. Private insurers, equally under pressure from rising drug costs, may seek to adopt the same restrictions as the relevant provincial formulary committees.

It appears that in each province, the CCOHTA guidelines have been accepted as a common template but these national guidelines are seen as guides not tight restrictions on what is acceptable. The emphasis is on complying with the general principles of the methodology. The guidelines have probably had an educational role and sensitised various of the stakeholders to the economic issues. It is suggested that the nature of the debate has changed, and that submissions to formulary committees have changed showing much greater scientific validity. There appears to be increasing emphasis on appropriate use, for example restricting the use of finasteride to older patients with moderate (rather than severe) disease for whom the evidence suggests that its use is cost-effective. But such changes as these are occurring in many other health care systems, without formal guidelines. It would need rather sensitive measures of knowledge and attitudes to ascertain what additional impact the local guidelines have had in Canada as compared to a country without such developments.

Anecdotally the acceptance of finasteride for particular categories of patients onto the Albertan and Nova Scotian formularies rapidly followed the publication of CCOHTA's report and is seen as assisted by it. Economic evidence is claimed to have been a key factor in the acceptance of sumatriptan onto the Ontario list.

What is needed is evidence that shows, or more realistically, suggests that different decisions are being made as a result of the newly required

economic information. Such evidence is scarce if not non-existent. Reports from CCOHTA can be used to support different conclusions. Even if produced to the highest methodological standards, evidence at an early stage in a drug's introduction is limited, contains uncertainties particularly about longer-term effects, and is open to different conclusions about the most likely outcome. Studies are complex, and may be difficult to understand or absorb even for well-informed decision-makers. CCOHTA has responded to the particular need for an independent, non-technical overview document. Even with certainty and perfect understanding, economic evidence involves value judgements for example as to how much society should be willing to pay for a QALY generated for a particular group of patients. Economic evidence always can, and probably always will, be used selectively to support political positions and agendas.

One element of the different decision-making that may have resulted from the existence of the guidelines and resultant greater emphasis on economic evidence might appear at the level of price-setting. Prices of drugs are reviewed at a federal level by the Patented Medicine Prices Review Board. The main criteria for drugs that are new to the Canadian market, and represent a 'breakthrough' or substantial improvement, is one of comparison with prices elsewhere – specifically seven countries – France, Germany, Italy, Sweden, Switzerland, the United Kingdom and the United States¹⁹. There is evidence that companies are increasingly including pharmacoeconomic evidence in these pricing submissions. Indeed, if the new guidelines were seen as making Canadian provinces more sensitive to cost-effectiveness then companies might seek lower prices than might otherwise be permitted, rather than have drugs excluded subsequently from provincial formularies because they were not viewed as cost-effective. The situation is further complicated by the news that reference-based pricing, with respect to the provincial formularies, is now being tried in British Columbia, so further changing there both the context and the nature of the relevant economic arguments.

Indeed the impact of the guidelines may lie hidden from public view further back in the process within companies, where both local (Canadian) and international decisions about development priorities, may be subtly but significantly influenced by the cumulative effect of the growing emphasis on cost-effectiveness. Australian and Canadian guidelines are being used as a basis for determining the necessary data collection and analysis of multi-country economic studies. Considerations of future likely cost-effectiveness are being used internally to influence development priorities, and pricing expectations.

CONCLUSIONS

At present, there is not enough evidence, and it would anyway be too soon, to come to firm conclusions about the impact of the two sets of Canadian guidelines. But even with more time, it will remain very difficult to identify and quantitatively disentangle the specific effects of guidelines from the myriad other changes in the environment within which decisions are made about the pricing, listing, and use of new drugs. These Canadian guidelines impact, if at all, within a much wider context of the changing environment of the health-care system. One conclusion of this account is that whilst it may be logical and intellectually valuable to try clearly to understand their specific impact, in the end it is likely to be practically impossible.

In which case, are there any other clear messages from the Canadian experience to date? The Canadian experience reinforces the conclusion that it is impossible to specify precise guidelines except where there is a particular decision-context and a specific decision-making body. The potential applicability of the CCOHTA guidelines makes the task of defining appropriate methodology much more difficult. It is one thing for a central decision-making authority or a specific advisory body to specify what evidence it wants to see to help it decide. It is quite a different matter to specify what a variety of devolved decision-makers may want (or ought to want) to help them with a range of only partially specified decisions. The implications for the UK are obvious. Guidelines will necessarily continue to be situation specific.

The initial experience with the guidelines suggests that the issue of the local applicability of the data, is likely to be as, if not more, important than, local methodological preferences. Costs vary from province to province: populations covered by formularies have different local characteristics. This implies that, even if an entirely common set of methodological guidelines were agreed internationally, local studies (or at least specific local adaption of studies) would still be required to make the analyses relevant to local decision-makers. Whilst a proliferation of differing local guidelines might make the situation more complex or confusing, it would not necessarily add to the amount of locally specific work that may anyway be needed.

The further implication is that local decisions will logically differ. Even within Canada decisions will vary from province to province. The decision-context, local costs, differences in existing practice, different potential alternative uses of available resources, local values – each or any one might logically lead to a different local view as to whether, and in what

circumstances a drug was cost-effective. Cost-effectiveness is not an inherent feature of the drug's pharmacodynamics but of the way a drug impacts within the context of a particular health care system. What is more at the time of most initial reimbursement decisions, little will be known about true cost-effectiveness in a real-world health care system, as opposed to efficacy and estimated costs from trial evidence.

Overall the conclusion seems to be that the current spate of guidelines is just part of a much more general movement that accepts the importance of good economic evaluation evidence, but recognises that to be good it must be tailored to local circumstances. The days of the one-off, multi-purpose economic study that could give a drug an international sobriquet of 'cost-effective' are gone – if they ever existed!

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3 THE DEVELOPMENT AND USE OF THE UK GOVERNMENT: ABPI GUIDANCE

Adrian Towse

26

INTRODUCTION

This chapter outlines the background to the development of the 1994 UK Guidance, and its intended role in stimulating the use of good quality information on the cost-effectiveness of medicines by the National Health Service (NHS). It discusses evidence to date on use of the guidance and on trends in the use of information from economic studies by prescribers.

CURRENT ARRANGEMENTS FOR ENSURING VALUE FOR MONEY IN THE NHS MARKET FOR MEDICINES

The NHS market for medicines amounted to approximately £4 billion in 1995 at manufacturers' prices to wholesalers. Of this around 17 per cent was sold to hospitals, where cash limited contracts from purchasers encourage hospitals to seek discounts, operate formularies, and monitor usage carefully. The main market, however, is in primary care. Although the growth rate of NHS pharmaceuticals expenditure in this market has been slowing down it continues to grow in real terms at a rate above the growth of NHS expenditure overall. Innovation, demographic factors, patient expectations, a shift towards care outside hospital, and proactive preventative care all play a role.¹

Ensuring GP prescribing gives value-for-money is complicated by several factors:

- NHS policy that 'patients get the drugs that their doctors judge appropriate to their clinical needs'²;
- the independent professional and contractual status of GPs;
- the difficulty of identifying a robust formula for estimating what a GP practice 'should' be spending on medicines. Health Authorities have found it hard to achieve the Department of Health (DoH) objective³ of moving towards a weighted capitation formula. ASTRO-PUs (age sex and temporary resident originated prescribing units) provide weightings, but have limitations⁴.

A 1987 White Paper⁵ and the 1991 'internal market'

reforms⁶ put in place a framework of advice, information, and incentives.⁷ It comprises:

- 'target' prescribing budgets for GPs. Performance is monitored by Health Authorities using Prescribing and Cost Analysis (PACT) information. GP Fund holders (GPFHs) can spend savings on their prescribing budget on other services. Health Authority incentive schemes for non fundholding GPs also allow practices to direct part of any underspend to alternative services;
- a series of Executive Letters requiring Health Authorities to put in place policies to manage prescribing, including the entry of new products, the prescribing of 'high tech' home medications⁸, the hospital/primary care interface⁹, and beta interferon¹⁰;
- information and advice to GPs from a number of sources including local Health Authority medical and pharmaceutical advisors, the National Prescribing Research Centre, which publishes the regular Medicines Resources Centre bulletins reviewing products and therapeutic areas, the Prescription Pricing Authority, which produces a medical bulletin and provides PACT information, and the National Consumer Council, grant aided by the DoH to produce the Drug and Therapeutics Bulletin.

In addition there are arrangements for the profit control of the pharmaceutical industry, the 'clawback' of discount from community pharmacists, a Selected List of medicines which cannot be prescribed, and for the continuing medical education of physicians.

PRESCRIBING IN THE INTERNAL MARKET: THE ROLE OF COST EFFECTIVENESS

Government policy is to push budget responsibility down the 'market' hierarchy to bring financial and clinical decision making together. Buxton has described this as a move from a 'traditional clinical decision model' in which clinicians try to do everything that might benefit a patient, to a 'clinical resource management model' in which clinicians

have control of budgets, and so 'have to balance the best interests of the specific patient with the interests of the patient group as a whole.'¹¹

Prescribing budgets for GPs imply prescribing cost-effectively, i.e. going beyond avoiding incurring more expenditure than necessary to achieve the desired health outcome for a patient, to trading off the needs of individual patients against those of the patient population. It is not clear that the DoH intends this to be the case. Government policy is 'based on two principles... patients should have access... to effective drugs to meet all real clinical need; and that the provision of those drugs should be... cost-effective.'¹² One interpretation is that these two principles conflict. Another would be that budgets are designed to achieve desired health outcomes at lower cost, rather than to ration care.

Some aspects of cost-effective prescribing are in line with this approach, for example:

- not prescribing where the medicine is not effective for the diagnosis (e.g. antibiotics for viral infections);
- reviewing repeat prescribing policies to cut out medicines that are no longer required;
- using generics rather than the originator product, where the GP is comfortable with quality and bioequivalence;
- using an expensive product that is likely to save on hospital costs or deliver superior health gain for the patient at a price per unit of health gain (e.g. cost-per-QALY) that is consistent with most other NHS activity.

Difficulties arise when cost-effectiveness implies:

- not prescribing a new expensive product because the health gain for the patient is obtained at 'too high' a price;
- switching to a lower priced, but less effective, product because it is more cost-effective.

One route through this dilemma is to use treatment protocols that start patients on a more cost-effective but less effective medicine, moving on to the superior product for those not successfully treated by the less effective product. There will be a cost for some

i The terms of reference of the Industry Strategy Group are: 'To consider jointly the future development of the pharmaceutical industry in the UK, its contribution to the UK economy and its role in the provision of health care; and in particular to consider issues of common interest such as the provision of affordable health care and the encouragement of a strong pharmaceutical industry.'

ii The author was one of the ABPI nominees.

patients in using this approach, but it may be deemed an acceptable trade-off.

All GPs should be interested in achieving health gains at lower cost, and in understanding whether higher priced medicines offer value for money (cost per effect) as compared to other things the NHS does. There will be important differences between GPs as to the decisions they then make on the basis of this information. GPs may be reluctant to ration given the DoH's position, and that there are no rules as to how society wants priorities to be set. Should it be on 'cost per QALY' grounds (i.e. to maximise health gain from given resources) or other preferences linked to age or type of disease? The ethical duty of doctors in relation to priority setting is keenly debated^{13,14}. Willingness to use information on cost-effectiveness will help to strengthen professional autonomy, by ensuring that prescribing is both clinically effective and cost-effective.

The Government encourages the industry to supply information on the cost-effectiveness of its products. A working party was established in late 1993 by the Industry Strategy Group (which brings together the Association of the British Pharmaceutical Industry, the DoH, Department of Trade and Industry, and Treasuryⁱ) to consider issues relating to the industry's supply of health economics information to the NHS.ⁱⁱ The DoH also pursues its own programme of studies and assessments using NHS R&D money, for example, through the work of the Pharmaceutical Panel, and the Centre for Reviews and Dissemination (CRD).

THE METHODOLOGICAL AND PRACTICAL ISSUES ADDRESSED IN DRAWING UP THE UK GUIDANCE

Content of Guidance about Methods

The working party examined existing literature including 'checklists' of questions to ask of an economic evaluation in assessing its quality¹⁵⁻²², and papers reviewing the status of economic evaluation²³⁻²⁶. A number of areas of methodological consensus and dispute were identified and the treatment of these issues in the 'checklists' compared.

A number of areas of continuing debate were noted. In particular:

- (i) the choice of comparator. The Australian guidelines requested use of 'the therapy which most prescribers would replace in practice', which is arguably the realistic measure of opportunity cost, whereas the Ontario guidelines sought comparison with 'both the least expensive

- currently available strategy as well as the most commonly used alternative product'. Comparison with the most cost-effective treatment currently available is, arguably the correct measure of opportunity cost. If this is not known or not widely used then the therapy to be replaced in practice is the correct choice, although identifying this may be difficult.
- (ii) measuring and valuing health benefits. There was no agreement as to which measures of effectiveness and of health states to use in particular circumstances. Controversy concerns the use of QALYs and of Cost Benefit Analysis (CBA). QALYs were preferred in the 1993 Ontario guidelines (although this emphasis was relaxed in later drafts). There has been a continuing economic^{27,28} and ethical debate about the legitimacy and reliability of the QALY. Australia ruled out CBA. It depends on the question being addressed²⁹. Comparisons of the benefits of extra resource consumption by the NHS and in other government programmes require the extra health benefits to be valued in monetary terms with CBA. Within the NHS, comparisons across treatment areas require a 'common currency' which can be provided by CBA or a Cost Utility Analysis (CUA). Within one treatment area, prescribers may be interested in disease specific outcome measures using a Cost Effectiveness Analysis (CEA), or if cost is the only issue because outcomes are assumed or known to be the same, then a Cost Minimisation Analysis (CMA) will suffice.
- (iii) choice of method of data capture and analysis. Australia has a preference for clinical trial efficacy measures, indeed the revised Australian guidelines are seen as requiring 'cost-efficacy' studies, whereas the Canadian guidelines are in favour of modelling to measure cost-effectiveness.
- (iv) specifying the analytical viewpoint. The costs and benefits considered relevant to decision making by a patient may be different to those taken into account by a hospital. A health authority purchaser will have yet another perspective. The overall net benefit to society will include elements drawn from all of these perspectives.
- (v) discounting health benefits expressed in utility, rather than monetary, terms. Both the Australian and Ontario guidelines required or recommended costs and benefits to be discounted at 5 per cent. In the UK the Treasury risk free rate for public sector costs and monetary benefits was set at 6 per cent. DoH policy is not to discount. DoH economists³⁰ argued that non-monetary benefits should not be discounted in principle, and that, in practice, there was evidence of low discounting by individuals.
- (vi) the treatment of indirect costs, or production losses. The Australian Guidelines discouraged their inclusion on the grounds that the Australian economy 'is constrained by macro-factors rather than by the lack of healthy workers'. Ontario proposed that indirect costs should be included but presented in a disaggregated fashion so that health care costs and a societal perspective including non health care costs can be separately identified.
- The state of the debate had been summarised as follows – although 'there is a general consensus among experts on the existence of a basic set of principles governing the design of socio-economic studies, there is no general consensus as to selection of a given design option in a given circumstance'²⁶.
- The broad conclusions of the working party on methods were therefore³¹ that:
- the application of economic evaluation techniques to medicines is still in the course of development;
 - such techniques can provide useful information to prescribers and purchasers;
 - it is important that the results of economic evaluations should command general respect;
 - the use of guidelines can help to achieve this.
- Accordingly, in drawing up the UK Guidance, the Working Party was keen to ensure that, where there were generally agreed methodological standards, these should be adhered to, but that where there were genuine differences of opinion about appropriate choice of study design, the emphasis should be on transparency, with justification of design choices and disclosure of study results.
- The guidance was structured to follow the logical sequence of issues to be addressed in designing, conducting and reporting the results of an economic evaluation. It is set out in Appendix 1.
- ### The role such guidance should play in the NHS
- A formal requirement for compulsory economic evaluations as a fourth hurdle was rejected. The Government noted that 'such studies, by their nature, cannot provide a satisfactory basis for banning a product from supply but are very useful in helping doctors to decide between competing products or interventions and will become more so as evaluation techniques continue to develop'³². It was expected that GP and advisor interest in information on the

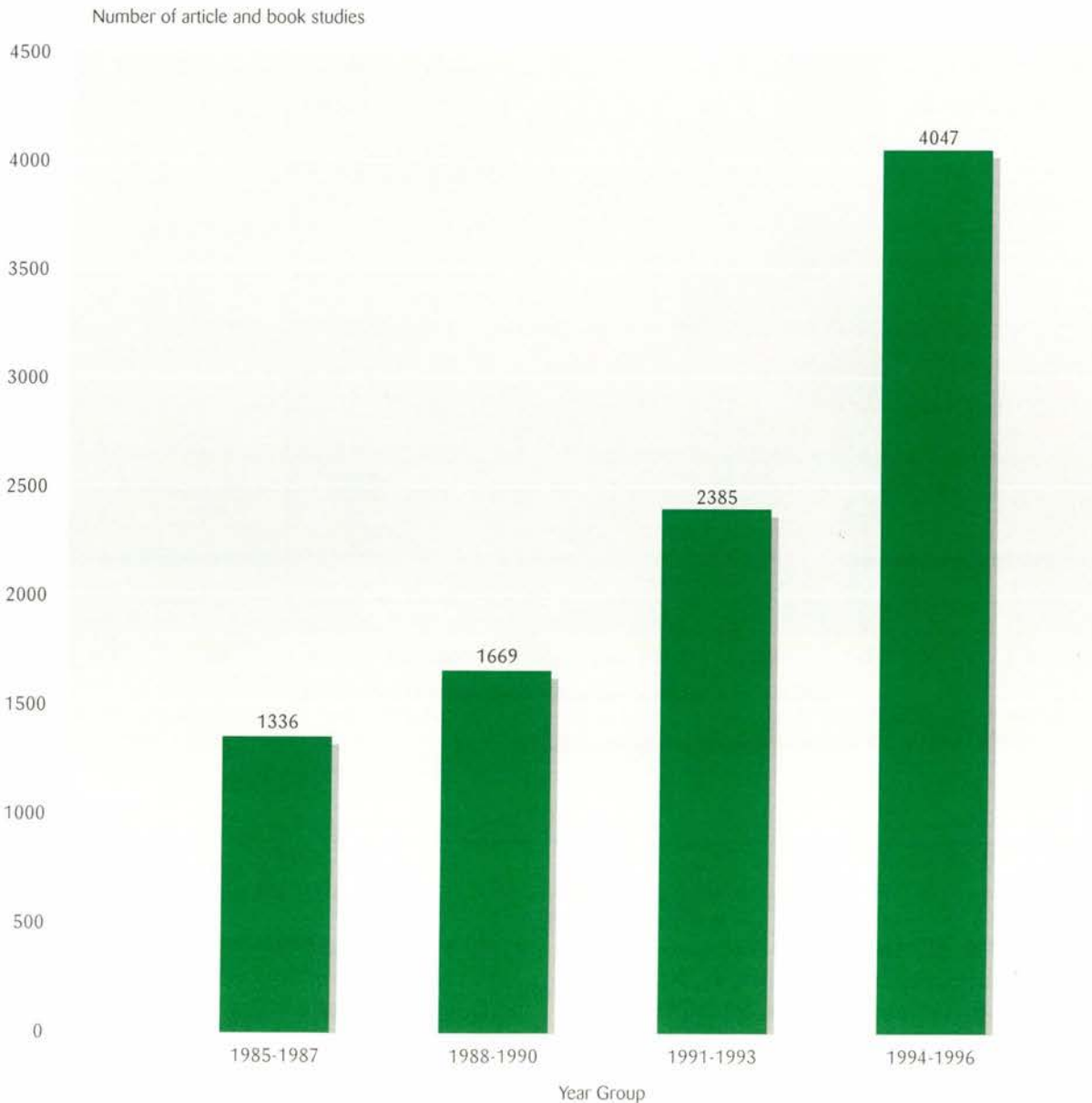
cost-effectiveness of individual medicines would grow. There would in most cases be a strong commercial incentive for companies to seek to provide it or lose credibility and sales to competitors who were able to supply information on the cost-effectiveness of their products. Whilst a requirement to undertake economic evaluations could add to the cost of supplying medicines to the NHS, information provided when purchasers and providers were likely to act upon it would displace other types of promotional expenditure.

Studies used to supply cost-effectiveness information

as part of promotional activity would therefore be covered by the guidance. Economic claims would be subject to the same standards of quality assurance and policing as promotional claims of clinical efficacy to ensure that GPs were not supplied with misleading information. The formal arrangements are discussed in chapter 4.

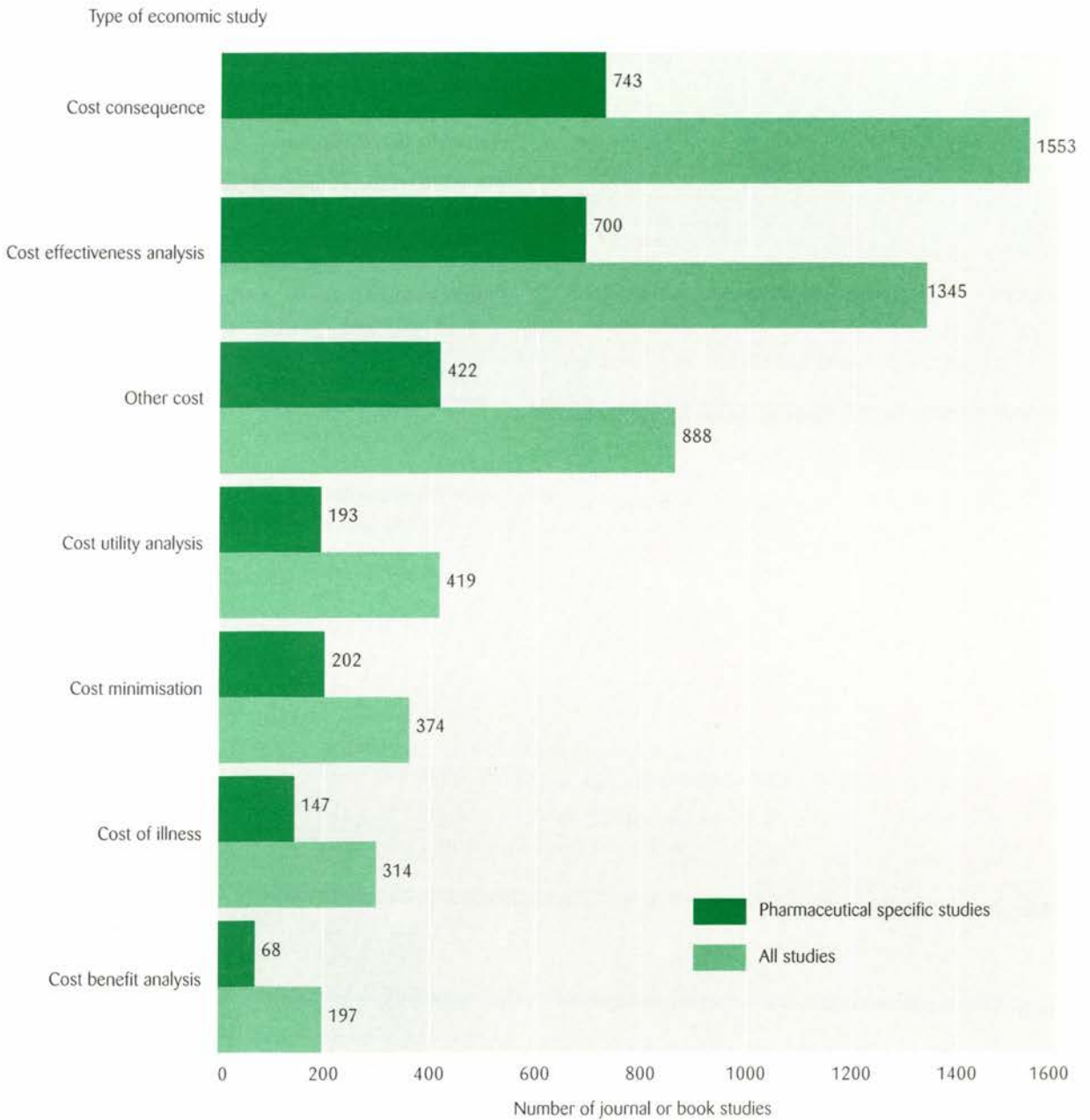
The NHS would continue to commission its own studies and reviews through the Pharmaceutical Panel of the R&D programme, and the CRD, and to include economic elements in more government funded clinical trials³³.

Figure 1 Total number of economic studies by year groupings



Source: OHE-IFPMA Health Economic Evaluations' Database (HEED).

Figure 2 Total by type of economic study, 1992-6



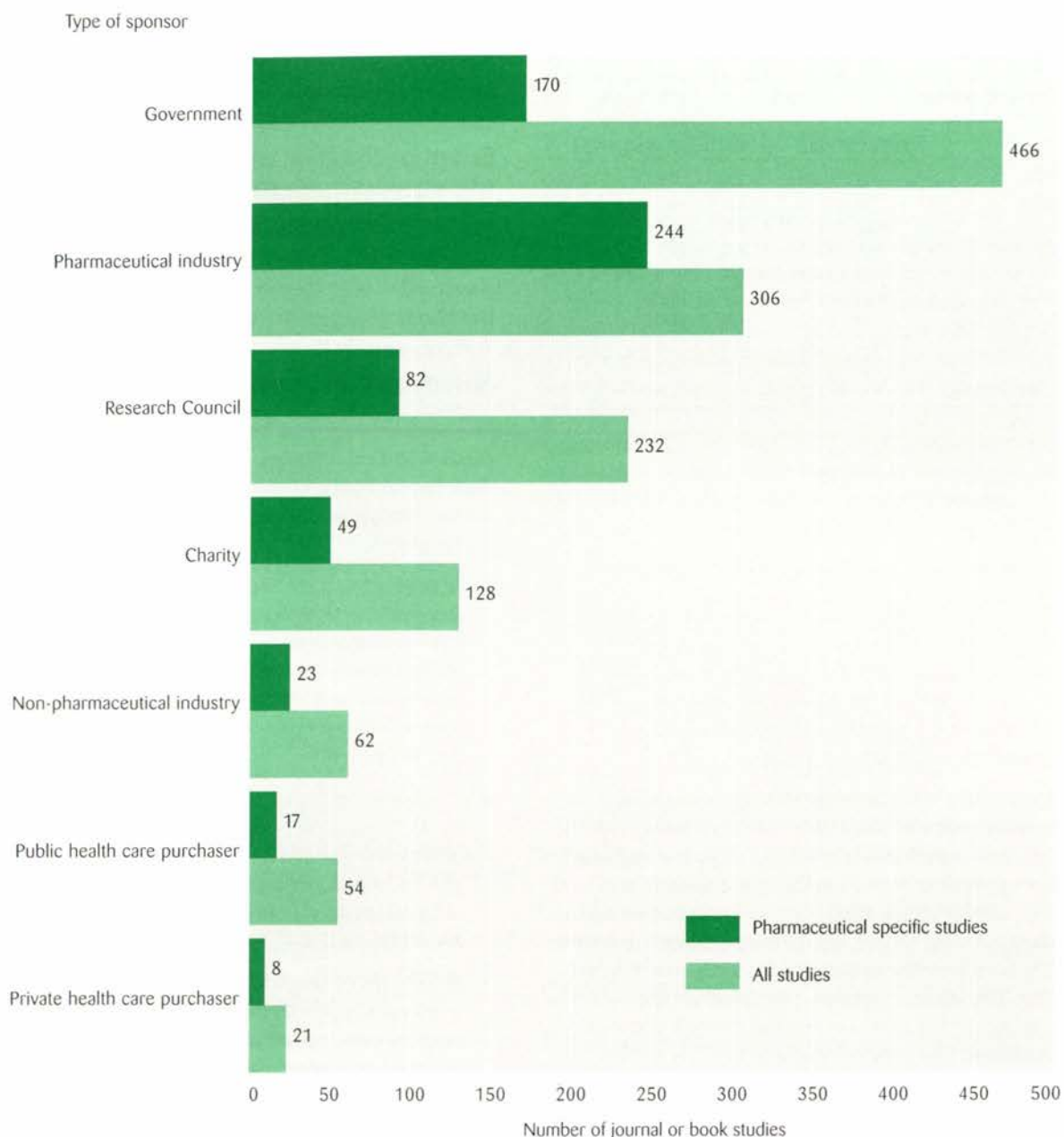
Source: OHE-IFPMA Health Economic Evaluations Database (HEED).

EVIDENCE TO DATE ON THE PRODUCTION, DISSEMINATION AND USE OF ECONOMIC EVALUATIONS OF PHARMACEUTICALS

There are a number of ways in which it would be possible to identify trends in levels of activity, and in use of the guidance. These include examining:

- the numbers of articles published, and their compliance with the UK Guidance;
- the extent of decision maker awareness of economic evaluation studies, and their willingness to use it;
- the numbers of economic 'claims' made by companies in their promotional material.

Figure 3 Sponsors of economic studies



Source: OHE-IFPMA Health Economic Evaluations Database (HEED).

Number of articles published and their compliance with the Guidance

The number of economic evaluation articles being published internationally has increased substantially. An analysis of the numbers of studies appearing on the OHE-IFPMA Health Economic Evaluations Database (HEED), set out in Figure 1, shows an annual output now in excess of 1,000 articles per annum. It is likely that there has been a similar growth rate in literature relevant to NHS decision

making. Many studies may, however, be of limited value for decision making. The breakdown set out in Figure 2 shows that less than 50 per cent of reviewed applied studies on the database are classified as CEA, CUA, CMA, or CBA. Others include cost and outcome information but do not necessarily assist decision making. Figure 2 also shows that around 50 per cent of applied studies include pharmaceuticals. Figure 3 indicates that where a sponsor of a study is disclosed, government is the largest overall sponsor, with the pharmaceutical industry as the largest

Table 1 Summary of the scores for papers accepted for publication assessed against the checklist based on the UK guidelines for good economic practice. Scoring was performed before any revisions to the papers

Types of article ^a	Scores			Total score Yes + N/A (maximum 12)
	Yes	No	N/A	
CEA	7.0	3.0	2.0	9.0
CEA	7.0	3.0	2.0	9.0
CEA	10.0	0.0	2.0	12.0
CA	9.5	0.5	2.0	11.5
CMA	6.0	3.5	2.5	8.5
CEA	10.0	0.0	2.0	12.0
Methodology	1.0	0.0	11.0	12.0
CEA	10.0	0.0	2.0	12.0
CA	8.5	1.5	2.0	10.5
Cost of illness	6.0	0.0	6.0	12.0

a CEA = cost-effectiveness analysis; CA = cost analysis; CMA = cost minimisation analysis.

Source: Raper and Hutchinson³⁴

sponsor of studies including pharmaceuticals.

The extent of published study compliance with the UK Guidance for one journal was reviewed³⁴. 12 manuscripts submitted to the BJME were assessed. Of the 10 accepted for publication, their compliance 'score', using 1 point for compliance with each guideline, was as set out in Table 1.

The average total score for these papers before revision was 10.9 (including 'not applicable' with the 'yes'). Usually indirect costs and discounting were not applicable. Non compliance included lack of explanation about choice of outcome measure and choice of data source, and of the sensitivity of results. The scores for the two rejected papers were 6.0 and 11.5. The latter comprised 'yes' 2.5, and 'not applicable' 9.0, and was rejected for lack of critical appraisal. The authors conclude that 'for papers describing economic analyses using recognised techniques, a high total score is a good predictor that the study is of reasonable quality'. However they note that peer review is also necessary as 'it is possible for a study to satisfy the majority of items but still have fundamental flaws relating to the credibility and value of the analysis.' The BJME now requires authors to meet the UK Guidance when submitting articles to the journal.

The British Medical Journal (BMJ) has published its own economic evaluation check-lists for authors, editors and peer reviewers²⁹ the first major clinical journal to do so. The objective is to achieve clarity to assist in editorial vetting and peer reviewing.

Overall it is likely that the quality of economic evaluations is improving. The difficulty of testing the impact of guidelines is discussed in the BMJ article. It

is likely however that the UK Guidance will have played a part in promoting transparency. We should, however, note the points made by Sheldon and Vannoli in Chapter 6. Critical peer review and reader interpretation are still needed.

Extent of Decision maker willingness to use economic information

Three surveys of UK decision maker attitudes to using information from economic evaluations have been carried out. The nature of these surveys and their findings are briefly set out below.

Survey of 450 key NHS professionals

This was a survey³⁵ of 450 medical and pharmaceutical advisors, hospital pharmacists and Directors of Public Health. The main group were medical and pharmaceutical advisors. The main findings were:

- 37 per cent had received training in health economics and 33 per cent were aware of published guidelines (in the main this meant the UK guidance). These figures were higher amongst the medical and pharmaceutical advisors (40 per cent and 43 per cent), and the DsPH (86 per cent and 49 per cent);
- in assessing whether a more expensive product is worth the cost, 96 per cent of medical and pharmaceutical advisors would look at clinical articles in peer reviewed journals and 77 per cent at formal economic evaluations if they were available;
- 50 per cent of hospital pharmacists were prepared to take savings both inside and outside of their hospital into account as well as the acquisition cost of a medicine when considering a formulary listing;
- when asked if they had been influenced by 11 studies, prescribing advisors were not convinced by the findings in the majority of cases. Where they were convinced, they had changed their advice around 30 per cent of the time. Unfortunately around 20 per cent also claimed to have seen two fictitious studies;
- pharmaceutical companies were the biggest single source of information about studies. Although the respondents were sceptical of industry motives, willingness to act on findings did not seem to vary with the source of information;
- inability to move resources from secondary to primary care was seen as the main barrier to using economic evaluation information.

In summary, cost-effectiveness information was being sought and used but only intermittently. A number of obstacles remained to its use.

Survey of 100 GPs

In this survey³⁶ a mix of fundholding and non fundholding GPs were sent two economic evaluations published in the BJME^{37,38} and asked a series of questions about their understanding of the studies and their willingness to act on the results. Both were cost minimisation studies. The main findings were as follows:

- after reading the evaluation, 83 per cent of GPs defined an economic evaluation as putting together the total cost to the NHS of using a drug and the health care benefits. Fundholders had a significantly better understanding;
- GPs' rating of the methodological quality of the articles was similar to that of expert health economists who were asked to peer review the studies;
- GP average rating of the key parameters of both studies (costings, efficacy rates and complication rates) was below 5 (0 low and 10 high);
- more than half of GPs regarded the results of both studies, if credible, as significant enough to change their prescribing behaviour;
- source of information was important. Reputable medical journals were the most credible source.

Thus overall, GPs appeared to be a more receptive and discriminating audience than previously thought¹³. They were prepared to act on economic evaluation information if they believed in it.

Survey of 15 Medical and Pharmaceutical Advisors

In a follow on survey³⁹ the same two studies were sent to a smaller ad hoc sample of prescribing advisors. Compared to the GPs, the advisors were more:

- aware of the purpose of economic evaluations, sceptical about study quality, and sensitive to study assumptions and parameters;
- unlikely to recommend change;
- sceptical of the role of the pharmaceutical industry and of the methodological quality of all economic studies.

They regarded the strict separation of primary and secondary care budgets as the major obstacle to the use of credible study results.

Overall these three surveys suggest interest and awareness of the potential value of economic information, but scepticism about industry supplied information and about the value of such information if expenditure and savings fall in different budgets.

Economic 'claims' by Companies

Most promotion is via advertising in medical journals, or by company medical representatives visiting GPs. Four pharmaceutical companies were asked to provide examples as to how the results of economic studies have been used in promotional activities. These are set out in Box 1. Economic claims in journal adverts are rare. Economic information is more likely to be provided in face to face discussion, with promotional material (detail aides) containing economic claims left with the doctor. Interactive computer models are used to enable health professionals and managers to estimate economic impact for their own institution.

Anecdotal data of the type set out in this section can only be used to develop a hypothesis. This might be that although use of economic information was increasing, this was from a low base, and in general, companies are not convinced that cost-effectiveness is the key message prescribers want to hear. Products perceived as 'expensive' are more likely to require information on cost-effectiveness to convince prescribers that the clinical effects are worth the price. In hospitals, prescribers look for cost savings to offset higher purchase prices. Generally, however, economic claims are viewed as secondary to clinical claims, used in meetings and in calls, rather than adverts.

CONCLUSION

The UK guidance was developed to encourage the provision of good quality cost-effectiveness information to NHS prescribers by the pharmaceutical industry.

Whilst the literature has grown and there is some evidence of a willingness to use cost-effectiveness information, it is clear that barriers remain. We can adapt Coyle's⁵² classification of these hurdles as follows:

- production. Is information generated?
- dissemination. Do prescribers know about it?
- understanding. Are they confident that they can interpret it?
- credibility. Do they believe it?
- relevance. Do they recognise it as relevant to their prescribing decision?

BOX 1 Examples from four Companies**SmithKline Beecham promotion of 'Augmentin' and 'Seroxat'**

'Augmentin' (co-amoxiclav) is an antibiotic licensed for use in a number of infections. SB commissioned an economic evaluation³⁷ comparing its cost-effectiveness in the management of chronic bronchitis with other antibiotics. It produced a leaflet promoting the product as cost-effective on the basis of this study, and developed a computer model which enabled doctors to change data and estimate effectiveness and cost savings for their practice.

'Seroxat' (paroxetine) is an SSRI for the treatment of depression. SB commissioned an economic evaluation⁴⁰ which used a simulation model to show that although Seroxat was more expensive than a tricyclic antidepressant, on the assumptions used, the direct cost per successfully treated patient was lower. A promotional leaflet was prepared using this information.

Glaxo Wellcome promotion of 'Zofran'

'Zofran' (ondansetron) is an anti-emetic used to prevent nausea and vomiting following chemotherapy. Glaxo Wellcome participated in an economic evaluation comparing the cost-effectiveness of 'Zofran' with an alternative product. The study⁴¹ concluded that although 'Zofran' was more expensive, its superior efficacy meant that it was 'equally cost-effective'. A promotional leaflet was prepared using the results of this study.

Zeneca promotion of 'Diprivan'

'Diprivan' (propofol) is an intravenous anaesthetic introduced into the UK in 1986. It is the UK's biggest hospital product by value, and is regarded as expensive relative to other agents. Zeneca argue that its superior clinical effectiveness in terms of reduced post-operative nausea and vomiting and faster recovery times offer economic benefits, particularly in the case of day surgery. Zeneca did not commission a UK economic evaluation but

sought to use data already available to look at the whole costs of anaesthesia, and the translation of clinical effectiveness into economic benefit. This included data from a number of clinical trials and from a US economic evaluation⁴². A computer model was prepared which can be used by a hospital to model economic savings using local data and a locally chosen comparator. Publications were commissioned on the economics of day case surgery and on the economics of anaesthesia⁴³.

The product is now also licensed for the sedation of ventilated patients in the ICU for periods of up to three days. To assist in the promotion of the product for this indication, Zeneca commissioned an economic evaluation⁴⁴ and has used another economic evaluation⁴⁵ in a detail aid. Again it produced a computer model based on a decision tree for use in discussions with health professionals and managers.

MSD Promotion of 'Innovace' and 'Zocor'

'Innovace' (enalapril) is a treatment for hypertension and heart failure. MSD sought to raise NHS awareness of the problem of heart failure by sponsoring a task force of specialists and GPs⁴⁶. MSD commissioned two economic studies^{47,48} showing the cost of heart failure to the NHS and the cost-effectiveness of the product as an adjunctive treatment for heart failure. The conclusions of these publications were outlined in representative detailing materials and in product advertising to medical audiences.

'Zocor' (simvastatin) is a statin used in the lowering of raised cholesterol. Following the publication of three economic studies⁴⁹⁻⁵¹ arising from the MSD sponsored Scandinavian Simvastatin Survival Study (4S), which showed that it reduced mortality and hospital costs, and was cost-effective in a range of patients. MSD is currently preparing a promotional campaign including an interactive computer model. Additional publications are planned demonstrating the effects of simvastatin in sub-groups of the 4S study, including women, elderly, post-MI and diabetes.

Relevance has several aspects:

- do prescribers accept that they should be making cost-effectiveness trade-offs? Rationing is not explicitly addressed in the NHS. Patients should receive all clinically necessary treatment. The emphasis in prescribing, as elsewhere in the NHS, is on improving technical efficiency, i.e. looking at ways in which prescribing costs can be reduced without affecting patient outcomes;
- do they think that the budget structure allows them to do this? Information on cost-effectiveness often trades off superior clinical effect for higher cost. Savings may be generated elsewhere in the NHS, or in future years;
- is the information seen as relevant to local cost and patient circumstances. Companies use computer models to enable prescribers to satisfy themselves that the economic effects are relevant to their circumstances.

It is likely that relevance is the key barrier.

Production is likely to be stimulated by demand. Credibility is clearly an issue, although the more confidence decision makers have in their ability to interpret a study, the less concern there will be with the source. There is no incentive, however, to developing understanding if the information is not seen as helpful.

Lack of expertise and poor quality information have been used to argue for an independent centre reviewing pharmaco-economic studies⁵³. However, as Sheldon and Vanoli point out in chapter 6, the NHS is now reviewing studies, and as Massam points out in chapter 4, the PMCPA does have the power to police claims rigorously. The transparency required by the UK Guidance should assist assessment. Two examples of poor studies have been cited¹³ but these pre date the UK Guidance. Drummond⁵⁴ cites a more recent case which the PMCPA adjudicated. Here, however, the issue was

not the quality of the study but the accuracy of the claim based upon it. Drummond also cites a (non pharmaceutical) cost-effectiveness claim which has been taken to the High Court by a competitor. It is hard to argue that mechanisms for ensuring quality are not in place.

It has been suggested lack of production be dealt with by making economic evaluations compulsory, but there is evidence that just giving prescribers more information 'will not lead to substantial changes in practice'.⁵⁵ Hence arguments for a 'fourth hurdle' with compulsory economic evaluations being provided to a central committee which would determine NHS reimbursement status either on licensing⁵⁶ or after a 5 year period⁵⁷. However, in the absence of centralised rationing criteria it is not clear how such a hurdle would operate⁵⁸. It is not obvious that the decentralisation of decision making in the NHS needs to be put into reverse. Prescribing is becoming more cost-effective without significant use of economic information. It may well be that the growing role of GPs in purchasing, and plans to give them the ability to move money between primary and secondary care⁵⁹, combined with continuing financial constraints, and diminishing opportunities for further efficiency gains will see increasing willingness to seek and use information on cost-effectiveness. The attitude of pharmaceutical advisors and of those developing clinical guidelines and devising local, practice, and hospital formularies, to the use of information from economic evaluations will, in these circumstances, be very important. Changing culture and behaviour takes time. There is no easy short cut to cost-effectiveness by consent.

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Appendix 1

GUIDANCE ON GOOD PRACTICE IN THE CONDUCT OF ECONOMIC EVALUATIONS OF MEDICINES

- 1) The question being addressed by the study, including the demographic characteristics of the target population group, should be identified and be set out at the start of the report of the study.
- 2) The conceptual and practical reasons for choosing the comparator should be set out and justified in the report of the study.
- 3) The treatment paths of the options being compared should be identified, fully described, placed in the context of overall treatment, and reported. Decision analytic techniques can be helpful in this regard.
- 4) The perspective of the study should ideally be societal, identifying the impact on all parts of society, including patients, the NHS, other providers of care, and the wider economy. However costs and outcomes should be reported in a disaggregated way so that the recipients of costs and outcomes can be identified. Attention should be drawn to any significant distributional implications. Indirect costs should normally be included in a societal perspective although care should be taken to avoid any double-counting and results should be reported including and excluding these costs.
- 5) The study should use a recognised technique. These include Cost-Minimisation Analysis (CMA), Cost Effectiveness Analysis (CEA), Cost Utility Analysis (CUA), and Cost Benefit Analysis (CBA). Any one of these could be appropriate according to the purpose of the study. The report of the study should include justification of the technique chosen.
- 6) In choosing the method of data capture and analysis, the use of one of, or a combination of, prospective or retrospective randomised clinical trials, meta-analysis, observational data and modelling should be considered. The reasons for choice of method and, where relevant, for choice of trials should be reported.
- 7) Assessment of the question should include determining and reporting what additional benefit is being provided at what extra cost using incremental analysis of costs and outcomes.
- 8) Outcome measures should be identified and the basis for their selection reported. Where CUA is used, proven generic measures of Quality of Life are preferred.
- 9) All relevant costs should be identified, collected

and reported. Physical units of resource use should be collected and reported separately from information about the costs of the resources. Costs should reflect full opportunity cost, including the cost of capital and administrative and support costs were relevant. Average cost data is often acceptable as a proxy for long run marginal cost.

10) Discounting should be undertaken on two different bases:

- all costs and outcomes discounted at the prevailing rate recommended by the Treasury, currently 6 per cent per annum;
- all costs and monetary outcomes discounted at the Treasury rate, currently 6 per cent, but non-monetary outcomes not discounted.

Both sets of results should be reported. The physical units and values of costs and outcomes prior to discounting should also be reported.

11) Sensitivity analysis should be conducted and reported. The sensitivity of results to all uncertainty in the study should be explored. This should involve the use of confidence intervals and/or ranges for key parameters, as appropriate. The ranges and choice of parameters to vary should be justified.

12) Comparisons with results from other studies, should be handled with care. Particular attention should be paid to differences in methodology (such as the treatment of indirect costs) or differences in circumstances (such as different population groups).

4 THE ROLE OF THE PRESCRIPTION MEDICINES CODE OF PRACTICE AUTHORITY

David Massam

THE CODE OF PRACTICE FOR THE PHARMACEUTICAL INDUSTRY

The Association of the British Pharmaceutical Industry (ABPI) first established a code of practice in 1958. It has been amended and expanded over the years and the current edition of the Code of Practice for the Pharmaceutical Industry came into operation on 1 January 1996.

The Code of Practice for the Pharmaceutical Industry applies to the promotion of medicines to members of the health professions and also to relevant administrative staff, such as hospital managers. It covers such promotion in any form, including journal and direct mail advertising, the activities of representatives and the materials used by them, the supply of samples, the use of inducements, the provision of hospitality and the holding and the sponsorship of meetings. The Code also applies to the provision of information to the general public about medicines so promoted.

The Code of Practice does not cover the promotion direct to the public of over-the-counter medicines intended for self-medication and nor does it cover the promotion of them to health professionals when the object of the promotion is to persuade the health professional to recommend the patient to buy the medicine. These are covered by other codes under the auspices of the Proprietary Association of Great Britain (PAGB). Advertising direct to the general public is covered by the PAGB's Code of Standards of Advertising Practice for Over-the-Counter Medicines and those to health professionals by the PAGB's Code of Practice for Advertising Over-the-Counter Medicines to Health Professionals and the Retail Trade.

In certain instances, preliminary consideration may have to be given as to whether particular items come within the scope of the Code of Practice. The fact that no product name is mentioned does not necessarily mean that it is outwith the scope of the Code. For example, company produced material on a therapeutic area in which the company has a commercial interest will come within the scope of the Code even if no product name is mentioned or

implied. Such material is often produced as part of the general promotional background for particular products. Advertisements in international journals are covered by the Code if the journals are produced in English in the United Kingdom even if only a small proportion of their circulation goes to recipients in the United Kingdom.

LEGAL REQUIREMENTS IN THE UNITED KINGDOM

There are a number of legal requirements in the United Kingdom which apply to the promotion of medicines. The Code of Practice incorporates the legal requirements so that companies need only comply with the Code to ensure they are complying with the law as well.

The Medicines Act 1968 includes a number of general requirements relating to the advertising of medicines. The Medicines (Advertising) Regulations 1994 (SI 1994 No 1932) implemented in the United Kingdom the EC Council Directive on the advertising of medicinal products for human use (92/28/EEC) and set out detailed requirements applicable when advertising medicines to both the public and to health professionals. Notwithstanding the Directive, harmonisation in the European Union is far from complete as a number of the Directive's provisions leave the detail to the discretion of individual member states. For example, the detail of the prescribing information which is required is not specifically set out in the Directive and thus varies from state to state.

Other Codes

There are two other codes with which companies in the United Kingdom have to comply. These are the European Code of Practice for the Promotion of Medicines established by the European Federation of Pharmaceutical Industries' Associations (EFPIA) and the Code of Pharmaceutical Marketing Practices established by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

There are also the Ethical criteria for medicinal drug promotion of the World Health Organisation (WHO). The Code of Practice incorporates all of the relevant requirements of these as it does in relation to UK legislation so that the Code is a complete document in itself incorporating all of the requirements which companies in the United Kingdom are obliged to follow.

The Prescription Medicines Code of Practice Authority

The Prescription Medicines Code of Practice Authority was established by the ABPI in 1993 to operate the Code of Practice independently of the ABPI itself. It reports directly to the ABPI Board of Management and not to the ABPI's Director General. It has its own staff but resides in the same offices as the ABPI.

The Authority was established because there was some perception, both within and outwith the industry, that a conflict of interest was involved when the ABPI operated its own Code. It was considered that it would be preferable for the Code to be administered by a separate body so that it would be seen to operate impartially between all parties without being influenced by the wider remit of the ABPI.

Complaints received under the Code of Practice, the majority of which come from health professionals with most of the remainder coming from pharmaceutical companies, are first considered by the Code of Practice Panel which consist of the three members of the Authority acting with the assistance of expert advice where appropriate. The Code of Practice Panel makes a decision in every case. A ruling of no breach can be appealed by the complainant and a ruling of a breach can be appealed by the respondent company. Appeals are heard by the Code of Practice Appeal Board which is chaired by an independent, legally qualified chairman, and includes three independent medical members, an independent pharmacist and an independent member from a body which provides information on medicines, together with twelve senior executives from the pharmaceutical industry, at least four of whom have to be medically qualified. The Code of Practice Appeal Board is the final arbiter as to whether the Code has been breached.

When there has been a breach of the Code, the company concerned must give an undertaking that the material or promotional practice in question will cease forthwith and an assurance that all possible steps will be taken to avoid a similar breach of the Code in the future. An undertaking must be

accompanied by details of the steps taken to implement the ruling. Additional sanctions can be imposed in serious cases, the most serious being reported to the ABPI Board of Management which can, for example, publicly reprimand a company or suspend or expel it from the ABPI. The outcomes of complaints made under the Code of Practice are reported in full in the Code of Practice Review which is published quarterly by the Authority.

Compliance with the Code and acceptance of the jurisdiction of the Authority is obligatory for ABPI members and, in addition, about fifty non-members have agreed to do so. The Code of Practice is thus followed by nearly all of the relevant companies in the United Kingdom.

The Authority is primarily funded by a levy payable by each member company of the ABPI and by administrative charges payable by companies making unfounded allegations and companies found in breach of the Code. No charges are payable by complainants from outside the industry. Other income comes mainly from the holding of seminars etc. The levels of charges are now such that the Authority has been self-financing from the beginning of 1996. It was subsidised by the ABPI in the first three years of its existence.

Economic Claims

Complaints about economic claims made in promotional material or by representatives etc are most likely to be made under Clause 7 of the Code. The most relevant provisions in this respect being Clauses 7.2, 7.3 and 7.4.

Clause 7.2 states that 'Information, claims and comparisons must be accurate, balanced, fair, objective and unambiguous and must be based on an up-to-date evaluation of all the evidence and must reflect that evidence clearly. They must not mislead either directly or by implication'.

Clause 7.3 states that 'Any information, claim or comparison must be capable of substantiation'.

Clause 7.4 states that 'Substantiation for any information, claim or comparison must be provided without delay at the request of members of the health professions or appropriate administrative staff. It need not be provided, however, in relation to the validity of indications approved in the marketing authorization'.

Clause 7.5 states that 'When promotional material refers to published studies, clear references must be given'.

Where information is provided in the form of a table,

bar chart or graph, Clause 7.6 is particularly relevant. Clause 7.6 states that 'All artwork including illustrations, graphs and tables must conform to the letter and spirit of the Code. Graphs and tables must be presented in such a way as to give a clear, fair, balanced view of the matters with which they deal, and must not be included unless they are relevant to the claims or comparisons being made'.

An important point in relation to comparative price charts and the like is that Clause 7.10 states that the 'Brand names of other companies' products must not be used unless the prior consent of the proprietors has been obtained'.

Price Comparisons

The majority of the complaints which have so far been made about economic matters have concerned price comparisons, frequently in the form of a table comparing a number of products. As required by Clause 7.10 referred to above, other companies' products can only be identified by using generic names. If a comparison is, however, one of branded products only, then that fact must be made clear. Otherwise prices of relevant generic products have to be included. It is not an easy matter to construct a comparative price table in such a way that all the companies whose products are mentioned will be satisfied as to its fairness. Frequently the basis of comparison is the cost of a day's treatment but problems have often arisen in identifying the appropriate dose to use for each product for comparative purposes. In some instances it may be necessary to compare the cost of a course of treatment. It is essential that the comparison is appropriate from the point of view of the prescriber. Additional difficulties can arise in the case of ointments and creams and the like where dosages are poorly defined.

An appropriate choice of comparator products must be made. It is not acceptable to exclude products merely because they are less expensive than that of the advertiser.

Straightforward price comparisons of groups of products usually relate to no more than the actual costs of the products and, unless the advertisement expressly or implicitly provides otherwise, no account is taken of the relative effectiveness of the products concerned. They are usually a comparison of the costs of treatment and nothing more.

Price comparisons must be up-to-date and promotional material including them will have to be withdrawn when prices change.

'Cost-effective' Claims

It occasionally happens that advertisements simply make the sweeping claim that the product is 'cost-effective'. The experience of the Authority to date suggests that companies rarely, if ever, have sufficient evidence to support such a claim. The claim is usually being made without thought being given as to how it might be substantiated. One defence offered by a company was that the product being promoted was effective, as it had a product licence, and it was cheap, and that it therefore must be cost-effective. Needless to say that advertisement was ruled to be in breach because the claim had not been substantiated. Something a little more sophisticated is required in support!

Pharmacoeconomic Claims

Very few complaints made to the Authority to date have involved pharmacoeconomic claims which were based on actual data. Complaints which have been dealt with include one where a breach was ruled because the claim made in the advertisement, which was supported by a published economic evaluation, was valid at a particular daily dosage but not at another and this had not been made clear. Another case involved a product where economic data was available but only in a limited group of patients undergoing particular procedures and it was misleading to extrapolate this to a general claim. One case set out potential savings to the last penny and this degree of precision could not be justified in view of the estimates and assumptions which had been made in the supporting study. In this particular case, it was also not made clear whether the savings related to the cost of medicines only or to overall treatment costs.

Based on experience in determining the few cases that there have been, the advice given in the supplementary information to Clause 7.2 in the Code of Practice was updated for the 1996 edition. This now states that to be acceptable as the basis of promotional claims, the assumptions made in an economic evaluation must be clinically appropriate and consistent with the marketing authorization. The supplementary information also states that care must be taken to ensure that any claim involving the economic evaluation of a medicine is borne out by the data available and does not exaggerate its significance.

It is advisable for companies to state the principal assumptions made in a study if not to do so might be misleading. It needs to be made clear whether figures given relate solely to the cost of the medicines or relate also to changes to other costs, such as the cost of hospital stays.

Complaints have on occasion related to claims where there was valid underlying evidence but this was based on limited indications and/or particular groups of patients and was found to be inadequate to substantiate the broad claims made on the basis of it.

Department of Health/ABPI Guidance

The supplementary information to Clause 7.2 of the Code of Practice draws attention to the guidance on good practice in the conduct of economic evaluation of medicines which has been given by the Department of Health and the ABPI and states that this is available upon request from the Authority.

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The prime task for the Authority in the event of a complaint is to assess whether the claims can be substantiated and the guidance will play a part in assessing the quality of the economic studies put forward as substantiation.

Overall Outcome

When complaints relating to pharmacoeconomic claims are considered, the outcome will usually depend upon an assessment of the relative merits of the evidence put forward by both parties, including the quality of any study used as substantiation for a promotional claim, and as to whether the claim is appropriate in the light of that evidence.

5 PRACTICAL ISSUES IN THE CONDUCT OF ECONOMIC EVALUATIONS OF MEDICINES WITHIN THE CONTEXT OF THE UK GOVERNMENT/ABPI GUIDANCE

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INTRODUCTION

The 'Guidance on Good Practice in the Conduct of Economic Evaluation of Medicines' published jointly by the Department of Health (DoH) and the Association of the British Pharmaceutical Industry (ABPI) is an important development for both producers and consumers of information regarding the economic benefits of medicines¹. The guidelines are succinct, non-prescriptive and written for readers who have a good degree of familiarity with the terminology and ingredients of economic evaluation of health care programmes. Like their counterparts in other countries²⁻¹⁰, they do not explain how to design and conduct an economic evaluation. Furthermore, no single comprehensive reference work is currently available: economic researchers have to refer to numerous and disparate sources in planning their studies. Some 'guidance on the guidance' is therefore warranted and is the purpose of this paper. Each of the twelve guidelines is considered in turn below. Key references of relevance to the topic are provided and some important considerations which are not addressed by the guidelines are enumerated.

GUIDANCE ON THE GUIDANCE

The guidelines assume that the reader is technically literate as far as economic evaluation is concerned. Those wanting to acquire a basic knowledge of the subject are advised initially to review some introductory texts^{11,12} and overview journal articles¹³⁻²⁰. A number of economic evaluation bibliographies have been published which provide comprehensive coverage of the applied and methodological literature²¹⁻²⁷. These collections of references are invaluable research documents.

Clearly define the question

This guideline requires explicit statements about the objectives and key characteristics of the study population to be reported so that readers can assess its relevance to different settings and patient populations. Economic evaluation is intended to inform decisions, which means that in defining the question, it is important to identify the decision the analysis seeks to influence, who the decision-makers are, and when and how the decision is to be taken. Relevance of an economic evaluation to the target audience is a major determinant of its impact²⁸, and so the question would ideally be defined in partnership with the ultimate decision-makers. Since each study is likely to have multiple audiences, careful prioritisation is required so that a focused approach can be adopted.

There are likely to be many economic questions pertaining to a drug. It is, therefore, important for the designer of the study to identify and prioritise them at the outset because it is unlikely that all could be answered by a single analysis, even if it were practical to do so. In this respect it is important to understand the differences between global and local questions²⁹ and between top and low level questions. A drug may be shown to be the most cost-effective within its class (local question) whilst the cost-effectiveness of that class might not have been established (global question). Similarly, whilst an analysis may demonstrate overall cost-effectiveness for a specific patient group (top level question), it may not investigate whether cost-effectiveness varies by sub-groups within that study population (low level question).

Justify the choice of comparator(s)

Economic evaluation of a medicine always involves a comparison with at least one other health care intervention (including the possibility of no treatment). Criteria for selecting comparators have been documented by economists³⁰. Any alternative treatment is permissible within the framework of the guidelines, provided that the rationale for the choice is clearly documented. The number of potential comparators is therefore likely to be large, but the guiding principle should be to aim for alternative(s) which are most relevant to the decision-makers for whom the analysis is intended.

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Firstly, the relevant comparator could be the most effective treatment which could be justified on the grounds that no other intervention offered greater benefits. However, the most effective technically feasible treatment may not be widely used, thereby limiting the interest in the findings. If the most commonly adopted practice is chosen, justification could be that the results are relevant to the greatest number of decision-makers. This would clearly not be the case in instances where the most prevalent treatment had only a simple majority share of all treatments given. Where no single treatment clearly dominates all others in terms of frequency of adoption, a comparison against a collection of alternatives weighted for their frequency of use might be justified. A treatment which has been unequivocally established as the most cost-effective practice would be an obvious and easy to justify comparator. However, at this point in time there are likely to be few instances where this is the case, and the most cost-effective therapy may not be the most commonly adopted. Finally, the least cost practice (provided it is more effective than doing nothing) is always likely to be an important candidate comparator, and would be essential for any assessment of global cost-effectiveness.

Clearly describe the options

This guideline encourages the use of decision-analytic techniques in a thorough description of the comparators. There are two major advantages in this. First, decision-trees provide a rigorous structured framework for setting out the logical and temporal sequence of clinical decisions and events relevant to the management of the disease of interest. This assists communication, interpretation and development of the results. Second, economic evaluations frequently require some modelling components and where this approach is used, little additional effort should be required.

Option description within a decision-analysis framework should begin early in the life of a study

and can make a valuable contribution to various aspects of planning and design, such as the identification of key events and probabilities; power calculations; validation with decision-makers; and insights into issues surrounding the logistics and process of data collection and analysis. Decision-analytic modelling is therefore a logical precursor to any definitive study, as well as being a core component of it.

Some excellent introductory texts and computer programmes are available³¹⁻³³ and there are many examples of the application of decision-analytic methods³⁴⁻³⁷. In some situations, simple probability trees can be cumbersome and difficult to apply and more sophisticated approaches are required³⁸⁻⁴⁰.

Adopt a societal perspective

Any perspective is permissible within the guidelines, although researchers are encouraged to construct and report a balance sheet encompassing all the costs and outcomes of the treatments being evaluated regardless of who in society bears them. By adopting the societal perspective and transparently disaggregating the overall results into the different viewpoints, the potential information needs of all individuals and organisations affected can be met simultaneously.

At a practical level, priority should be given to incorporating the range of information identified by the key decision-makers as being of relevance to them. However, it is desirable to adopt the comprehensive societal approach so as not to mislead decision-makers. If a narrow perspective is taken and the balance sheet looks favourable, an inefficient treatment might be adopted where, for example, significant costs borne by others have been ignored. Conversely, value for money practices may be rejected if a focused viewpoint leads to the omission from the balance sheet of important elements, such as savings elsewhere.

There is considerable debate amongst economists concerning the handling of indirect costs in economic evaluation⁴¹⁻⁴². In particular, a key issue concerns how losses in productive activity should be valued, especially in periods of relatively high unemployment. Unlike the Australian guidelines which explicitly reject consideration of indirect costs², UK analysts are correctly encouraged to consider them. This reflects their obvious importance as measures of the benefits of treatment. However, the UK guidelines are right to encourage them to be valued carefully and reported separately to enable the reader to assess how much the conclusions hinge on this aspect.

Use a recognised technique

There are four recognised forms of economic evaluation: cost-minimisation analysis (CMA), cost-effectiveness analysis (CEA), cost-utility analysis (CUA) and cost-benefit analysis (CBA). The differences between them are well documented¹⁴⁻¹⁷. CEA is by far the most common form of evaluation²¹, reflecting factors such as the rarity of the circumstances under which CMA is likely to be applicable (few treatments ever generate benefits which are identical in every respect), and the theoretical and practical problems associated with measuring and valuing health outcomes for the purposes of conducting a CUA⁴³⁻⁴⁵ or a CBA⁴⁶.

Unlike the Ontario guidelines³, no particular form is encouraged. However, the guideline requires justification for the chosen form of evaluation. This should include honest statements about why some approaches were rejected. Such a declaration permits both the relevance and the quality of the study to be assessed, which is an important consideration given that many studies are not what they purport to be²⁴⁻²⁷.

A number of practical and theoretical considerations will drive the form of economic evaluation adopted. Above all else, the choice will be driven by the decision which the analysis seeks to inform and the acceptance of the methods on the part of the decision-maker. In most situations, researchers will be seeking to provide information about how best to allocate a limited budget within a specified disease area, in which case CEA is likely to be adopted. On the other hand, CUA or CBA would be used if the target audience was concerned with making decisions across different disease areas. CBA would be chosen if the goal was to assess whether the treatments being evaluated are worthwhile.

At a practical level, it is important to recognise that the different forms of evaluation are not mutually exclusive. There is significant overlap, which means that the incremental effort associated with conducting two or more types of analysis simultaneously may not be significant. There are clear benefits to be gained from conducting more than one type of analysis, including the ability to inform a wider range of decisions and the research value of being able to compare the results of different approaches.

Justify the sources of data

Economic evaluations can be conducted prospectively or retrospectively drawing data from randomised experiments (clinical or naturalistic)⁴⁷, observational research (no random assignment to treatments)⁴⁸ or systematic overviews of

experimental evidence (meta-analyses)⁴⁹. Studies which draw on a number of sources involve the synthesis of data within models which can range in complexity from simple decision trees³⁵ to elaborate Markov processes involving simulation^{38,49,50}. There is therefore a large number of possible design permutations. Each has its strengths and limitations and there is no consensus about the preferred approach. Moreover, it is difficult to glean from the literature which approaches might be most appropriate in different circumstances.

Most published economic evaluations have been based on models, so there is a large literature from which the researcher can learn^{21,22}. These typically combine clinical probabilities and outcomes from randomised trials together with resource use (cost) and health outcomes data from sources unrelated to the clinical experiments. Such studies offer advantages in that the resource use data may be more relevant to actual clinical practice, are not particularly expensive to conduct and may generate more timely results. However, there are also disadvantages such as the perceived credibility of drawing data from disparate sources and the making of assumptions.

Very few studies have been conducted as an integral component of randomised experiments, and there are even fewer examples of good analyses undertaken in this way²⁷. Interest, experience and opportunities in this approach have grown in recent years. A number of invaluable references are available to guide study designers⁵¹⁻⁷², and some successful recent applications can be found^{47,73}.

To overcome the potential drawbacks of 'piggy-backing' economic data onto some restrictive forms of clinical trial, researchers are increasingly looking to randomised studies specifically for economic evaluation. These are designed to be naturalistic in terms of factors such as trial population, patient management and duration of follow-up. Observational studies also provide a valuable source of naturalistic data, but may have biases inherent in the comparisons made due to the absence of randomisation.

In practice, the choice of data sources is unlikely to be an 'either - or' decision and some combination of study design is almost always necessary. For example, whilst data on the physical quantities of resource use may be captured in a clinical trial, prices for the items will almost always be generated through a parallel exercise. Moreover, most situations will require some element of modelling, for example to extrapolate beyond the period of the observed data⁷⁴. This guideline acknowledges that data can be generated in a number of ways, each of which is capable of generating robust conclusions.

Perform incremental analysis

Investment decisions in health care, like in business, are typically concerned about whether it is worth expanding or contracting an existing programme. This guideline reflects this fact by requiring that the conclusions of an economic evaluation be drawn primarily from an incremental analysis. Incremental analysis involves calculating the additional cost of changing the level and/or nature of services currently being provided and dividing it by the additional benefits associated with the proposed alternative programme. The result of this calculation is an incremental cost-effectiveness ratio, i.e. a value for money ratio, such as cost per life-year gained. This tells the decision-makers how much more they will have to pay to obtain one more unit of benefit.

In addition to the incremental analysis, it is important to present decision-makers with data on the total costs and the total benefits of each separate programme being evaluated. This will enable them to establish the overall impact on the relevant budgets of any change in practice. Furthermore, it is valuable to present differences (as well as totals) of the physical quantities of resources used by each programme, and not simply the monetary value (cost) of them. There are many useful references on conducting and presenting incremental analyses^{12,20}.

Justify the choice of outcome measure

There is a substantial number of outcome measures which can be used in health care research^{75,76}. However, economic evaluation requires the benefits of a programme to be expressed in a single index measure so that ratios of costs to benefits can be calculated. No such measure has been universally recognised as the gold standard, so this guideline requires the basis for the chosen outcome measure to be clearly documented. The choice of approach will be driven by many considerations, most notably the form of economic evaluation to be adopted and the availability of valid, reliable and sensitive instruments which lead to a single index score.

If CEA is undertaken, outcomes need to be measured in units which are 'natural' to the programmes or disease area under investigation. Life-years saved⁷⁴, successfully treated patients³⁵ and symptom-free days⁷⁷ are examples of some of the measures which have been used. CUA involves measuring outcomes in terms of quality-adjusted life-years (QALYs)⁷⁸ or healthy-year equivalents (HYE)⁷⁹. Essentially, these approaches involve valuing outcomes in terms of patient or general public preferences. It is possible to measure preferences either directly with instruments developed for this purpose^{80,81}, or indirectly through

a two stage process which involves the construction of descriptions of health state scenarios followed by valuation with time trade-off or standard gamble techniques^{82,83}. For CBA, outcomes are valued in monetary terms using either the human capital or willingness-to-pay (WTP) methods^{46,84-86}.

At a practical level, an eclectic approach should be considered given the interrelationships between different types of measure⁸⁷ and the value of subsequently being able to conduct more than one form of economic evaluation. Thus, an ideal study strategy might involve: collecting clinical data in a format for producing a composite outcome measure, such as symptom-free days⁷⁷; use of a disease-specific quality of life measure, which could be used as an input to the construction of health state scenarios^{87,88}; application of one of a number of proven generic quality of life measures, which could also be used in the construction of scenarios⁸⁹⁻⁹¹; use of one of a number of direct preference measurement systems^{81,82}. Any measures used must be proven, which means they must have been subjected to rigorous scientific development, including testing of sensitivity, validity, reliability and appropriate cultural adaptation where measures developed in other countries are being used^{92,93}.

Report costs in detail

Costing for economic evaluation involves three stages, namely the identification, measurement and valuation of the resources relevant to the study. The scope (boundaries) of the cost analysis will be driven by the perspective of the study. To identify the relevant costs it is useful to consider which resources (e.g. hospitalisations, diagnostic tests, informal care) would not be used in the absence of the treatments being evaluated, and which might change, by how much and why if a new practice were adopted. Following identification, the relevant cost items need to be measured in physical quantities for each treatment (e.g. number of hospital admissions and length of stay by level of care). Finally, unit costs need to be obtained for each item of resource use (e.g. cost per inpatient day in intensive care) so that they can be valued in monetary terms. If these three steps are systematically followed and the outcomes of each are reported, it will be relatively straight forward to comply with the first part of this guideline.

The biggest practical problem which is likely to be faced is how to obtain data for valuing resource use. In Australia, a set of standard costs has been published for use in conjunction with their guidelines⁹⁴. No such document is available in the UK so unit costs and market prices will have to be obtained from various sources such as published

studies, NHS accounts and tariffs or original research. A number of particularly useful sources are available⁹⁵.

The guidelines emphasise the importance of valuing resources in terms of their next best use (opportunity cost), using marginal rather than average unit costs, and handling capital and joint costs correctly. Routinely available data are unlikely to address these aspects, and few studies have done so in practice. Nevertheless, researchers operating within the guidelines should strive to deal with these issues, and a number of papers are helpful in this regard⁹⁶⁻⁹⁹.

Undertake discounting

Discounting is a fundamental component of investment appraisal in both the private and public sector. Good descriptions of the methods and applications are available¹⁰⁰⁻¹⁰¹. Discounting is undertaken to allow for the fact that costs and outcomes can occur at different points in time. Most people would prefer to have benefits as soon as possible and delay costs as long as possible (a positive time preference). In essence, therefore, discounting places an increasingly lower weight on costs and outcomes the further into the future they occur. Currently, there is a debate amongst economists concerning whether outcomes as well as costs should be discounted and which discount rate should be used¹⁰²⁻¹⁰⁶. This is an important debate because the results of an economic evaluation can be affected greatly by the approach adopted.

This guideline adopts a pragmatic approach to discounting by requiring results to be presented for three scenarios. The first scenario requires all data to be presented undiscounted enabling the user of the information to assess the impact which discounting has on the conclusions. The second scenario is where both costs and outcomes are discounted at the prevailing test discount rate (the rate recommended by the Treasury for use in public service investment appraisal). In the third scenario, costs, but not outcomes, are discounted at the test rate. These permutations are relatively straight forward to conduct and if coupled with a sensitivity analysis of the discount rate, should ensure that information needs of most interested parties will be met.

Perform sensitivity analysis

Sensitivity analysis is used in economic evaluation to assess how the results of a study are affected by uncertainties associated with the chosen methods of data capture and analysis¹⁰⁷. If uncertainties are not thoroughly investigated and reported, together with their consequences, decision-makers could be

mislead about the likely value of treatments. To comply with this guideline, the potential causes of uncertainty and types of sensitivity analysis need to be understood. A recent overview article is particularly useful in this regard¹⁰⁸. Uncertainty relating to variability in sample data, generalisability of results, extrapolation beyond the observed data and choice of analytical methods can all be present in a study. These can be dealt with using a combination of simple sensitivity analysis, threshold analysis, analysis of extremes and probabilistic sensitivity analysis. A number of references illustrate their application¹⁰⁹⁻¹¹².

Each variable in an economic evaluation will have a plausible range of values within which the actual value will fall. Sensitivity analysis should involve varying the estimated value of each parameter within its plausible range, either alone or in combination, to assess the impact of the uncertainty on the overall study results. Neither variables nor their possible values should be selected for sensitivity analysis on an arbitrary basis. Where parameter values are estimated from sample data, for example in a clinical trial, the plausible range can be defined by calculating confidence intervals using conventional statistical techniques¹¹³. However, where values are simply point estimates, for example those based on assumptions used in modelling, the researcher should provide sources and explanations for the range of possible values.

Most economic evaluations in the future are likely to involve a mix of sampled and non-sampled data. The results of important research into the application of standard statistical principles to dealing with uncertainty in economic evaluation are now being published^{67,70,114}.

Compare like-with-like

The purpose of economic evaluations in health care is to inform decision-makers about which treatments are worth the investment of scarce health care resources and where interventions stand relative to each other in terms of priority for funding. Inevitably, therefore, researchers and decision-makers will wish to compare the results of an individual study with those from studies of different health care interventions¹¹⁵. Such a use of economic evaluative data is exemplified by the number of studies which have brought the results of different works together in the form of 'league tables' of relative cost-effectiveness^{74,116,117}. This guideline highlights the relatively primitive state of knowledge and experience in making such comparisons, emphasising the need to ensure 'like with like' comparisons where results are being placed in a broader context.

An overview of the state-of-the-art has pointed to the fact that the outcomes of comparisons could be as much to do with heterogeneity of methodologies adopted as opposed to real differences in relative value for money¹¹⁸. Specifically, differences in factors such as discount rates, methods of valuing outcomes, scope of cost and outcome analysis, choice of comparators, date of study, country of study and patient populations can all give rise to false positive and false negative conclusions about relative value for money. Researchers operating within the guidelines are urged to familiarise themselves with the state of the art article and its recommendations. The DoH/ABPI guidelines are consistent with five recommendations made in the article for ensuring ultimately that like-with-like comparisons can be made.

As more and better studies are conducted, the scope for conducting more meaningful comparisons will grow. The study database published by the DoH provides a valuable step in the right direction¹¹⁹.

OTHER CONSIDERATIONS

In working within the framework of the guidelines it is important to be aware of a number of additional issues which, whilst not explicitly covered by the guidelines, have a potential bearing upon the conduct of studies undertaken within their framework.

Firstly, there is no requirement to specify the time-horizon of a study. Since cost-effectiveness can vary over time, it is important to state the time period to which the analysis relates. This could usefully be incorporated into the definition of the question or the description of options. A number of studies have looked at the methods of extrapolating beyond the period of observed data in order to derive more comprehensive estimates of the value of treatments¹²⁰.

Secondly, economic evaluations are increasingly being conducted as multi-centre and multi-national analyses where data are generated in a number of different institutional and cultural settings. This raises issues of transferability and generalisability of results with which researchers need to be familiar¹²¹. Thirdly, the economic terms used in the guidelines have very precise definitions although in practice they are frequently used incorrectly. To avoid confusion and misunderstanding, economic terms need to be clearly understood and applied consistently across studies.

Fourthly, whilst the guidelines have been developed to ensure that promotional claims can be substantiated by a well conducted study, they give no

guidance on the criteria under which a drug could be regarded as 'cost-effective'. Economists have developed criteria which need to be fulfilled for such a claim to be substantiated, and these should be considered when making a claim based upon the findings of a study¹²². Fifthly, there is growing concern in a number of quarters that the results of studies might be biased as a result of the incentives facing the sponsor or investigators. Whilst the guidelines do not explicitly address such questions, researchers are advised to familiarise themselves with the issues and the remedies being proposed or adopted, and to take all necessary measures to maximise the integrity of the analysis¹²³⁻¹²⁹.

It needs to be recognised that the quality, credibility and relevance of a study will hinge heavily on the establishment of sound processes governing the management and conduct of the research. Multi-disciplinary project teams encompassing project management, statistical, clinical, data handling as well as economic expertise need to be established at the outset of the project. A steering committee should be set up to ensure the integrity of the research. The roles and decision-making authority of the committee's members, and the relationships between sponsor and independent investigators, should be well documented and reported. Researchers should strive to ensure that protocols, analysis plans and publication plans are produced and finalised prior to completion of the data collection effort. Finally, the human and financial resources required for a well conducted study should not be underestimated. It is unlikely that many studies could be completed within a twelve month timescale.

CONCLUSION

Adherence to the UK DoH/ABPI guidance will help to ensure that economic evaluations sponsored or conducted by pharmaceutical companies are of a consistent, comparable and high standard of methodology and presentation. Moreover, their flexible nature provides a framework within which the science can develop. Thus, DoH and National Health Service decision-makers will, in the future, be able to have confidence in the quality of the evidence about economic value presented to them, and will have at their disposal sufficiently detailed information to enable them to interpret and use the results in the planning of their services. The guidance will contribute to the achievement of economic efficiency (value for money) in health care provision by ensuring a flow of relevant and reliable economic information.

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6 PROVIDING RESEARCH INTELLIGENCE TO THE NHS: THE ROLE OF THE NHS CENTRE FOR REVIEWS AND DISSEMINATION

Trevor Sheldon and Alessandra Vanoli

BACKGROUND – THE NEED FOR RESEARCH INTELLIGENCE IN THE NHS

It is generally agreed that health services should be as efficient as possible, subject to other policy objectives such as equity. The importance of basing health care decision making on a sound appreciation of the evidence of effectiveness and cost-effectiveness has also been espoused by Ministers and officials in the Department of Health. For example, at the 1993 British Medical Association conference on priority setting in the NHS the then Secretary of State for Health asserted that:

‘Before we can be confident that we are using resources appropriately, we need to have a much better knowledge of the outcomes of clinical interventions. At the same time, we need to understand more clearly the health gain that can be obtained from different procedures. When we do have information on effectiveness we must ensure that it is being properly used in routine practice, in the right way and on the right patients.

We must consider cost as well as clinical effectiveness... we must search relentlessly for ways of achieving better outcomes and improving health gain, while providing better value for taxpayers’ money¹.

In practice however, most of the emphasis on efficiency has concentrated on rather narrow aspects of technical efficiency. That is getting as much product out from a given set of inputs once the nature of the products has been decided. Thus the government is always exhorting the system, like Boxer in *Animal Farm*,² to ‘work harder’, to be more efficient or to make ‘efficiency savings’ which basically means doing more for less investment. Many would subscribe to the view that the likely effect of this grinding emphasis on narrow technical efficiency (with little data to show where the technical inefficiencies are) on the NHS and the people who work in it will suffer the same fate as Boxer – the knacker’s yard!

Of greater importance are the possible improvements in the technical and allocative efficiency associated with the type of health care which is practised. In other words trying to use the NHS resources to produce the maximum gain in health by allocating the resources to clinical areas where the technologies are most cost-effective. Thus it would be wasteful and unethical to devote millions of pounds to a treatment which resulted in a small improvement in health where those resources could produce greater improvements if invested in some other health technology or another condition.

The current allocation of resources to technologies is unlikely to be optimal. It reflects a range of influences such as historical patterns, commercial pressure, professional interest, enthusiasms and beliefs, consumer demands and political wishes. None of these by themselves are likely to result in an efficient allocation. Consumers are not always aware of the costs or benefits of treatments and commercial interests may be in direct contradiction to this aim unless the right set of incentives is in place. Clinicians have a range of interests influenced by consumers and suppliers all underscored by a deeply felt imperative to do what they think is best for each individual patient at the time of treatment, a decision generally taken in isolation from the broader consequences for others.

In any cash limited system rationing of some sort must occur since neither all the demand of consumers can be met nor the desires of professionals to supply services funded.³ The way that rationing decisions are taken however, even when they are explicit, rarely take into account evidence on the likely benefit and cost of interventions. For example, the decision by some health authorities not to fund assisted conception for some subfertile couples – a technique which is effective in a significant proportion of cases – is in stark contrast to their funding gynaecology budgets which includes surgery on moderate or severely blocked fallopian tubes, which is relatively ineffective.⁴

As in other health care systems there has been a

significant push in the NHS to try and promote the uptake of information on clinical effectiveness. This forms part of the 1996/7 Planning Guidance⁵ and a clinical effectiveness initiative has been launched by the NHS Executive⁶. Associated with this has been an increase in the production of clinical practice guidelines and other initiatives to promote more effective care. All this activity however, has mainly been focused on clinical effectiveness – assessing the effect on health outcomes – rather than cost-effectiveness or efficiency.⁷ There appears to be rather a sharp divide, with discussion of efficiency referring either to the sort of vague but narrow technical efficiency discussed in section above or to broad productivity as measured by such misleading indicators such as the ‘efficiency index’ which is about demonstrating more activity (independent of the health effects) for any given unit of resource.⁸

One obstacle to decisions being made which promote efficiency in health care is the absence of reliable information on the relative costs and benefits (in particular, when these are formulated as final outcomes) of health care interventions. Without this information it is impossible to assess the room for improvement and what action needs to be taken. This intelligence can only come from a systematic consideration of high quality relevant research. It would be a positive step for the health service if more attention were paid to the scientific evidence about cost-effectiveness in determining health policy. Whilst a ‘scientific’ empirical approach will not always be the sole determinant of action, evidence about benefit and cost is an appropriate and necessary (if not sufficient) condition for an efficient allocation of society’s scarce resources.

This chapter describes the role played by the NHS Centre for Reviews and Dissemination in identifying and disseminating research intelligence to the NHS. In particular it outlines the way in which information on the economic evaluation of health care is handled. The chapter finishes with a discussion of some of the problems of reviewing and disseminating the results of economics studies.

The Role of the NHS Centre for Reviews and Dissemination in Providing Research Intelligence in the NHS

In order to make available research intelligence in a more systematic way, the NHS Research & Development Programme developed the Information Systems Strategy which established the UK Cochrane Centre, the NHS Centre for Reviews and Dissemination and the National Research Register. The NHS Centre for Reviews and Dissemination

(CRD) was established in January 1994 at the University of York. The aims of the CRD are primarily to:

- a) Carry out and commission credible, intellectually rigorous, timely, relevant reviews of research findings about the effectiveness and cost effectiveness of health care. To contribute to an improvement in the general standard of reviews by preparing ‘good practice’ guidelines.
- b) To improve the accessibility of these and other research reviews by maintaining and updating an international register of research reviews (both completed and in progress) and providing a single access point to this information for NHS enquirers.
- c) To provide simple and effective mechanisms by which the results of NHS R&D and other research can be communicated rapidly to relevant audiences (dissemination).

a) Reviews

CRD carries out and commissions reviews in order to provide intelligence to the NHS on topics on which information is needed to help to develop policy or to reduce uncertainty. The topics reflect the priorities of a number of organisations such as the NHS R&D Health Technology Assessment Programme, health authorities, professional associations, the Department of Health, the Health Education Authority and consumer organisations.

These reviews cover a wide range of clinical topics in areas of prevention and treatment (such as management of cataract, BPH, menorrhagia and prevention of accidents) and also consider the effectiveness and efficiency of forms of organisation and management of care. For example, CRD is continuing to look at the research evidence on the relationship between the volume and quality and cost of care and health service interventions to reduce inequalities in health.

b) Databases

It is important that information from effectiveness and cost-effectiveness studies should be readily accessible to all those who may wish to use them. CRD makes this possible by providing two databases which offer summaries of evidence from Systematic Reviews of effectiveness and single studies of cost-effectiveness, and which complement the Cochrane Database of Systematic Reviews.

The Database of Abstracts of Reviews of Effectiveness (DARE) is a set of records of reviews of the effectiveness of health care interventions and the organisation of health care delivery published since

1994. These are culled from the world literature, carefully filtered for quality, and summarised as structured abstracts by researchers in York. These abstracts explain the aims of the review and its main findings, and also include a critical appraisal of the methods used. The second set of abstracts is the NHS Economic Evaluation Database, which contains detailed summaries and critical appraisals of economic evaluations of health care.⁹

Both these databases can be searched on-line by title, topic, or author, and the results can be saved to a file or printed out. They are available free of charge to anyone who can access the CRD computer via the Wide Area Network (Janet or the Internet via TELNET), direct dialling using a modem, or the York University World Wide Web home page. They will also be accessible through the NHS wide network.

CRD has an information service which provides support to in-house reviewers and commissioned reviewers, manages the database structure and associated systems and ensure accessibility for searching to users and maintains an enquiry service. This offers the following functions:

- advice on how to locate reviews
- advice on how to access our databases
- searches of CRD databases on behalf of enquirers who do not have access.

CRD is organising a number of training sessions and open days for professional information providers such as librarians to try and increase the availability of our information sources at a local level.

c) Dissemination

Many of the reviews carried out or commissioned by CRD are disseminated to the NHS in an accessible format as Effective Health Care bulletins. CRD also summarises the results of important and reliable reviews already published for dissemination via a new publication, Effectiveness Matters. A recent issue, for example, looked at the more cost-effective treatment of ulcer by the eradication of the bacteria *H. Pylori*. All CRD publications are carefully peer reviewed before publication.

About 50,000 copies of both Effective Health Care and Effectiveness Matters are distributed widely in the NHS to a variety of people within commissioning authorities, provider units and general practice and elsewhere. Summaries are also written for various publications aimed at managers and clinicians, such as Health Director and professional journals. CRD has also been exploring ways of translating these reviews into forms which can be used to promote research-informed choice by patients. For example,

the Informed Choice Initiative, launched in January 1996 in collaboration with the Midwives Information and Resource Service disseminated high quality leaflets for patients and professionals on specific topics in maternity care.

HOW CRD CONTRIBUTES TO DISSEMINATING THE RESULTS OF ECONOMIC EVALUATIONS

Need for an NHS economic evaluations database

One of the key roles, of the CRD is to provide research intelligence to help people in the NHS make more rational, or at least informed, decisions whether at a more general policy or micro clinical level. This is particularly challenging when it comes to economic information. For some time now economists have been urging health care decision makers to look at the resource implications of their actions and use cost-effectiveness data.¹⁰ As this publication shows, in some countries regulations have been introduced to ensure that approval is only given to new drugs that can demonstrate a cost-effectiveness advantage over existing preparations or that have at least been subjected to a rigorous economic evaluation. For this and other reasons a lot of energy has been focussed on producing guidelines for the conduct of economic evaluations; though there are doubts as to whether economic evaluation is sufficiently intellectually mature to provide a basis of coverage decisions.¹¹

A precondition for using the results of economic evaluations is the ready accessibility of this information so that it can be drawn on when needed. In addition, because of the complexity often found in published economic analyses some form of critical appraisal to help NHS users judge the quality and to interpret the results should improve the quality of decisions they make using economic evaluation information. Though some local or regional projects have been active in developing and using this information on specific topics and in particular contexts, what was felt necessary was the development of a comprehensive database of the results of economic evaluations for use by the NHS. A start was made on this in the early 90s by the Economics and Operational Research Division of the Department of Health which assembled the beginnings of a register of cost-effectiveness studies. The studies on this register have since been pruned, reviewed and published.¹² CRD has been commissioned to update the register and to make it more user friendly and accessible by putting it on a publicly available database – the NHS Economic Evaluation Database.

Surveys in Britain¹³ and Australia¹⁴ have found that whilst decision makers think that formal economic evaluations published in peer reviewed journals are an important source of information there were several problems associated with their use. For example, the majority wanted easier access to the studies, but often found them to be poorly written or too technical and difficult to understand. Respondents were also suspicious of industry sponsored evaluations and wanted some form of independent assessment. These concerns are well founded: a review of the studies in the Department of Health register found many to be of low quality¹⁵. This is confirmed more generally by other reviews of quality which report the general lack of methodological rigour¹⁶.

By providing these summaries and detailed critical appraisals based on theoretical principles of economic evaluation in the form of structured abstracts it is hoped that the database will not only increase access to the material but also help the users to understand the methods used, the strengths and weakness of the study and how it may be useful in decision making. The fact that this database is also accompanied by the Database of Abstracts of Reviews of Effectiveness (DARE), containing records of high quality reviews of effectiveness, also allows the user to check and see the extent to which estimates of treatment effects used in economic evaluations are compatible with those derived from the best reviews.

How the NHS Economic Evaluation Database is produced

This database contains structured abstracts of economic evaluations of health technologies relevant to the NHS. A weekly search of Current Contents Clinical Medicine, a monthly search of MEDLINE, a handsearch of key journals along with a search of 'grey' material is carried out by the information service. In order to reduce the chance of missing important studies, this search is being expanded to include a range of Dialog on-line databases covering specific subject areas (e.g. Embase, Economics Literature Index etc).

Studies of all languages are included; those not in English are translated. There are no quality entry criteria for economic evaluations as there are in the DARE reviews database but the abstract structure is designed to highlight the methodological strengths and weaknesses and a commentary is provided by the abstractor.

A process of sifting and checking titles, abstracts and then papers has been developed to identify and then write structured abstracts for studies which are 'full

economic evaluations' (cost effectiveness, utility or cost benefit studies¹⁷. Cost studies, papers discussing methodologies for economic evaluations and reviews of economic evaluations are also stored on the database but only as bibliographic records. Papers to be abstracted are passed to one of around 15 health economists and health service researchers around the country whom we have trained to abstract papers for the database. A detailed manual for abstracting papers has been developed based upon methodological principles for clinical and economic evaluation¹⁸. These abstracts are checked by another abstractor and then by the CRD health economist before being loaded onto the database. An international advisory group for the NHS Economic Evaluation Database has been established. This has a mixture of academic health economists, public health, and Department of Health representation.

The process of developing the database and its quality assurance is summarised in Figure 1. Based upon the work done so far we estimate that in one year we will retrieve about 1,500 references searching current contents and handsearching of which about 400 will be full economic evaluations for which structured records will be written.

In order to ensure that users have a clear summary of each study and a critical appraisal of the methods used, a detailed abstract structure was developed which is illustrated in Figure 2. An example of a completed abstract is shown in the Appendix. One of the key features of the abstract structure is that it identifies the nature and source of the estimates of clinical effectiveness and provides an appraisal of the validity of this information as well as the cost data. The full database structure and guidance to abstractors and the manual for users are available from CRD.

Over the coming year we shall be exploring in more detail the quality of the economic evaluations, identifying studies which are reliable and how this material can be better used by health care decision makers. In addition we shall be researching whether valid and reproducible quality criteria can be defined. Once this is developed it will be possible to develop quality criteria for reviews of economic evaluations. Reviews of economic evaluations at the moment generally are of poor quality being unsystematic and not of comparable standards to the systematic reviews of clinical studies¹⁹.

Generating Cost Effectiveness Information

CRD is also involved in conducting systematic reviews of the evidence of treatments and disseminating these along with the results of high quality reviews which are of key importance to the

Figure 1 Administration of the NHS Economic Evaluation Database

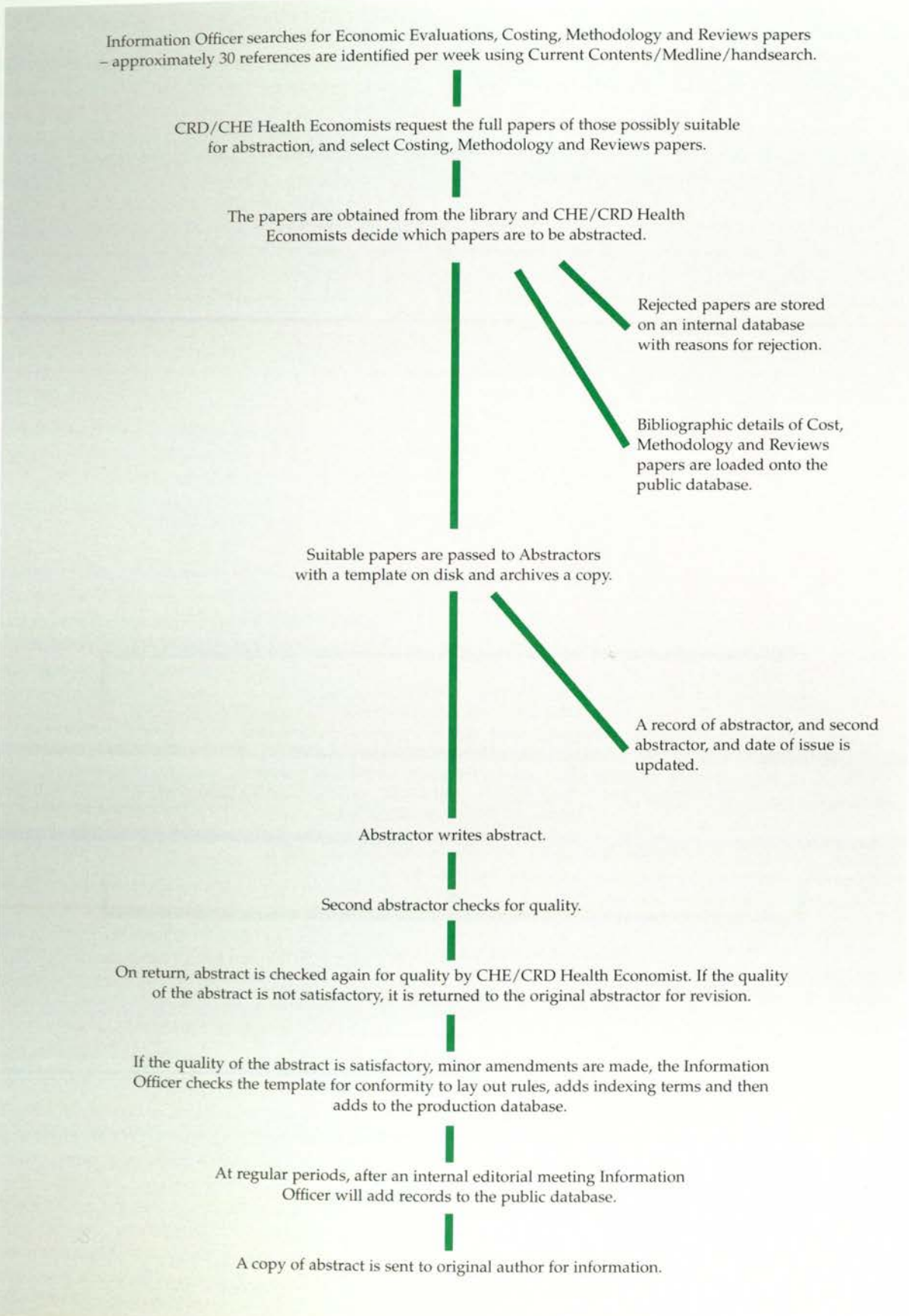
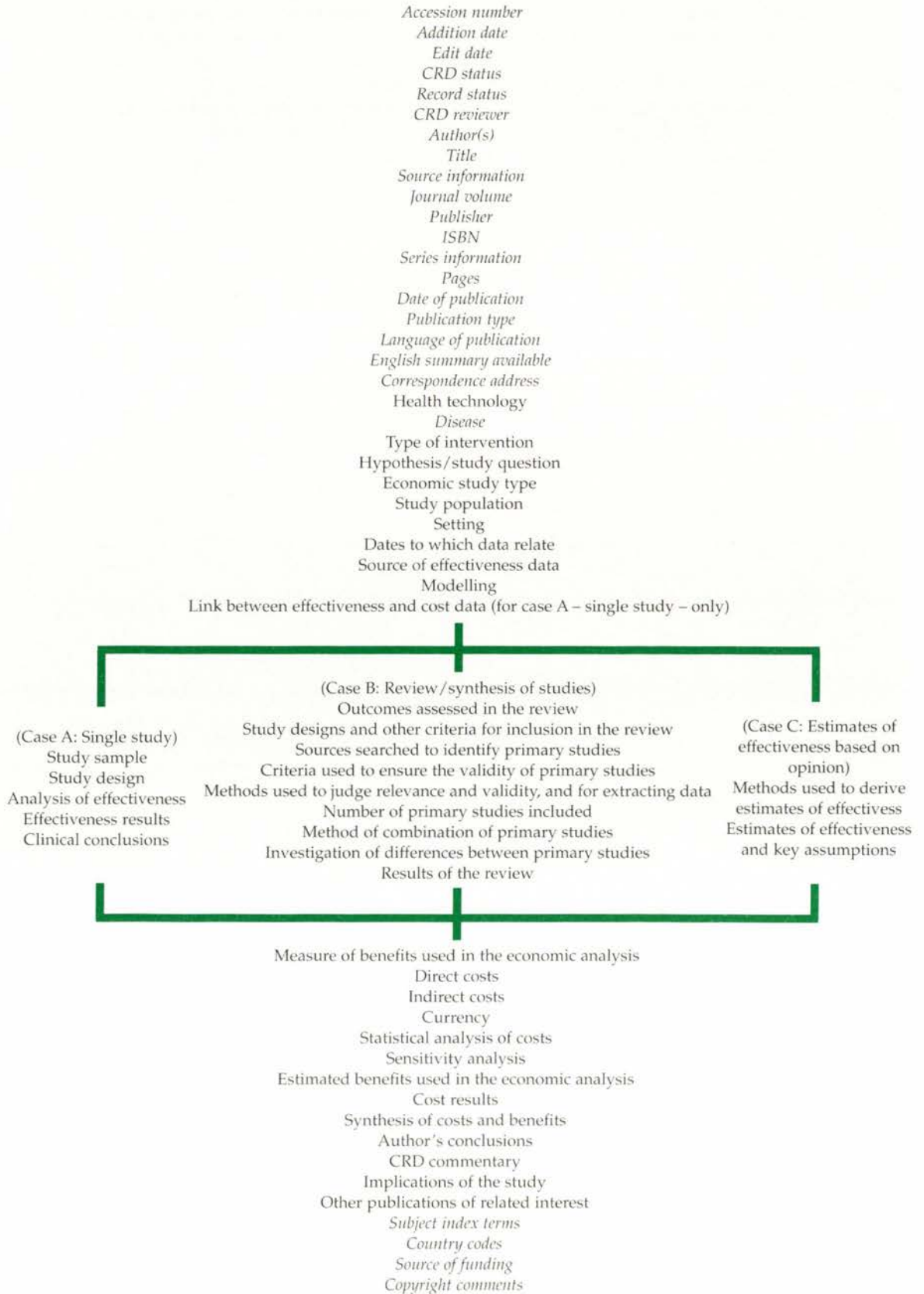


Figure 2 Contents of the abstract structure for the NHS Economic Evaluation Database



NHS. Because economic evaluations often have been carried out as part of developing or promoting a new technology (in particular pharmaceutical products) there are gaps in the economics literature in many established health technologies and manoeuvres and many of those studies which are available are of poor quality and so reliable summaries of cost effectiveness cannot be produced²⁰. However, there are cases when we have been able to build in cost-effective information. For example there have been some high quality evaluations of the cost effectiveness of eradication of H Pylori compared with long term acid suppressant therapy which produce unambiguous results which can be disseminated alongside clinical research evidence²¹. A recent issue of *Effectiveness Matters* recommended the increased use of flu vaccination in older people, which is driven to some extent by evidence of the cost effectiveness of this preventative intervention.

Where relevant high quality evaluations are not available CRD, in collaboration with colleagues from the Centre for Health Economics, attempts to include some estimates of cost-effectiveness. However, using secondary data can be difficult, and there are serious pitfalls when attempting to use models to produce reliable estimates²². Examples of *Effective Health Care* bulletins which disseminate the results of inhouse assessments include the estimates of the cost per percentage reduction in alcohol consumption with brief interventions to reduce alcohol consumption²³ and the cost per life-year saved in substituting SSRI anti-depressants for the older tricyclics²⁴.

Disseminating Evidence of the Cost Effectiveness of Healthcare

The dissemination principles which CRD uses do not distinguish between effectiveness and cost-effectiveness. The main reason for the emphasis on clinical effectiveness rather is the relative paucity of relevant and high quality information. Filling this gap is a major research priority which has to an extent been recognised by the NHS R&D programme which regularly includes economic evaluation as part of commissioned health technology assessments and other evaluative research.

Although the principles of dissemination are the same for all the material, different sorts of obstacles are encountered. Whilst it may be hard to get evidence on clinical effectiveness implemented there is still a general acceptance that this sort of information is relevant and should, where possible, be applied. A whole 'evidence based' health care movement has developed to promote this policy. However, there is still not such a general acceptance of the use of information from the literature of

economic appraisals. Whilst the clinical effectiveness message is really about doing more good than harm to any individual or groups of patients with a particular condition, the economic perspective may mean not doing something effective for particular cases or individuals because greater welfare for the community can be obtained by treating other patients. This perspective is social rather than individual and so can conflict with the individual ethic which pervades the clinical professional relationship. Also, because the rhetoric of economics has been adopted in recent years in the service of policies to cut expenditure or reduce services, cost-effective care is now often confused with the notion of cheaper care. Thus many people in the NHS see economic evaluation as a fig leaf for cost cutting. There is also a suspicion that companies and other providers are using economic evaluations as a way to market their products and legitimise an increase in health care expenditure (more expensive but more cost-effective).

Much of the emphasis of this chapter has been on the issue of quality of reported economic evaluations. Although this is a major issue, there are other limitations on the use of cost-effectiveness information²⁵. These include imprecise estimates, lack of comparable outcome measures, problems of generalisability (including variations in unit costs), etc. These limitations mean that considerable care is needed when applying the results of even high quality economic studies to particular decisions.

A more general education is required about the potential value of the results of economic analyses. However, this is unlikely to be successful until the quality of evaluations improves and the high quality studies are demonstrated to be useful for decision making. Passive dissemination of the results of these studies is unlikely to have much impact. CRD over the next year will be exploring ways of identifying the key reliable messages and more actively presenting them in ways in which they can be more easily applied. For example, CRD is providing some of the R&D input into the Clinical Outcomes Group's guidance to purchasers on the commissioning of cancer services. The first set of guidance on breast cancer carries a strong message about the importance of the 'triple test' in the diagnosis of breast cancer after referral. Two good economic evaluations have shown this combination of techniques to be cost-effective, increasing accuracy of diagnosis and reducing the number of more expensive surgical biopsies required^{26,27}. Including the results of economic evaluation in guidance is more likely to have an impact than dissemination out of context. Thus the main use of the NHS Economic Evaluations database may be to act as a pool of knowledge which

can be used where relevant to incorporate into policy and guidance.

CONCLUDING COMMENTS

It is easy for academics to urge the incorporation of scientific evidence in policy making and for policy makers to adopt the rhetoric of 'evidence-based policy'. However, it is difficult to change the behaviour of public and private organisations. There are a variety of obstacles which retard the use of research evidence in the making of public policy. For example²⁸:

- 1 Policy formation requires the integration of 'facts' and social values. However, there is rarely agreement from 'the experts' about the 'facts' and similarly neither consensus nor consistency in the expression of community values.
- 2 Scientific statements and particularly projections of likely impact of alternative options are usually probabilistic with confidence limits stated. This does not fit in well with the policy maker's needs to make singular discrete choices.
- 3 Researchers generate and public policy makers use scientific information within a political context. Thus politics may well influence the types of alternatives explored and presented in an assessment and choices of preferred option.

Research rarely produces conclusive results that are good for all situations and all the time, particularly when technologies are changing rapidly. For example, costs may vary locally. The results of economic evaluations require careful and continuous appraisal and interpretation. Few policy makers or health care professionals have either the time or the expertise for this and are dependent on either their advisers or professional organisations and peers who also may not have the scientific background, do not always speak with one voice and may be uncritical of provider advocacy.

A classic example is provided by the decision in 1988 by Prime Minister Thatcher to contribute £6 million pounds of NHS money and up to 60 per cent of the running costs for a cyclotron for neutron treatment of cancer at St Thomas's hospital, despite the ongoing MRC clinical trial²⁹. In 1990, the trial was stopped because of increased mortality in patients with advanced pelvic carcinomas treated using the cyclotron compared to conventional radiotherapy³⁰.

It would be naive to think that policy making will be purely science based. In a democracy health care choices are inherently very complex and many interests can force their attention on policy makers. One thrust of the NHS supported by the Research

and Development strategy is that policy making at all levels should become better informed by valid evidence about what really works in health care and about the cost effectiveness of alternative ways of delivering care. Economic evaluations of health care are, of course, central to this scientific endeavour. The provision of an international database of critical appraisals of economic evaluations will help to identify these studies which are of sufficient quality to underpin policy decisions. The dissemination of this key information will contribute to more rational policy. The database, by 'exposing' the studies which are of a poor standard may also help to improve the quality of research in this area as systematic reviews have done in the clinical research field.

Final choices, however, will be informed not only by such evidence, but a host of other factors, notably social values, but also, inevitably, special pleading and political expediency.

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Prevention of DVT after Total Hip Replacement**CRD REVIEWER**

AV

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TITLE

Cost-effectiveness of enoxaparin versus warfarin prophylaxis against deep-vein thrombosis after total hip replacement

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HEALTH TECHNOLOGY

Prevention of deep vein thrombosis (DVT) after total hip replacement using: a) low-molecular-weight heparin derivative; b) low dose warfarin.

DISEASE

Cardiovascular diseases

TYPE OF INTERVENTION

Primary prevention

HYPOTHESIS/STUDY QUESTION

Is enoxaparin more cost-effective than low-dose warfarin in preventing DVT after total hip replacement? The latter has been chosen as a comparator since it is the most commonly used cheap anticoagulant.

ECONOMIC STUDY TYPE

Cost-effectiveness analysis

STUDY POPULATION

Patients undergoing total hip replacement

SETTING

Hospital. The economic study was performed in Ontario, Canada.

DATES TO WHICH DATA RELATE

Effectiveness data were extracted from studies published in the period 1982-1992. The resources were estimated using data for 1990-91. 1992 prices were used.

SOURCE OF EFFECTIVENESS DATA

Review of previously completed studies

MODELLING

Expected net benefits and costs were derived using a decision tree model.

OUTCOMES ASSESSED IN THE REVIEW

Deep-vein thrombosis

STUDY DESIGNS AND OTHER CRITERIA FOR INCLUSION IN THE REVIEW

Randomised controlled trials (RCTs) comparing enoxaparin or warfarin with any other prophylactic agents between Jan 1982 - Dec 1992. The inclusion of the primary studies was determined by: a) English language; b) RCTs comparing enoxaparin or warfarin with any other prophylaxis against DVT in patients undergoing elective total hip replacement; c) prophylaxis started no later than 24 hours after surgery and continued for at least 7 days; d) the warfarin dose was adjusted to maintain a prothrombin time of 14 to 16 seconds, a prothrombin time ratio of 1.2 to 1.5 or an international normalised ratio of 2 to 3; e) the enoxaparin dosage was 30 mg twice daily; f) DVT was confirmed by bilateral venography.

SOURCES SEARCHED TO IDENTIFY PRIMARY STUDIES

Not stated

CRITERIA USED TO ENSURE THE VALIDITY OF PRIMARY STUDIES

Not stated

METHODS USED TO JUDGE RELEVANCE, VALIDITY, EXTRACTING DATA

No judgement criteria were applied by the authors for assessing validity of primary studies.

NUMBER OF PRIMARY STUDIES INCLUDED

Four RCTs of enoxaparin and six RCTs of warfarin, not compared directly one with the other, were included in the review.

METHOD OF COMBINATION OF PRIMARY STUDIES

Overall risk of DVT with each drug was separately estimated as the sum of events divided by the sum of patients at risk.

INVESTIGATION OF DIFFERENCES BETWEEN PRIMARY STUDIES

Homogeneity of rates between studies was tested by Chi-square analysis. Test results of heterogeneity for overall rates of DVT were significant ($P < 0.05$) for the enoxaparin trials but not for the warfarin trials. The author explored the impact of this with sensitivity analysis.

RESULTS OF THE REVIEW

Comparing the overall risk of DVT with RCTs of enoxaparin and the overall risk of DVT with RCTs of low-dose warfarin therapy, the difference in pooled rates of DVT overall and of distal DVT was -7.1 (95% CI: -2.8;-11.2) and -8.2 (95% CI: -11.9; -4.5) respectively. For proximal DVT the difference in the pooled rates was not statistically significant at the 5% level.

MEASURE OF BENEFITS USED IN THE ECONOMIC ANALYSIS

Life-years gained

DIRECT COSTS

Quantities and costs were analysed separately. Only health service costs were considered: prophylactic drugs, diagnostic tests and treatment (hospital stay + therapy). The estimation of the quantities (length of hospital stay, duration of prophylaxis) was based on hospital records, 1990-1991 data.

Appendix continued

Costs of procedure and additional hospital stay were estimated using a corporate cost model for a group of hospitals in Hamilton. The cost of physician services was calculated from the physician fee schedule for Ontario. The drug costs were estimated by an informal survey of hospital pharmacies in Hamilton. The price date was 1992.

CURRENCY

Canadian \$

SENSITIVITY ANALYSIS

A sensitivity analysis was carried out. The methods and the parameters used were not specified.

ESTIMATED BENEFITS USED IN THE ECONOMIC ANALYSIS

The incremental life years gained were calculated to be 41.52 (=4*10.38; where 4 is the incremental number of death and 10.38 is the life expectancy discounted by 5%).

The duration of the intervention and comparator benefits was the lifetime.

COST RESULTS

The intervention cost per patient was \$355. The comparator cost per patient was \$234. Therefore, the incremental cost per patient was \$121.

The cost of adverse effects was not considered because of the lack of standardised criteria to measure them.

SYNTHESIS OF COSTS AND BENEFITS

An incremental analysis was performed. 5% was the discount rate for benefits. The incremental cost per life-year gained was \$29,140.

Sensitivity analysis revealed that results were most sensitive to alternative assumptions about enoxaparin efficacy. Using the lower limit of the 95% CI for the rate of DVT with enoxaparin, C-E ratio falls to \$6,000. Using the upper limit, enoxaparin becomes both less effective and more costly with respect to warfarin.

AUTHOR'S CONCLUSIONS

Enoxaparin is more effective than warfarin but will increase the cost per patient. On the basis of current Canadian guidelines, a cost of \$29,120 per life-year gained would give evidence for adoption.

However, the author recognises that there are many threats to the validity of inference drawn from the meta-analysis. The author stresses the uncertainty around the estimates because of the limited data available.

CRD COMMENTARY

a) Because there is no evidence of a systematic search of the literature for trials of effectiveness, it is not clear the extent to which all relevant studies were included; b) the analysis pooled the DVT rate in enoxaparin arms of trials and compared it with the pooled DVT rate of low dose warfarin. However, since these come from separate trials there is no evidence that the groups of patients were comparable. Therefore, it is not clear that the difference observed between the groups can be attributed solely to the treatments. This study is therefore hypothesis generating; c) more detail about the sensitivity analysis methods used would have been useful.

IMPLICATIONS OF THE STUDY

A well designed RCT directly comparing enoxaparin with low dose warfarin is needed.

SUBJECT INDEX TERMS

Comparative Study; Cost-Benefit Analysis; Enoxaparin/ec [Economics]; Enoxaparin/tu [Therapeutic Use]; Hip Prosthesis; Human; Postoperative Complications/pc [Prevention & Control]; Support, Non-U.S. Gov't; Thrombophlebitis/pc [Prevention & Control]; Warfarin/ec [Economics]; Warfarin/tu [Therapeutic Use]

COUNTRY CODES

Canada

SOURCE OF FUNDING

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7 OVERVIEW

Adrian Towse

INTRODUCTION

The purpose of this publication is to explore the impact in Australia, Canada and the UK of guidelines for the production of information on the cost-effectiveness of particular medicines. Information on the economic value of a pharmaceutical should help decision makers achieve society's health care objectives. However, the generation of this information has a cost, and its use to restrict access to treatment raises important issues about how health care is allocated. In this overview we discuss the extent to which we can draw conclusions for the NHS from the evidence set out in the preceding chapters about the role of guidelines and the use of information from economic evaluation in these three countries.

A FRAMEWORK FOR ANALYSIS

In seeking an outcome of greater efficiency in the use of pharmaceuticals, the process for using the information has to take account of health care system design and culture. The type of health economics information required as an input will in part reflect country specific matters, but also more general issues.

The Outcome: Defining Efficiency

There are several dimensions of efficiency. We comment on three aspects.

Productive and allocative efficiency

Productive efficiency requires us to achieve outcomes at minimum resource cost. Allocative efficiency requires the mix of outcomes we achieve to be those sought by society. Cost per QALY thresholds and QALY maximisation objectives will, if met, lead to productive efficiency, but only to allocative efficiency if the sole objective of the health care system is to maximise health gain, irrespective of whether some patients and diseases are left untreated as a consequence. In practice, as Sheldon and Vanoli point out (page 60) in the context of the NHS, 'in a democracy health care choices are inherently very complex... policy making at all levels should become better informed by evidence... final choices, however, will be informed not only by such evidence, but a host of other factors, notably social values, but also inevitably special pleading and political expediency.' Clarity of rationing rules is important if economic

evaluations are to be used. In none of the three countries has the public 'signed up' to an explicit cost per QALY type threshold for rationing care.

The use of economic evaluations to increase productive efficiency is therefore likely to be less contentious than their use to support allocative decisions. However other measures, for example to increase generic prescribing or reduce repeat prescribing may be more cost-effective ways, at least in the short run, of achieving productive efficiency gains. Arbitrary reductions in pharmaceutical prices may also be attractive to payers, although this raises the question as to the trade-off between short term 'static' gain and longer term 'dynamic' benefit.

Static and dynamic efficiency

'Static' efficiency is about achieving productive and allocative efficiency from the resources available today. 'Dynamic' efficiency means getting the best outcomes over time. Use of economic evaluations raises two issues of dynamic efficiency.

The first is in relation to the efficient pricing of pharmaceuticals. A product may be cost-effective at a range of prices bounded by a 'bottom' price reflecting the marginal cost of producing the product, (at which the manufacturer would receive no return to sunk R&D investment) and a 'top' price at which society pays a sum equal to all of the value of the health benefits to the manufacturer. Within this range there is no objective 'rule' to set the price. A number of possible rules have been discussed.¹ One is to set an incremental cost per QALY threshold. A second rule would be to split the range of benefit according to a predetermined fixed percentage – say 50/50. The precise choice of rule reflects a judgement as to the overall importance of encouraging pharmaceutical innovation and society's willingness to pay for health gain. This may involve higher prices for medicines today in order to provide the necessary incentives to increase innovation. It will always be tempting, however, for payers using economic evaluations as part of a listing and price setting process to seek to pay lower prices to maximise static efficiency.

If the company is setting price then the static/dynamic trade off is determined by the willingness of prescribers to use more expensive products if they deliver more health gain, and the degree of competition. Economic evaluations here assess value but only determine price indirectly through decentralised decision making.

The secondly implication for dynamic efficiency arises from the timing of economic evaluations. Cost-effectiveness may be different in clinical practice from in clinical trials, and change over time as a medicine is used with different patient groups, or for different treatments. There are two reasons why this may happen:

- cost-effectiveness may differ from cost-efficacy, because use in practice differs from use in the trial. This may reflect differences in accuracy of diagnosis, in patient compliance, or a number of other factors;
- knowledge of the most effective ways of using a product may change as experience of patient response in clinical practice accumulates over time.

If cost-effectiveness increases over time then there is an issue as to who bears the cost of 'learning'. If failure to pass a cost-effectiveness hurdle means a product is never prescribed, then knowledge of more cost-effective use may never be acquired. Of course cost-effectiveness in a clinical setting may be poorer than in a trial setting. The point is that there are dynamic issues that may not be efficiently resolved by a one-off snap shot approach.

A 'second best' environment

Health care decision making takes place in a 'second best' environment. Rules designed to achieve efficiency may fail to do so because the rest of health care system is not efficient.

An explicit or implicit cost-effectiveness hurdle applying to part of the system has to be used with care. As Buxton notes, Ontario operated a fixed pharmaceutical budget for a period. Thus as a new medicine was made available an existing medicine had to be delisted. In the extreme, pharmaceuticals may be delisted which are within the hurdle because other products are even more cost effective. The NHS survey evidence discussed by Towse indicates that separate primary and secondary care budgets are seen to hinder the optimal use of economic evaluation information.

If a hurdle is applied only to **new** pharmaceuticals (or other new treatments) and is set at a level above the average cost effectiveness of health care services, medicines may be delisted, or not listed, which are more cost-effective than other pharmaceutical or non-pharmaceutical treatments that are still being funded, and the average cost effectiveness of health care may be lower than if they were adopted. Concentrating the use of economic evaluations in one area will lead to anomalies, some of which will reduce efficiency.

Of course, most decisions that make sense at the 'local' margin are likely to make sense overall –

assuming as Backhouse notes (page 47) that 'like-for-like' comparisons are made. An economic evaluation that examines the incremental cost effectiveness of one treatment as compared to another and arrives at a cost per effect that is deemed too high to be acceptable (or low enough to be accepted) is probably achieving productive efficiency given the constraints faced by the decision maker. Whether the allocative and productive efficiency of the overall health care system is enhanced, however, will depend on the system's structure and incentive mechanisms, its culture (in particular health care professionals' and patients' views about access to medicines) and the quality of the information used.

The Process: The respective approaches of the three health care systems to getting value for money from pharmaceuticals

Australia, Canada and the UK currently use economic evaluations of pharmaceuticals differently. Use has to be put in the context of the overall approach to the public funding of pharmaceutical treatments, and of ensuring value for money. We can summarise the approaches as follows:

- Australia has a requirement that companies provide an economic evaluation for a new medicine if they wish it to be listed on the public reimbursement scheme – the Pharmaceutical Benefits Scheme, which comprises 90 per cent of the Australian prescription pharmaceuticals market. The government publishes guidelines for the presentation of information which must be followed, although there is no policing as to who produces the information. As well as being used to help determine listing, the economic evaluation is also used to help determine the price at which the product is listed, although other factors are taken into account. There is no cap on the pharmaceuticals budget, and no separate arrangement for ensuring that GPs prescribe in a cost effective way once products have been listed (except when products are put on a restricted indication for reimbursement, or on a named patient basis). The decision to list, and the related price setting is thus the main method of achieving value for money from the use of pharmaceuticals. There is a separate programme of health technology assessment led by the Australian Health Technology Advisory Committee;
- The Canadian Guidelines are promulgated by the Central Coordinating Office for Health Technology Assessment, and are advisory, aimed at all of those undertaking economic evaluation in Canada. There are no restrictions on who does the studies, but funding and 'leadership' arrangements should

be disclosed, and the investigators should have independence regarding methodology and right of publication.² However, CCOHTA's guidelines are also intended to be used by interested Provinces as a basis for requiring companies to submit economic evaluations of new pharmaceuticals in order to obtain listings and a reimbursement price on the Provincial formulary. Indeed the CCOHTA Guidelines were developed as a response to a mandatory requirement from the Province of Ontario, and now form the basis of submissions to that Province. As in Australia, there are no separate controls on prescribing, and the Provincial budgets are not capped (although Ontario has operated an effective cap in the past). The publicly funded health care system, administered by the Provinces, includes only a limited pharmaceutical benefit. Thus the publicly funded market comprises around 40 per cent of the Canadian prescription medicines market. Unlike Australia, maximum prices are set for both the public and private sector by a completely separate national body, the Patented Medicine Pricing Review Board, using international price comparisons (which were used in Australia to set public sector prices prior to the introduction of economic evaluations). Like both the other countries, there is a national programme of health technology assessment. This is led by CCOHTA, which commissions its own studies, with a number of Provinces also having their own Offices of Health Technology Assessment. All of these programmes include economic evaluations of pharmaceuticals;

- the UK has voluntary guidance for those wishing to undertake economic evaluations aimed at National Health Service (NHS) decision makers and a voluntary code of practice governing the supply of promotional information (including any claims of cost effectiveness) by the pharmaceutical industry to the NHS. The publicly funded NHS pharmaceutical market comprises more than 95 per cent of the UK prescription medicines market. Companies are able to set their own NHS prices for new products. There is a separate profit control scheme (the PPRS) which is designed to keep industry prices to reasonable levels while allowing reasonable profits on sales of medicines to the NHS. The NHS pharmaceuticals budget is not capped, but GPs are given prescribing budgets and quarterly reports of their performance against budget. The system has a number of incentives to encourage the cost-effective use of pharmaceuticals by GPs. A programme of research, review and dissemination designed to influence GP prescribing behaviour is undertaken by the NHS R&D Directorate, which finances the

NHS Centre for Reviews and Dissemination (CRD) and the National Prescribing Research Centre. NHS sponsored clinical trials are also expected to include an economic component.

It is possible to draw out the similarities and differences in the design and culture of the three health care systems in respect of the use of pharmaceuticals. In all three:

- product licencing, or market authorisation, is completely separate, determined only on grounds of safety, quality, and efficacyⁱ. Cost-effectiveness is a purchase criteria not a market entry barrier;
- pharmaceuticals are treated differently to other health care services and are not cash limitedⁱⁱ.

In Australia and Canada, the pharmaceutical benefit was added at a later stage and is administered separately. By implication entitlement is less comprehensive than for other health care services. This is not the case in the UK. Countries like Australia and Canada, where there is central listing and price setting, have historically given less responsibility to the prescriber to achieve value for money – the implicit message being 'the centre decides what is available, the doctor decides if the patient needs it'. In the UK, the reverse has been the case, with GPs increasingly being expected to achieve value for money, and so to stimulate price competition by manufacturers. Here the implicit message is 'the centre decides what the nation can afford – the doctor's job is to deliver care within it'.

This raises the question as to which type of system is likely to be most effective in getting value for money from the use of medicines. Doctors have to be involved. The alternative is ever greater central intervention in prescribing (such as requiring doctors to seek permission before prescribing certain medicines or using medicines outside of the listed indication, or monitoring doctor adherence to guidelines on pharmaceutical use³). However, decentralising value for money and rationing decisions requires budget holders to have appropriately broad budgets to substitute different types of care and to have access to relevant information, together with the competence, willingness and incentive to use that information.

i In Australia, companies can submit economic dossiers to the listing authority at the same time as they file for product registration with the licensing authority, but this is to reduce the time delay between obtaining permission to launch a product and obtaining a PBAC listing for public reimbursement.

ii In the UK GP Fundholders, in effect, opt to take on a cash limited prescribing budget as part of the fund.

The Input: Information Requirements

All three health care systems expect the pharmaceutical industry to provide information on the cost-effectiveness of its products, and all have separate programmes of health technology assessment for non-pharmaceutical treatments. However, whilst Australia and the Canadian Province of Ontario impose detailed requirements on companies to provide information, which are scrutinised by formulary committees, the NHS and national Canadian (CCOHTA) approach is to permit companies to undertake studies that meet the published guidelines and disseminate their results whilst the NHS and CCOHTA commission separate studies of pharmaceuticals to be made available to local decision makers. This raises three important issues.

Firstly, does it matter who commissions or undertakes the studies? Some^{4,5} have argued for independence from the pharmaceutical industry or for transparent investigator contracts⁶. Evans⁷ has argued that there will still be structural potential for bias, given what is at stake. Similarly guidelines on content can never be specific enough to overcome the potential for bias, and indeed may provide a cover for the introduction of bias. Each study must be assessed on its merits as a piece of scientific work. Powerful buyers can always hire their own evaluators or, as in the NHS, ensure decentralised decision makers have access to expert advice and support. Thus who does the study is not key. Disclosure and contractual clarity can help the reader interpret the potential for bias, but it is more important that decision makers can assess study quality and relevance.

Secondly, how prescriptive can the framework for designing and reporting an economic study be? This is a practical issue about the needs of the decision makers as Buxton discusses in contrasting the Ontario and CCOHTA approaches. If decision makers are clear about their information needs they can be very prescriptive about methods and presentation, as Drummond and Aristides point out in noting Australia's insistence on RCT-based (cost-efficacy rather than cost effectiveness) information.

However, as Sheldon and Vannoli point out, referring to Drummond⁸, there is also an issue as to the scientific maturity of economic evaluation. It has been described as 'a half way technology'⁹ and with many methods used 'in an experimental stage'¹⁰. Problems of comparing QALY studies are discussed in Chapter 5 by Backhouse. Issues of QALY validity and reliability have been discussed elsewhere¹¹. Similar issues arise about the importance of costing methods and about the handling of uncertainty.

Towse quotes Luce and Simpson's conclusion that although 'there is a general consensus among experts on the existence of a basic set of principles governing the design of socio-economic studies, there is no general consensus as to selection of a given design option in a given circumstance'.¹² Hence the controversy around the prescriptive content of the Australian guidelines^{13,14}.

Thirdly, when to do a study? This is easily resolved. There is no 'right' or 'wrong' time. Again it depends on the decision to be made. Studies could be undertaken at several points in the diffusion process as knowledge about the pharmaceutical increases^{15,16}. Assessing cost-effectiveness in routine clinical practice is most important, but it may not be appropriate to allow diffusion to this point. Conducting a series of iterative studies may, however, be costly and time consuming. A variable approach for each product may be optimal, depending on the expected benefits of further research at each stage. Unfortunately this does not present a simple institutional solution.

Our discussion of the framework for achieving greater efficiency in the use of pharmaceuticals does not suggest that one solution is likely to fit all countries. However, evidence on the effectiveness of different approaches to the use of guidelines for economic evaluation may help to identify which ones work and the implications for the NHS. We now turn to consider this.

THE EVIDENCE

The Australian experience

Drummond and Aristides note that in evaluating the Australian guidelines we face the difficulty that deliberations are secret and that cost-effectiveness was, in principle, a criteria for listing prior to the introduction of guidelines. Both process and outcome assessments are therefore difficult. They conclude, however, that preliminary evidence suggests the regime is having an effect:

- some new 'breakthrough' products such as finasteride and sumatriptan are not listed – presumably on grounds of cost effectiveness. (We can note that D-nase and beta interferon were initially rejected);
- other products are listed for more restrictive indications than those for which they are licensed (e.g. G-CSFs);

They conclude that evidence is needed as to whether some products (for example line extensions) are listed at lower price premiums than elsewhere, and

whether delays and restrictions in listing push up other health care costs.

Some evidence on pricing trends was supplied by the Australian industry to the Industry Commission Inquiry into the Pharmaceutical Industry in Australia¹⁷. It shows that prices of new products in Australia are around one third lower than the world average. However, the same study showed that the best selling products in Australia are, on average, close to two thirds below world prices. This suggests that new products are getting better prices under the new regime than under the old, although lower than the world average. Freemantle et al¹⁸ argued that the use of economic evaluations to help set prices was benefiting the industry by ensuring it was 'more efficiently rewarded for its innovative work'. Good economic analysis had achieved higher prices than under a more arbitrary regime. The Australian pharmaceutical industry¹⁹ argued in response that there was no clear cost-effectiveness threshold for manufacturers to aim at, and that once products had demonstrated cost-effectiveness, the price was then negotiated down. Hence in practice economic evaluation was a cost containment tool, rather than an efficiency tool. It may be that the PBAC is operating an informal cost-effectiveness threshold that does enable effective products to get higher prices than under the old regime, although not the prices companies believe their analysis supports.

The potential weaknesses of the Australian regime are, in part, a consequence of its strengths:

- the operation of a threshold, however informal, will as Drummond and Aristides preliminary evidence suggests, tend to rule out expensive products for chronic diseases. It is not obvious, however, that society would wish patients with these diseases to go untreated, even if more health gain could be achieved by spending the money elsewhere;
- an informal threshold will always be open to charges of manipulation. Expensive new products for common diseases may not be cost-effective, or only be cost-effective at lower prices than those proposed by the companies. It is also possible that governments would prefer not to incur the potential cost of making them available. Drummond and Aristides note the concern about lack of transparency, and the agreement by the PBAC in 1996 to begin giving reasons for its decisions;
- the process is resource intensive for both sides. The Commission of Inquiry found that the current approach imposed unnecessary costs on companies and delays in market access and recommended that companies should have the

option of delaying cost-effectiveness analyses for two years after launch, although this was rejected by the Government in its response²⁰. Drummond and Aristides comment on the methodological and practical issues arising from the emphasis on cost-efficacy and on choice of comparator. They also report that less than 2 per cent of studies used cost per QALY measures, which are most relevant to health care resource allocation decisions across treatment boundaries;

- once prices are set, there is no monitoring of GP prescribing (unless, the drug is placed on a 'restricted benefit' or 'on authority' list);
- like most price setting regimes there is little incentive for price cutting by suppliers of competing products or generics. Prescribers are not price sensitive believing price is dealt with centrally. Drummond and Aristides observe that 'me-too' drugs tend to compete on a non-price basis only;
- there is no evidence that the rate of growth of pharmaceuticals expenditure is slowing down. It could be argued that the objective is to ensure that increases can be justified as cost-effective, because of the hurdle. However, whilst the hurdle may be used to support the view that expenditure now represents value for money, the link is tenuous. It could be many years before the majority of PBAC expenditure is on products introduced after the hurdle.

The Canadian experience

Buxton concludes that:

- guidelines can only be precise where there is a particular decision making body and a precise context. The Ontario guidelines are context specific. For example, it gives stronger emphasis to the use of cost per QALY measures to enable cross disease and sector comparisons, and implies the usefulness of willingness to pay studies. The CCOHTA guidelines stress the methodological interest of willingness to pay, and are more educational. Lack of a particular decision maker focus makes it much more difficult to prescribe a single preferred approach;
- the process of guideline development was characterised by frustration on the part of Ontario at the slow pace of the CCOHTA initiative, and, within the CCOHTA guideline process by the strong rival interests of local academic groups;
- tensions between national and provincial initiatives remain strong. It is not yet clear whether the CCOHTA initiative will succeed in

preventing a proliferation of Provincial guidelines with different methodological content. The more important issue, however, is the local applicability of data. Unit costs and population morbidity vary from province to province, although within one health care system the potential for variation needs to be kept in proportion. Nonetheless, decision makers want locally applicable data;

- this also means that local decisions will differ. Products may be listed by one province but not by another;
- the CCOHTA guidelines are helping to change the culture of provincial decision making towards the acceptance of economic evidence;
- the CCOHTA commissioned studies (notably on finasteride and sumatriptan) appear to be having an impact on provincial decision making. In these two cases CCOHTA studies were followed by formulary listing in several Provinces;
- economic studies are likely to have an impact on the PMPRB's national price setting for newly licensed pharmaceuticals.

In conclusion Buxton argues that guidelines will necessarily continue to be situation specific. To be good economic evidence must be tailored to local circumstances. 'The days of the one-off multi-purpose economic study that could give a drug an international sobriquet of 'cost-effective' are gone – if they ever existed!' (page 25).

The UK experience

It is hard to find evidence that economic evaluations of pharmaceuticals are having an impact on NHS prescribing. In part this reflects the structure of decision making – in the absence of highly visible formulary 'hurdles' it is much harder to pick up changes in patterns of GP or hospital prescribing and to attribute them to any particular factor. Towse concludes, however, that efficacy and effectiveness rather than cost-effectiveness remain the main criteria for NHS prescribing decisions and that cost-effective prescribing is being achieved in other ways, for example by the growth in generic prescribing resulting from allowing GPs to use savings made from prescribing budgets. He notes that:

- both the NHS and the pharmaceutical industry are commissioning studies, some companies are using health economics messages in their promotional mix, and more studies are now published;
- studies of GPs and advisors suggest a willingness, in principle, to use economic evidence. One survey found evidence that advisors had changed their advice as a result of economic evaluations, but

inability to move money between primary and secondary care budgets was seen as the main barrier to use.

Towse concludes that the key problem is that prescribers do not see economic studies as relevant. This could reflect lack of applicability to the decision making environment, a view that cost-effectiveness is not a relevant decision criteria, or a view that the system does not allow cost-effectiveness results to be implemented.

Sheldon and Vanoli argue that the poor accessibility of economic evaluation information is an important barrier to its use. The assessment of studies by the CRD will raise credibility and quality. Whilst they have doubts about the scientific maturity of economic evaluation, and prescribing policy and note that decisions have to take account of social values as well as science, the dissemination of high quality information will improve NHS prescribing. Backhouse notes that adherence to the UK guidance will help to ensure high standards of methodology and presentation. Improved peer review using checklists will raise quality. The Code of Practice requirement that 'information, claims and comparisons must be accurate, balanced, fair, objective and unambiguous and must be based on an up-to-date evaluation of all of the evidence and must reflect that evidence clearly' (Massam page 40) will also be important.

IMPLICATIONS FOR THE NHS AND THE PHARMACEUTICAL INDUSTRY

It is too early in any of these three countries to reach conclusions about the overall effectiveness of their respective use of guidelines on the cost-effectiveness of prescribing. Research is difficult to undertake given the lack of transparency of decision making and the number of confounding factors. This book has set out evidence, often anecdotal, as to some of the strengths and weaknesses of each approach. The centralised compulsory approach of Australia and the Province of Ontario in Canada not surprisingly raise most sharply the problems associated with using cost-effectiveness information in decision making – the absence of clear publicly accepted rationing criteria, its failure to generate unambiguous pricing rules, and the lack of methodological consensus. The national Canadian approach is not, in practice, that dissimilar to that of the NHS, with less prescriptive guidelines and a mixture of government and industry sponsored studies likely to lead to different decisions in different parts of the country. However, in Canada the historical development of the health care system means that the Provinces all have formulary committees and there is a national price

setting body – all obvious ‘customers’ for economic information. In the UK, prescribing decisions rest with the GP who faces a number of incentives and constraints to reduce the cost of, and improve the efficiency of, prescribing. Less cost-effectiveness information about pharmaceuticals is being used or generated than was anticipated when the UK Guidance was put in place. On the basis of the analysis presented by the authors there is not a de facto case for abandoning the decentralised approach in favour of a centralised one. There is a need, however, to examine further whether NHS policy, and public and medical attitudes on rationing access to medicines, the relevance, quality, or availability of the information, or lack of incentives or ability to use it, reduce the value of cost-effectiveness information to the NHS, and if so how or whether they should be tackled.

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