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**Promoting Cost-Effective Prescribing  
in the UK National Health Service**

*edited by*

Karen Bloor and Nick Freemantle

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# Introduction

Karen Bloor and Nick Freemantle

## Background

Pharmaceutical prescribing currently represents around 10 per cent of total National Health Service expenditure, and is one of the most inflationary elements of spending (Parliamentary Office of Science and Technology 1993). Between 1980 and 1990, the overall cost of a prescription increased by 87 per cent in real terms, while the number of prescriptions issued increased by 19 per cent. Pharmaceuticals are one of the most commonly used and important interventions available to doctors in clinical practice, and their appropriate use can reduce mortality, morbidity and costs falling on other parts of the health care system. However, evidence from systematic reviews demonstrates that current prescribing may not always be effective or cost-effective (Effective Health Care 1993).

A number of policy initiatives have been introduced which attempt to contain prescribing costs. These include provision of Prescribing Analysis and CosT (PACT) data; the limited list; the indicative prescribing scheme and GP fundholding. However, these schemes have had limited impact and tend to focus on cost containment rather than cost-effectiveness in prescribing. Confusion remains concerning current knowledge and good practice in cost-effective prescribing. This confusion could be reduced with appropriate research making use, where possible, of the valid and reliable routinely collected activity data available on prescribing in the UK.

In other countries, particularly Australia and Canada, policies have been introduced to limit the introduction of new drugs to those which demonstrate cost-effectiveness. Other countries, including European countries and the United States, are encouraging provision of economic evaluations of pharmaceuticals and have introduced varying initiatives to control prescribing costs and increase cost-effectiveness. UK policy initiatives should be informed by the experience of other countries.

There is considerable inertia in prescribing habits, and evidence of effectiveness and cost-effectiveness, when it exists, is not always used. A number of organisations are attempting to improve this situation. The NHS Centre for Reviews and Dissemination, at the University of York, produces and commissions systematic reviews of specific health-related questions, and disseminates these findings throughout the NHS. The Cochrane Collaboration, at the UK Cochrane Centre in Oxford and around the world, aims to produce systematic reviews of randomised controlled trials. The Cochrane Collaboration for Effective Professional Practice, an international collaboration with an editorial office at the University of York, conducts systematic reviews of initiatives aimed at changing professional behaviour. These and other organisations all attempt to improve the process of getting good evidence about health care interventions (including prescribing) into practice.

## **Promoting cost effective prescribing in the NHS**

This project aimed to bring together key specialists who may contribute to strategies to improve the cost-effectiveness of prescribing, developing a framework and research agenda for informing policy, identifying areas of agreement and controversy and disseminating results throughout the NHS. This was initiated by organising a symposium in March 1995 at the University of York, and this book summarises the proceedings of this meeting. The format of the symposium was:

Position papers were commissioned from four experts in the field of pharmaceuticals, effectiveness and cost-effectiveness analysis in order to stimulate debate on the relevance of currently available information and techniques to prescribing practice. These papers were produced and circulated in advance of the symposium, to ensure focused debate;

Experts from multidisciplinary backgrounds relating to the cost effectiveness of prescribing, analysed and commented upon the position papers, appraising critically the key points of each paper and advancing debate;

An invited audience of around 60 interested people from the NHS, the Department of Health, academic institutions, the pharmaceutical industry and user groups attended the symposium;

The symposium was structured to maximise productive audience debate. The authors of the four position papers were limited to only a short presentation summarising key issues in their papers. Discussants then developed ideas in short presentations and audience participation was encouraged throughout.

An overview was presented at the end of the day, and developed for this book. This overview includes suggestions for development of a clear research agenda in prescribing, and a strategy for promoting cost-effective prescribing in the UK NHS.

The papers presented in this volume include the four key position papers circulated in advance of the symposium. The book also attempts to reflect the considerable and varied debate stimulated by these papers, summarising presentations of the expert discussants and the audience discussion.

## **Acknowledgement**

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**Chapter 1****Using Economic Data for Prescribing Decisions**

Michael Drummond

**Introduction**

Clinicians are increasingly being urged to prescribe in a 'cost-effective' manner. This message is reinforced by the feedback given to general practitioners on their prescribing costs through PACT (Prescription Analysis and CosT) and the derivation of indicative prescribing amounts. For fundholding general practitioners, the allocation for prescribing in the fund represents real money, so presumably there is an incentive to consider costs and to prescribe in a cost-effective manner, in order to maximise the use of the fund. The cost-effectiveness message to prescribers is further reinforced by the Drug and Therapeutics Bulletin and the MeReC (Medicines Resource Centre) Bulletin, which both report the comparative costs of similar medicines.

In the hospital sector, formularies and treatment protocols may also encourage cost-effective prescribing, by limiting the use of certain medicines or outlining their appropriate use, although cost-effectiveness is not normally a major criterion in formulary or protocol development. If economic considerations do enter into decision making, it is most likely that these reflect simple comparisons between the acquisition costs of medicines.

Although the cost-effectiveness message may be coming through loud and clear, it is by no means certain that all parties understand what is meant by 'cost-effectiveness' or how to assess it. In addition, it is not clear where a clinician would find cost-effectiveness data should he or she desire them, nor whether such data would be sufficiently valid to form the basis for prescribing decisions.

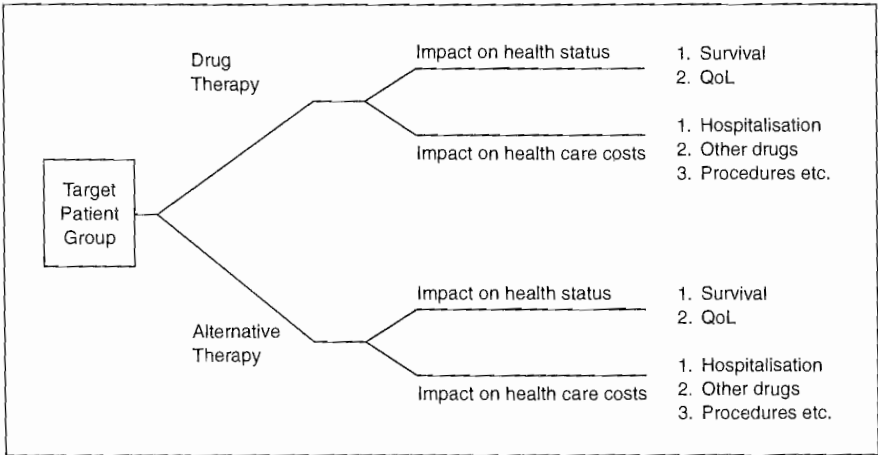
Therefore, this introductory paper discusses popular misconceptions about cost-effectiveness, outlines how to assess cost-effectiveness, describes two contrasting examples of economic evaluations of medicines undertaken in the UK, discusses the main practical problems in undertaking economic evaluations of medicines and outlines some of the main issues and controversies in using cost-effectiveness data in prescribing decisions.

**1. Economic evaluation**

Economic evaluation assesses the costs and consequences of alternative health care treatments and programmes. The approach is outlined in Figure 1. Here a drug therapy is being compared with an alternative, which may be another drug, surgery, or 'doing nothing', in situations where there is currently no effective therapy for the group of patients concerned.

In comparing alternative therapies, assessments are made of their impact on health status and on health care costs. Changes in health status may be measured in terms of survival, quality of life, or a mixture of the two, depending on the health condition being studied. Assessments of the impact on health care cost are not confined to the costs of the drug and the alternative therapy. They also include the costs of hospitalisation, other drugs and medical procedures. An economic evaluation undertaken from a societal perspective would also include costs outside the health care sector, such as those falling on the patient and his or her family, and the impacts on productivity due to changes in health status.

**Figure 1: Nature of Economic Assessments**



Although all economic evaluations follow the same basic approach, different forms of analysis are defined in the literature (Drummond et al. 1987). Cost-minimisation analysis is the analytic form used where the health consequences of the two treatment alternatives are equivalent. Therefore the comparison reduces to one of costs alone. In cost-effectiveness analysis the costs are expressed in money terms and the health consequences in the most obvious natural units, such as years of life gained or days of disability averted. In cost-utility analysis a generic measure of health improvement is used, such as the quality-adjusted life-year. Finally, in cost-benefit analysis the costs and consequences are expressed in money terms.

There are several common misconceptions surrounding the use of the term 'cost-effective' (Doubilet and Weinstein, 1986). First, the term tends to be used generically, covering all types of economic assessments and not just the form of analysis described as cost-effectiveness analysis above.

Secondly, it is clear from Figure 1 that assessments of 'cost-effectiveness' consider more than just comparative costs. Therefore the most cost-effective therapy is not necessarily

the cheapest; it depends on whether the additional health status gained from a more expensive therapy justifies the extra cost. Formally, such assessments can be made only through a cost-benefit analysis, although in practice they are often made by comparing interventions in terms of gains in incremental cost per life-year or cost per quality-adjusted life-year.

Comparisons of health care interventions, by developing such rankings or 'league tables' have been the subject of considerable debate in recent years. Drummond et al. (1993) point out that league tables can be misleading if there are considerable differences among studies in terms of methodology. Analysis of existing league tables shows that there is very little standardisation of methods. A particular problem is that all the cost-effectiveness estimates are incremental to a given baseline alternative, which differs between studies. In some cases the intervention of interest is compared with 'doing nothing'; in others it is compared with 'current care'.

Birch and Gafni (1994) argued that the selection of therapies, in the order that they appear in a given 'league table' will lead to a misallocation of resources. Instead they argue that decision makers in a given setting need to identify the true opportunity cost of adopting a particular intervention. Drummond et al. (1995) argue that the data presented in league tables should not form the basis for making decisions, but that they can be useful in stimulating local debate. This debate is beyond the scope of this paper.

However, the main point to note here is that assessments of comparative 'cost-effectiveness' require some weighting of all the costs and consequences of the therapies concerned, not just comparative costs. Registers of cost-effectiveness studies, like that recently produced by the Department of Health, can help in this process, but they need to be interpreted carefully (DH 1994).

Thirdly, it is clear that assessments of comparative cost are not restricted to the costs of the medicines themselves. They may also include the costs of drug administration and the costs of treating side-effects. Therefore, comparisons of drug costs in terms of the cost per tablet or the cost per defined daily dose will only be good indicators of comparative cost if all the other costs are identical for the two therapies. This may not often be the case. In a study of hospital-based antibiotics, Plumridge (1990) showed that the ranking of drugs by acquisition cost was completely changed when the costs of drug administration were considered.

## **2. Examples of economic evaluations of medicines**

In order to illustrate these basic principles, two contrasting examples of published economic evaluations are discussed below. The first, on the costs and benefits of drug therapy for treatment-resistant schizophrenia, is an example of a modelling study. Here,

clinical and economic data from a number of sources are synthesised in an economic evaluation. The main methodological issues arising in such studies relate to the validity of the model used and the quality of the data inputs. The second study, on the prophylaxis of chemotherapy-induced neutropenia in patients with small cell lung cancer, is an example of a trial-based study. The main methodological issues arising in such studies relate to the suitability of the particular trial as a basis for an economic evaluation.

Both studies have their imperfections and are not presented as examples of ideal methodology. Rather, they are presented to illustrate the genuine difficulties in undertaking economic evaluations of medicines and the uncertainties that often remain once a study is completed

### ***2.1. Assessment of the costs and benefits of drug therapy for treatment-resistant schizophrenia***

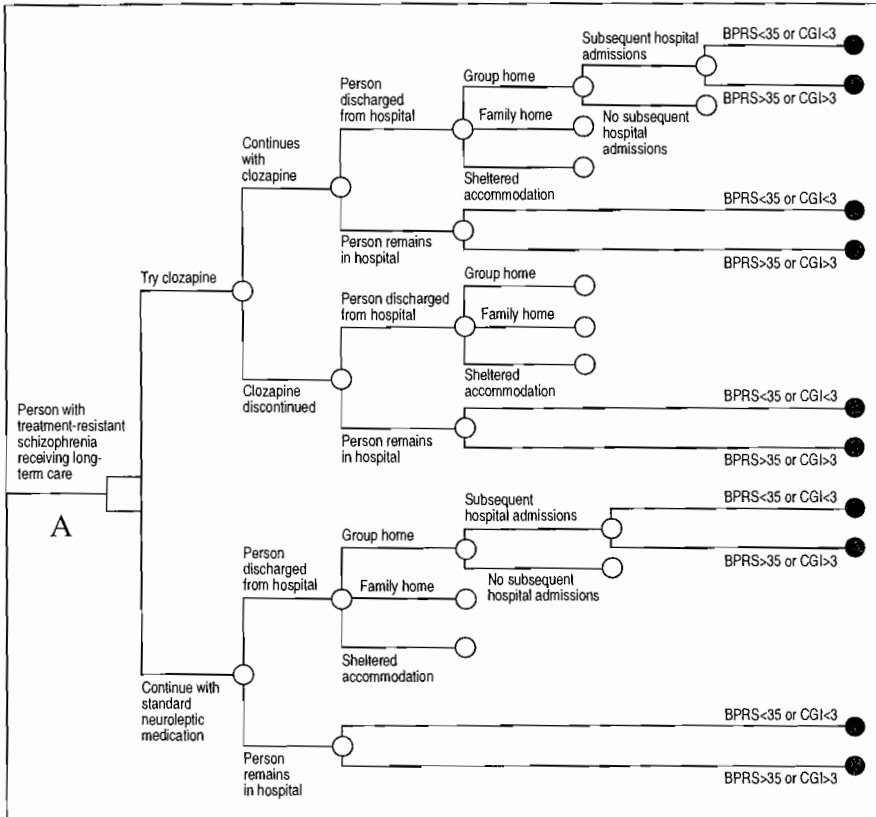
Davies and Drummond (1993) conducted an analysis, on the basis of available data, to assess the economic consequences of clozapine therapy for people with moderate to severe schizophrenia in long-stay institutions or staffed group homes. Data from an economic evaluation conducted in the USA, supplemented by other literature sources, were used to construct a clinical decision tree for likely clinical outcomes for such patients.

A panel of UK psychiatrists provided consensus on how these patients would be managed in the UK. The costs associated with each patient outcome were estimated and a sensitivity analysis performed to test the assumptions made. (In a sensitivity analysis the impact of uncertainty in the estimates is employed by varying key parameters in the model. The objective is to assess the robustness of study results, in the light of uncertainty over the assumptions made.)

The decision tree for patients receiving long-term hospital care is shown in Figure 2. At decision point A, the choice is made to continue with standard neuroleptic medication or to try clozapine. If clozapine is given, a certain proportion of patients will discontinue. Depending on whether clozapine is tried and whether patients continue with therapy, a given proportion of patients (different in each case) will be discharged from hospital. If discharged, a certain proportion of patients will be accommodated in family homes, group homes or sheltered accommodation. Some patients will have subsequent hospital admissions and a given proportion will have mild or no disability. This is defined as a Brief Psychiatric Rating Scale (BPRS) score of less than 35 or a Clinical Global Impression (CGI) score of less than three.

The key elements in judging modelling studies, apart from the structure of the model itself, are the quality of the data and the assumptions made. The data, along with the sources, are given in Tables 1 and 2. When combining these in the model it was found that clozapine would lead to a net gain (per patient) of 5.87 years of life with no disability or

**Figure 2: Decision tree used by panel to decide on care likely to be received by chronic, treatment resistant schizophrenic patients**



only mild disability. The base case analysis also showed that the total direct costs of using clozapine were £91 less per annum (or £1333 per lifetime) than for standard neuroleptic therapy, when the effect on all health-care resources was taken into account.

The sensitivity analysis showed that clozapine would be cost saving or cost neutral under many different assumptions. However, Davies and Drummond still argued that a prospective health economic study with clozapine in the management of schizophrenia would be desirable to confirm their results. Subsequently, it has proven difficult to mount a prospective randomised study, but at least one well-executed 'before and after' study has been undertaken in the USA (Meltzer et al. 1993). This demonstrated a clear saving in the costs of hospitalisation from using clozapine over a two-year period, but must be interpreted in the light of the well-known weaknesses of 'before and after' designs, in particular the fact that other factors could have changed over the period studied.

**Table 1: Probability of events associated with drug therapy for treatment-resistant schizophrenia (BPRS scores > 54)**

Event	Probability (range)	
	Clozapine	Standard neuroleptics
Clozapine discontinued within one year	0.34 <sup>1</sup> (0.11-0.57)	0.00
Patient fit for discharge	0.94 <sup>2</sup> (0.05 <sup>3</sup> -1.00)	0.33 <sup>4</sup> (0.03 <sup>3</sup> -0.94)
Fit patients discharged	0.19 <sup>1</sup> (0.00-0.47 <sup>4</sup> )	0.19 <sup>1</sup> (0.00-0.47 <sup>4</sup> )
Discharged patient lives in: <sup>4</sup>		
own home	0.67	0.67
sheltered accommodation	0.33	0.33
Subsequent admission	1.00	1.00
BPRS score <35, or CGI<3 discharged patients	0.67 <sup>1</sup> (0.30-0.67)	0.04 <sup>5</sup> (0.00-0.10 <sup>3</sup> )
hospital in-patients	0.67 <sup>1</sup> (0.30 <sup>5</sup> -0.67)	0.04 <sup>5</sup> (0.00-0.10 <sup>3</sup> )
<sup>1</sup> Revicki et al (1990) <sup>4</sup> Fischer-Cornelissen & Ferner (1976) <sup>2</sup> Delphi panel <sup>5</sup> Kane et al (1988) <sup>3</sup> Marder & van Putten (1988)		

**Table 2: Annual use of resources and unit costs for treatment and care (BPRS scores >54)**

Event	Resource use: days	Unit costs £1989/90
<b>Drug therapy</b>		
Clozapine discontinued:		
(a) clozapine	47	5.58/day
(b) standard neuroleptics	318	0.82/day
Clozapine continued	365	5.58/day
Standard neuroleptics	365	0.82/day
<b>Discharge to own home / sheltered accommodation:</b>		
Out-patient visits	4	46.13/visit <sup>6</sup>
Day care	48	24.17/day <sup>6</sup>
Community psychiatric nurse/social worker	12	6.12/visit <sup>7</sup>
General practitioner	7	7.01/visit <sup>8</sup>
Subsequent in-patient care	42	50.20/day <sup>6</sup>
Sheltered accommodation	365	16.10/day <sup>9</sup>
<b>Long-stay in-patient care / staffed group home</b>		
Residential care	365	50.20/day <sup>6</sup>
Day care	48	24.17/day <sup>6</sup>
<sup>6</sup> Chartered Institute for Public Finance and Accountancy (1987) <sup>7</sup> Review Body (1989) <sup>8</sup> Office of Health Economics (1987) <sup>9</sup> Davies (1988)		

## 2.2. Prophylaxis of chemotherapy-induced neutropenia in patients with small-cell lung cancer

Drummond and Davies (1994) undertook an economic evaluation of lenograstim, a recombinant human granulocyte colony-stimulating factor (G-CSF), in prophylaxis of chemotherapy-induced neutropenia in patients with small-cell lung cancer. The study was conducted alongside a randomised controlled trial, undertaken in one centre in the UK.

In the trial the patients received VICE (vincristine, ifosfomide, carboplatin and etoposide) chemotherapy and were randomised to receive lenograstim or no lenograstim. The aim of the clinical study was to determine whether the use of lenograstim would permit a significant increase in the dose intensity of chemotherapy in patients with good prognoses. Chemotherapy may in turn lead to improved survival, but this is yet to be proven in clinical studies.

Data on the use of health care resources were collected as part of the clinical trial. These included the number of hospital inpatient days, the number of days of antibiotic therapy and the number of days of chemotherapy. The unit costs of the relevant resources were obtained either from the clinical centre where the trial took place or, where these were not available or where local costs were known to differ greatly from costs in similar centres in the UK, national statistics.

Some of the clinical trial results are summarised in Table 3. It can be seen that the chemotherapy dose intensity index was higher with lenograstim. There was also a trend towards more people being alive at two years in the lenograstim group (32%; 95% CI 16 to 48) compared with the control (15%; 95% CI 2 to 27). Such a difference would be clinically important. However, it would need to be confirmed at the conventional level of

**Table 3: Clinical trial results of chemotherapy with or without adjunctive lenograstim administration**

Outcome	Lenograstim (n=34)	Control (n=31)	p value
Chemotherapy dose intensity index (cycles 1-6)			
median	125.00	118.00	<0.03
range	105-15	388-131	
No. (%) people with > 1 chemotherapy delays	1.00 (3)	2.00 (6)	
No. (%) of people withdrawn from study (all reasons)	18.00 (53)	11.00 (35)	
No. (%) of people died before end of study	6.00 (18)	1.00 (3)	
% people alive at 2 years	32.00	15.00	
No (%) of people with >1 documented infections	11.00 (32)	15.00 (45)	0.19
Mean days of follow-up	133.71	140.97	0.29

statistical significance by a larger study before any conclusions could be reached about increased survival from dose intensification in small cell lung cancer.

There was also a trend towards a higher short term mortality rate in the lenograstim group (18%) than in the control group (3%). This was attributed to the toxicity of the more intensive chemotherapy regimen administered to patients in the lenograstim group (Woll et al. 1994).

The health care resource utilisation by patients receiving chemotherapy with or without adjunctive lenograstim administration is given in Table 4. It can be seen that there were no statistically significant differences in the four resource categories selected *a priori* as key items for statistical analysis. Most categories of resource showed a trend towards higher utilisation with lenograstim. In general, the resource use data were consistent with the findings of the clinical trial, which reported a lower rate of infections in the lenograstim group. Also, the greater use of blood products is consistent with the more intensive chemotherapy given to the lenograstim patients.

When the resource use was costed, it was found that the cost of health care for the lenograstim group (excluding lenograstim acquisition costs) was around £700 higher per patient (95% CI - £930 to £2300). The authors concluded that any increased costs need to be balanced against the potential cost savings and increased survival associated with the possible long-term benefits resulting from chemotherapy dose intensification.

Therefore, even though this economic evaluation was carried out alongside a clinical trial, many uncertainties remain. The most fundamental uncertainty relates to the clinical benefits of dose-intensification itself. If none exist, then the whole premise for using lenograstim in this way does not hold, although there may still be a case for the use of G-CSF to reduce neutropenia in patients receiving a traditional chemotherapy regimen. (This has been evaluated from an economic viewpoint for other forms of cancer (Drummond et al. 1994)).

The other main uncertainties relate to the wide confidence intervals around the estimates of resource use and cost. These arise because, in keeping with many economic evaluations alongside Phase III clinical trials, sample size was not calculated with the estimation of costs in mind, but was based on the main clinical endpoint. Therefore it is quite common to find that studies do not have the power to detect differences in cost.

Finally, a judgement would need to be made about the generalisability of the results beyond the clinical centre concerned. To some extent this issue was addressed in the costing and in a sensitivity analysis on the cost estimates. However, the chemotherapy regimen used could probably only be administered in tertiary centres and the impact on outcomes of the particular skills and expertise in the trial centre itself is hard to evaluate.



**Table 4: Health care resource utilisation by patients receiving chemotherapy with or without adjunctive lenograstim administration**

Item	Lenograstim (n=34)	Control (n=31)	Difference	95% C	p value
<b>All inpatient stay (days)</b>					
General ward					
mean	32.71	31.68	1.03	-5.03 to 7.08	0.72
SD	12.32	13.98			
Intensive care					
mean	0.94	0.00	0.94	-0.16 to 2.04	
SD	3.06	0.00			
% admitted to ICU	11.76	0.00	11.76		
<b>Inpatient stay: general ward (days)</b>					
Administration of chemotherapy					
mean	15.94	15.71	0.23	-2.14 to 2.60	
SD	4.61	4.95			
Other					
mean	16.76	15.97	0.81	-4.99 to 6.59	
SD	11.28	12.08			
<b>Blood products used (units)</b>					
Blood					
mean	10.50	8.39	2.11	-0.45 to 4.67	
SD	5.80	4.34			
Platelets					
mean	26.29	14.94	11.36	1.22 to 21.50	
SD	25.04	13.66			
Drug therapy					
Antibiotics (days)					
mean	11.68	14.35	2.68	-8.29 to 2.93	0.65
SD	9.62	12.91			
Prophylaxis (days)					
mean	14.09	26.19	12.11	-26.09 to 1.88	0.38
SD	14.77	37.78			
Chemotherapy (days)					
mean	19.47	19.29	0.18	-2.88 to 3.24	0.85
SD	5.91	6.43			
Lenograstim (days)					
mean	66.44	n/a	n/a	n/a	
SD	22.27				
All laboratory investigations (no.)					
mean	50.00	46.22	3.77	-3.93 to 11.48	
SD	15.06	16.03			

### **3. Practical problems in undertaking economic evaluations of medicines**

The two examples discussed above illustrate some of the practical difficulties in undertaking economic evaluations of health care interventions. In addition, a number of reviews have identified methodological weaknesses in the published literature (Udvarhelyi et al. 1992; Mason and Drummond 1995). It is important to be aware of these difficulties when interpreting economic evaluation results.

#### **3.1. *Inadequate clinical data***

Probably the most significant problem is that, in one way or another, the clinical data used in economic evaluations are almost always inadequate for the task in hand. At first sight this may seem surprising, since new medicines have to demonstrate efficacy and safety prior to being given a licence. The efficacy data for medicines are certainly better than those for equipment or most medical procedures!

However, there are a number of ways in which the existing clinical data may be inadequate for an economic evaluation. First, the existing clinical studies may compare inappropriate alternatives. For economic evaluation, the most relevant clinical studies are those that compare the drug of interest with the most widely used therapy (e.g. 'current practice'). However, many clinical trials compare the new drug with a placebo or an out-moded therapy. This is because to obtain a licence it is only necessary to show that the drug is efficacious, not that it is more efficacious than existing therapy. (Indeed, the Medicines Act in the UK forbids assessments of comparative efficacy, except in relation to safety.) Only in jurisdictions with formal listing of medicines for reimbursement does comparative efficacy need to be demonstrated. (See the chapter by Maynard et al., which discusses the situation in Australia and Canada.)

Therefore, the economist may be faced with a situation that there are no head-to-head clinical studies of the relevant alternatives. He or she may, therefore, be tempted to synthesise such a comparison by combining data from two or more different studies. However, this is fraught with difficulties, since one cannot be sure that the various studies are truly equivalent.

The techniques applied in systematic overviews, including meta-analysis, offer one potential way forward (see the chapter by Russell). The major advantages are that: (i) only well-designed trials are included; (ii) increased precision in estimation is obtained and; (iii) the issue of generalisability of findings is partially addressed if trials from a number of settings are included.

However, a few difficulties remain, and systematic overviews are not a panacea for the clinical data requirements for economic evaluation. First, judgements are still required

about which trials to include or exclude, although recent work by Schulz et al. (1995) has shown that the quality of a study may be indicated by the method of concealment of allocation of patients to study therapies. Secondly, meta-analyses usually examine a whole drug class (e.g. selective serotonin reuptake inhibitors, or low-molecular weight heparins), or the use of related classes of drugs (e.g. cholesterol-lowering therapy). Conversely, most economic evaluations compare individual products within a class. Sometimes there may be differences in efficacy or side-effects between products, and of course, costs of therapy often differ from drug to drug. Thirdly, systematic overviews are limited by the comparisons made, and the range and quality of measurements undertaken in the original trials being summarised.

This leads on to the second problem with the available clinical data, namely the published clinical studies may not measure the appropriate endpoints for economic analysis. Economists tend to favour long-term endpoints, such as survival, but many clinical trials measure intermediate endpoints such as disease progression, or biological markers such as mmHg blood pressure reduction or percentage total serum cholesterol reduction. Hence the question is whether there is a reliable method of predicting final outcomes from such short-term measures. This issue is important for assessing both clinical benefit and cost-effectiveness, and is likely to depend on the clinical field concerned. In some fields, such as treatment for hypertension, clinical trials have shown that control of blood pressure does indeed reduce the incidence of strokes. In other fields, such as treatment for hypercholesterolaemia and osteoporosis, there is much more debate, so extrapolations to final endpoints are subject to considerable uncertainty. In the field of HIV, extrapolations based on the data from a 12-month clinical trial (Schulman et al. 1991) have been proven, by longer-term studies, to be overoptimistic.

One might ask why economists insist on extrapolating to final outcomes when the data are not available. However, one might also ask why clinicians treat on the basis of biomedical markers. In both cases there is a belief that there is some relationship between the intermediate and long-term outcomes. Perhaps economists make the mistake, through their studies, of trying to explore this relationship explicitly! Certainly we all need to be careful in how we use clinical data in our studies and in prescribing decisions (Freemantle and Maynard 1994; Jönsson 1994).

The third problem is that, even when the clinical studies measure the appropriate endpoints, they may be undertaken in settings that are atypical of normal clinical practice. For example, clinical studies of ulcer therapies measure the incidence of lesions as detected by gastroscopy (although some also measure symptom relief). Similarly, clinical studies of prophylaxis for deep-vein thrombosis (DVT) measure rates of DVT as detected by venography. Whereas these are totally appropriate for assessments for efficacy, the economic evaluation needs to be based on events that would occur in normal clinical practice. Since not all ulcers or DVT would exhibit symptoms or be judged clinically

important, some adjustments to the clinical data are normally required in order to use them in an economic evaluation.

For example, Knill-Jones et al. (1990), in a study of drug prophylaxis for NSAID-associated gastric ulcer, assumed that 30% of the lesions detected by gastroscopy would not become clinically important. Economic evaluations often depend critically on the validity of such assumptions. Of course, the ideal would be to conduct a clinical study under more pragmatic conditions, reflecting normal clinical practice. However, such studies are time-consuming and costly to conduct. This explains the relative lack of them in the published literature.

### ***3.2. Timing of economic evaluations***

Many of the problems outlined above arise because of the need to conduct economic evaluation around the time the drug is launched. This is because several important decisions, about the price of the drug and whether it will be reimbursed (i.e. paid for by the government or third party payer for health care), are made at this time in many countries. This is not the case in the UK, but presumably it would be useful to give advice on the cost-effectiveness of new drugs to prescribers sooner rather than later.

It may be best to view many of the current economic evaluations of drugs to be preliminary assessments, that should be confirmed by additional data after a number of years of normal clinical use. However, given the cost of long-term Phase IV studies, particularly randomised trials, one would need to consider carefully the relative roles of industry and health care purchasers in initiating and financing such research. Certainly, it may not be realistic to expect industry to finance studies to the same extent as in Phase III, although there are examples of high-profile industry-funded research that has yielded reliable and important results (Mark et al. 1995).

Nevertheless, there are signs of such research partnerships being forged between individual pharmaceutical companies and large health maintenance organisations in the USA. For example, Merck Sharp and Dohme and Kaiser Permanente have jointly conducted a cost-effectiveness study based on a randomised controlled trial of a stepped-care regimen for treatment of elevated cholesterol versus one using a statin as first-time therapy (Oster et al. 1994). Whether this approach can be followed in other jurisdictions remains to be seen.

### ***3.3. Differing perspectives for economic evaluation***

It is usually argued that economic evaluations should be undertaken from a broad, societal perspective. However, prescribers may not be adopting such a broad perspective in practice. Fundholding GPs may not be concerned about some of the costs of hospitalisation (e.g. for emergencies) which are not charges on the fund under standard fundholding.

Although economic issues are being more widely discussed, it seems unlikely that GPs would allow cost consequences to take precedence over clinical considerations when prescribing and more unlikely that they would consciously make decisions on budgetary grounds that may disadvantage their patients. Therefore, if we wish to encourage cost-effective prescribing, the rather narrow budgetary perspectives of fundholding GPs and hospital providers are likely to pose problems.

Similarly, the budgetary divisions between the hospital and family practice sectors are known to lead to inefficiencies. These are most apparent in the case of high cost drugs, where the prescribing decision is taken in the hospital, liable only for the clinical responsibility for the case, and the cost to be borne by the GP (Crump et al. 1995). However, there may be a more general problem for efficiency, where drugs are reduced in price to the hospital sector in the hope (on the part of the pharmaceutical industry) that, once established on a particular drug therapy, the patient will be prescribed the same therapy by his or her GP.

This problem may be lessened as more joint Health Commissions are established and as these follow government advice to become more involved in prescribing issues (DH, 1994). However, it is still not clear why an individual GP should prescribe in a way that increases cost-effectiveness overall. Hawkes and Drummond (1993) reviewed some of the options for fundholding GPs and concluded that there were very few situations where there would be economic benefits for the GP from changing his or her prescribing behaviour. The division of budgetary responsibility, rather than the paucity of economic evidence, is probably the biggest obstacle to the encouragement of cost-effective prescribing.

### **3.4. Variations in cost-effectiveness among patients and settings**

One of the problems for the prescriber in interpreting economic data is that the relative cost-effectiveness of alternative health care interventions could vary by patient and setting. The reasons for variations by setting have been well documented (Drummond et al. 1992). These include basic demography and the epidemiology of disease, clinical practice patterns, relative price levels and the incentives to health professionals and institutions.

Hawkes and Drummond (1993) explored this in relation to treatment of gastric oesophageal reflux disease (GORD). Based on data presented by Bate (1991), they pointed out that the relative cost-effectiveness of treatment by ranitidine or omeprazole depended on whether, after eight weeks therapy, the GP was likely to request a gastroscopy in patients who were still experiencing symptoms.

The issue of variations in cost-effectiveness among patients has not been widely discussed, although Johannesson (1992) suggested that the Australian approach, of giving a global approval for listing of drugs in terms of their average incremental cost-effectiveness, compared with a relevant comparator, was fraught with difficulty. For example, certain

drugs may only be cost-effective when given to patients at high risk. To some extent the 'authority system' operating in Australia, where drugs can only be used for certain defined indications, deals with this problem.

Prescribers are used to the fact that general advice on which drugs to use may not suffice for the individual patient. In this respect the advice from economic studies is no different from that obtained from clinical trials. That is, the trial result gives the mean and variance, or odds ratio, for the patients enrolled in the trial concerned. It may not necessarily be a good predictor of the likely outcome for the next patient to be treated and would only be valid if the patient concerned would have met the entry criteria for the clinical trial from which the data are taken.

Not enough is known about the influence that communication of clinical trial results has on the behaviour of prescribers. Some data from the USA suggests that the provision of information needs to be supplemented with other strategies (Soumerai et al. 1990). Much less is known about the impact that economic data has on clinician behaviour. I suspect that in most cases prescribers use a mixture of information from published studies and their own experience. Therefore, for cost-effectiveness arguments to have much force, GPs would need to be convinced that, in the case of their own patients, the use of a more expensive medicine does indeed reduce the use of other resources, such as their own time or referrals to hospital.

## **4. Using economic data in prescribing decisions: issues and controversies**

### **4.1 *Are the methods reliable enough?***

Much has been written about the imperfections in published economic evaluations. There is also continuing debate among economists about issues such as: (i) the most appropriate way to value health state preferences; (ii) the discount rate to be used for the health benefits of treatment and; (iii) the wisdom of making comparisons of the relative cost-effectiveness of different health care interventions in 'league tables'.

It would be wrong to gloss over these controversies, but compared to the current information used by prescribers to decide on the most cost-effective therapy, data from economic studies would represent an improvement. That is, everyone knows that economic studies are imperfect. The question is, given the increased interest in cost-effective prescribing, are they an improvement over what we have already?

### **4.2 *What are the pros and cons of trial-based versus modelling studies?***

The examples discussed in Section 2 included both trial-based economic evaluations and those modelling data from various sources. Consumers of data on the efficacy of drugs

are used to the results from randomised controlled trials. These data have a number of advantages. First, they have stronger internal validity in that bias relating to selection of therapy is minimised by the randomisation process. Secondly, RCTs usually involve a commitment to publish the results no matter how the data fall, although the problem of under-reporting of negative results, even from trials, is well known.

By contrast, the methodology of modelling studies is often less well defined and such studies usually incorporate many assumptions. Therefore it has been argued that there is much more analyst discretion (Kassirer and Angell, 1994). On the other hand, the treatment protocol in many clinical trials is often very strict and may or may not reflect regular clinical practice. Therefore, modelling studies offer the potential for more external validity in economic evaluation results in that, potentially, they can reflect normal practice.

Ultimately the preference would be for randomised trials conducted under more pragmatic conditions (Schwartz and Lellouch 1967), but this is likely to be unfeasible in many situations. (The large Phase IV studies mentioned above are probably the exception.) Therefore, a mixture of trial-based and modelling data will have to be used for deciding upon cost-effective prescribing. Over time the following may be predicted:

- (i) More trial-based studies are likely to be undertaken in situations where these are feasible; namely, where the time required to observe a relevant endpoint is quite short, where the setting for the trial is fairly generalisable, and where the potential benefit to patients is substantial, thereby justifying the high cost involved.
- (ii) The conduct of modelling studies is likely to improve, with more explicit statements being made, at the outset of the study, about the analytic approaches to be used and the intention to publish the results. Also, more attention is likely to be given to the nature of the clinical evidence used in modelling studies, with more emphasis being placed on using data from systematic overviews.
- (iii) Trial-based data and modelling data will be presented alongside each other, so as to satisfy the equally important concerns of internal and external validity.

#### ***4.3 Should economic data be communicated directly to individual prescribers?***

The Department of Health appears to be encouraging the communication of economic data to prescribers. The pamphlet outlining the indicative prescribing scheme, argues that “it is important that evaluation of drugs should include consideration of the higher costs which might result from alternative hospital treatment and the improved quality of life for patients which such drug treatments may confer”. It further suggests that “the pharmaceutical industry can play an important role by producing cost-benefit and cost-effectiveness evidence for new products which are brought to market”.

However, some concerns have been raised about the advertising claims made on the basis of economic studies (Walley and Edwards 1993) and about the fact that the studies themselves may be misleading (Bate 1994; Hatoum and Kong 1994). Also, Davey and Malek (1994) have pointed to a potential conflict of interest, faced by the clinician, between the needs of individual patients and the priorities of society as a whole. This being the case, would it be better to shield prescribers from the discomforts of considering economic data?

Even if this were feasible, it would be unlikely to be desirable. In today's National Health Service, decision makers, including prescribers, need to consider cost-effectiveness. Therefore, it does not seem sensible to suppress some of the most relevant data. However, there clearly needs to be more debate about the ways in which cost-effectiveness data are produced and communicated to prescribers. Also, more emphasis needs to be placed on educating prescribers about economic evaluation so that they become a more informed and critical audience for these studies.

#### ***4.4 To what extent should the production and use of economic data be regulated?***

In two jurisdictions, Australia and Ontario, economic studies are now mandatory for new medicines (see the chapter by Maynard et al.). Also, in both cases the methodology to be followed in undertaking economic studies has been fairly well specified. Strictly speaking, these regulations govern the production and use of economic data in submissions to official committees deciding on the listing of drugs on the national or provincial formulary. However, they may also guide, albeit indirectly, the use of economic data in promotional material in the countries concerned.

In the United Kingdom there is not a formal listing process for new medicines, beyond the selective list. Therefore there is currently no suggestion that economic studies be made mandatory. However, a joint government/industry working party has produced a set of guidelines for undertaking economic evaluations of medicines (DH/ABPI 1994). These are intended to offer general guidance to companies planning or commissioning studies and are consistent with current thinking on the methods of economic evaluation. Nevertheless it remains to be seen whether they are sufficiently specific to be helpful in arbitrating on cases of (alleged) misuse of cost-effectiveness claims in promotional material.

In general, the regulations for the use of cost-effectiveness claims should mirror those in operation for clinical claims. Certainly economic evaluation should be viewed as science rather than marketing (Drummond 1992). However, there are difficulties in specifying the standards of evidence as tightly as for clinical data. For example, for the reasons outlined above, it does not seem sensible to argue, as for clinical data, that cost-effectiveness claims should only be made on the basis of two well-conducted randomised controlled trials. However, the question is, if we reject this standard, what standard do we apply? Some



groups of economic researchers have discussed standards in the past (Drummond et al. 1993) and the government guidelines in Australia and Ontario also lay down standards for analysis and reporting of economic data. More sets of guidelines are likely to follow (Task Force on Principles for Economic Analysis of Health Care Technology 1995), and the British Medical Journal has convened a working party to devise standards for the reporting of economic studies submitted to the journal. Perhaps these activities will eventually form a basis for regulating the quality of economic data used in promotional claims.

## 5. Conclusions

This paper has demonstrated that 'cost-effective prescribing' can be elusive, both in conceptual terms and in the design and conduct of studies to provide reliable economic data for decision making.

There are a number of misconceptions about the cost-effectiveness of medicines. The most important point to note is that assessments need to take account of not only the relative acquisition costs of drugs, but also their relative effectiveness (in impact on health status) and their relative impact on health care costs.

The examples have illustrated that there are a number of practical difficulties in undertaking economic evaluations of medicines, whether these be modelling or trial-based studies. The main challenge is in obtaining relevant clinical data and in using it appropriately in the economic study. There are also important issues of interpretation of economic data, particularly in generalising from one setting to another.

Finally, there are a number of issues and controversies surrounding the generation of economic data and its use in prescribing decisions. Attention needs to be paid to improving the reliability of economic studies and guidelines are being developed. One should also be careful when communicating economic data to prescribers and they need to be educated about economic evaluation methodology so that they become a more informed and critical audience for such studies.

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## Using economic data for prescribing decisions: discussion

### Alan Williams (chair)

One of the themes that seems to be emerging is that one cannot expect individual clinicians faced with individual patients to start thinking then about cost effectiveness. This thinking should be done earlier and internalised so that when GPs see a patient there is already a policy.

This means that clinical guidelines need to be established for common conditions, constructed as decision trees. For example, assuming that 1000 patients present with a set of indications, what then happens to them as they work through diagnostic and therapeutic practice? This should set the guidelines firmly in the context of realistic practice. Clinical guidelines also need to be informed by cost effectiveness information from the outset. Currently, guidelines seem to be initially informed by clinical effectiveness, devising some kind of 'gold standard' care, then if the costs are 'acceptable' this is put forward as cost effective. Results from this approach may of course be very different from those which would have been obtained had cost effectiveness principles been operated all the way through (Williams 1994).

To develop these guidelines we must first be clear what the viewpoint is, as different viewpoints will require different decision trees. Next, both costs and benefits must be identified, and benefits must be expressed in terms of survival and quality of life. This is where the views of patients really count, as endpoints need to reflect the values of patients.

In aiming for this system of clinical guidelines to be developed incorporating cost effectiveness principles, a number of questions and issues are raised:

1. Who is in the best position to do these studies? They are always multidisciplinary and cannot be carried out by clinicians or economists alone.
2. They need to be constructed so that decision trees can be updated continuously as new information becomes available and so that the structure can be modified if cost structures change or if more alternatives become available.
3. How should the results be communicated to practitioners? The studies are often complicated and the approach needs to be taught in medical schools and postgraduate medical education, as techniques of statistical inference and not a set of 'cookbook' rules.

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**Dr D P Clappison**

Professor Drummond is right in saying that many of us use cost-effectiveness as a generic term. It is my view that it is more important that our clinical colleagues should fully take on board the concept of evidence based care and the necessity to consider cost-effectiveness in their practice. The Department of Health takes these matters very seriously as resources are not, and never have been, unlimited. This has led to Department of Health setting up the new Centre for Reviews and Dissemination and the database of cost-effectiveness studies, both here in York; the Effectiveness Bulletins; the Clinical Effectiveness Initiative guidelines, and support for the UK Cochrane Centre.

Health economics studies are indeed very dependent on the assumptions made and the quality of the data. It cannot be stressed too greatly the importance of obtaining full advice from health professionals at the initial stage of health economics studies, in averting avoidable errors. The quality of the data itself is also obviously vital. Nevertheless, it may be worthwhile to perform studies on areas where they are needed even if data is not ideal. Clarity as to the reliability and validity of all studies is vital as is the understanding that quality of life measures are value judgements, i.e. subjective.

Information necessary for cost minimisation analysis is widely available through GP computer systems, BNF, Drug and Therapeutics and Medicines Resource Centre Bulletins and other sources, and has contributed to the dramatic rise in generic prescribing, currently over 54% of total prescriptions. Where clinicians believe that minor differences between differing drug treatments are not of clinical significance (the 'so what?' test) it is reasonable to look for cost minimisation. This is fundamental to savings on prescribing made by GP fundholders, and by practices entering prescribing incentive schemes (which often have additional quality targets). In both cases the incentive is that additional resources are released to improve services for their patients.

GPs' therapeutic decisions should ideally be debated outside the pressured clinical setting. This provides a strong argument for practice formularies, preferably computerised. The Department provided guidance in 1991 and 1994 to Health Authorities on policies for the coherent provision of medicines across primary and secondary care. Others have argued in favour of unitary budgets for health care at national or local level. It should be borne in mind that these would inevitably be cash limited.

In conclusion, it is important to increase the desire for the insight given by health economic studies and to implement their findings in the light of their reliability.

**Dr George Rae**

[Dr George Rae is a member of BMA Council, and of the prescribing sub-committee of the General Medical Services Committee. However, his input to the symposium was as a

working GP, not involved in academic medicine, but at the coal face, involved with patients. He comments on Professor Drummond's paper from that perspective].

The Department of Health encourages the communication of economic data to prescribers, but there needs to be more debate about the way in which that data is produced and communicated. GPs are constantly swamped with information from companies and from the NHS Executive. The paper by Drummond was not an easy read, and some of the phraseology was foreign; this will be reflected by GPs. Cost-effectiveness information should be communicated to GPs, but it has to be presented in a way which will be understood. GPs are saturated with information, and are beyond the threshold for obtaining and retaining more information. GPs need to be able to assess and to understand the information about cost effectiveness which is given to them.

It is important to note that UK GPs are aware of cost, and are cost effective, particularly relative to other countries in Europe and elsewhere. The government sometimes appears either to be unaware of this fact, or chooses to ignore it.

The need for a societal perspective was discussed in the paper. This is also being accepted by GPs, who are becoming more aware of public health issues, and considering the needs of the practice population. Locality purchasing extends this: all practices in an area meet, caring for a total population of 50,000-60,000 people. This is also a good forum for inclusion of patient views, and community health councils are included in these meetings. Whatever the outcome of the next election, locality purchasing is unlikely to go away.

The practical problems in undertaking economic evaluations were interesting from a GP perspective, particularly that of inadequate clinical data. Drummond discussed the problems of trials comparing a new drug and a placebo, which is not a relevant comparator to a prescribing GP. Meta-analysis was also discussed, but as yet this is a new technique which will be unfamiliar to many GPs. This also emphasises the point that communicating information to GPs on cost effectiveness issues needs to be in terminology which is not foreign to them. Also of particular interest was the emphasis on long term endpoints. GPs are of course also interested in intermediate endpoints: for example hypertension can cause symptoms, such as headaches and dizziness, which are intermediate outcomes, but nevertheless need to be addressed. Economists predict final outcomes from intermediate outcomes, such as reductions in strokes resulting from reducing blood pressure, which would sometimes appear difficult in such an 'inexact science'.

The paper suggests that prescribing GPs may not consciously think of cost when they write a prescription. This is surprising: as a result of fundholding and other reforms increasing cost awareness and the business ethos, GPs are aware of cost and cost effectiveness, even at the level of an individual prescription.

There is still an important problem of consultants in the secondary sector shifting costs to the primary sector, by prescribing on GP budgets. In theory they also shift clinical responsibility (as alluded to in the paper), but in practice this is limited. Many GPs when asked to prescribe esoteric and unusual substances may be unaware of some of the side effects which may result, which could create potentially serious difficulties.

Finally, ethical issues are raised by the paper's attitude to elderly people. It is suggested that cost effectiveness depends upon settings and patients, and it may be more cost effective to prescribe cheaper drugs to elderly patients. This raises controversial questions such as what age 'old' is: is 70 old? Many patients now live to age 90, and would they live this long if prescribed cheaper drugs at age 70? Important ethical questions need to be considered with this type of approach.

### **Nick Wells**

In the introduction to the paper, Drummond suggests that the 'cost-effectiveness message may be coming through loud and clear' and identifies a number of initiatives currently in place to heighten doctors' awareness of the resource implications of their prescribing decisions. It is probably more accurate to argue, however, that whilst cost consciousness has very successfully been raised throughout the NHS, the understanding of true cost-effectiveness is still relatively limited. Apart from this quibble, there is little else to disagree with in Drummond's paper - it provides a succinct summary of the many issues currently confronting the economic evaluation of medicines. This brief response will therefore simply highlight some of the more significant questions which need to be addressed in fostering the development of 'pharmacoeconomics'.

From a methodological perspective, outcomes measurement represents a major challenge. Drummond distinguishes between biomedical markers and the long term endpoints (e.g. survival) preferred by economists. Given the infrequent availability of the latter, both types of measure are relevant in the economic appraisal of medicines. Beyond this, however, there are other equally important issues. How much change in any given measure defines successful treatment? In asthma, for example, what magnitude of improvement in peak expiratory flow or weekly symptom occurrence constitutes therapeutic success? Further, how should the time taken to achieve success and the period for which it is subsequently sustained be incorporated into the measure? Gaining consensus among and between clinicians, economists, and health care purchasers on such matters may present as great a challenge as determining the appropriate type of outcome measure in the first instance.

Drummond also draws attention to the question of the choice of comparator in pharmacoeconomic studies. Comparisons against placebo in isolation, clearly offer very little information to help guide the resource allocation process. Some pre-launch trials do



nevertheless compare against currently employed treatments, although the information they provide may also be limited if therapeutic fashions have changed by the time of market launch or if dosage, efficacy and market position are different in the 'real world' setting from that envisaged at the time of setting up and running the trial.

In this latter respect, Drummond is quite right to suggest that pharmacoeconomic information generated prior to market availability should best be regarded as preliminary guidance on a medicine's resource implications. If it follows that the most valuable data only become available once the medicine has found its therapeutic niche(s) a series of other questions are then raised about the responsibility for, and funding of, such later stage pharmacoeconomic studies, the setting for these investigations and their integration in the wider context of disease management.

Success in resolving the issues discussed above and those raised in Drummond's paper will have a substantial bearing on the pace and extent of the technical development of the economic evaluation of medicines. The understanding of economic thinking and methods among health service decision makers and the removal of barriers within the NHS which currently prevent the system from responding to economic data will, however, determine the degree to which this relatively new source of information can promote greater efficiency in the deployment of health care resources.

### **Audience discussion**

A number of GPs, both in academic departments (Dr R Taylor, Dr T Avery) and at the 'coal face' (Dr L Kamal and others) emphasised that prescribers are aware of costs and interested in cost effective prescribing (as distinct from cost cutting, which appears too often to be the focus of policies). Dr Avery reported the results of a questionnaire to 580 GPs and an interview study in Lincolnshire which suggested that GPs do consider costs when prescribing, but there are a number of other influences on prescribing decisions.

The issue of how to communicate the results of evaluations in a form which could be incorporated into decision making was raised (S Roberts), and a consensus was established in favour of the use of computer aided clinical guidelines. However, Professor J Howie suggested that only around 50 per cent of patients presenting at a GP surgery could be classified into groups for whom guidelines could possibly be developed, as patients frequently present with a myriad of symptoms and are not 'computer friendly'.

David Gilbert emphasised that the view of patients is what matters, and that good outcome evaluation should take this into account. In the example of the evaluation of clozapine, additional questions are raised regarding how non-drug alternatives are evaluated (and who pays). Consumer groups should be represented in regulation.

Mark Campbell addressed the question of timings of economic evaluation, suggesting that the best time is post launch, but it can be difficult to stop use of a registered drug after launch, which means that decisions as to when recommendations are made are difficult.

David Henry commented that intermediate (surrogate) outcome measures can be used more imaginatively than has been implied. For example, Glaxo has convinced the Australian regulators that two intermediate measures are useful in evaluating asthma therapies: loss of nocturnal wheezing and reduced use of corticosteroid inhalers. These can be useful measures and go some way along the track to the desirable final outcome measures.

Peter Clappison replied to the comments on Department of Health policy, which had suggested that the DH is not simply interested in cutting the drugs bill. Obviously, DH is interested in cutting it but not simply cutting it! There is room for savings but the evidence of DH supported publications (e.g. Effective Health Care) shows that we should do more in some areas, e.g. ACE inhibitors, asthma. However, funding for drugs is not unlimited, therefore if we want to do more of the good things we need to be more careful where the evidence is not so good.

Final comments from Mike Drummond:

1. In economic evaluations, different assessments are possible at different times as more evidence becomes available. This means that evaluations are not a final answer: investigators need to keep going back and refining the available estimates.
2. There are two levels at which cost effectiveness policies can be developed:
  - guidelines can be refined, and more studies can be undertaken, incorporating patient views;
  - at the level of the individual patient: we do not understand enough about the decision making process with individual patients, and considerable information gaps remain. Institutional issues and patient preferences may cut across general guidelines of what is or is not cost effective.

## Using Economic Data for Prescribing Decisions. Key Points

- Clinicians are increasingly being urged to prescribe in a 'cost-effective' manner, but it is not clear that all parties understand what is meant by cost-effectiveness, how to assess it or where to find reliable data to inform prescribing decisions. Although cost consciousness has been raised throughout the NHS in recent years, but understanding of true cost-effectiveness is still relatively limited;
- Economic evaluation assesses the costs and consequences (impact on health status) of alternative health care interventions. Four main forms of analysis can be defined: cost-minimisation analysis, cost-effectiveness analysis, cost-utility analysis and cost-benefit analysis;
- Assessments of comparative cost require some weighting of all the costs and consequences of the therapies concerned, not just those of medicines. For example, costs and consequences of drug administration and side effects should be included;
- Economists ideally use final outcome measures, but intermediate outcome measures may sometimes have to be used. Both intermediate symptoms and final outcomes are relevant to GP prescribing, and patients' own views of their health represent the most relevant effectiveness measure;
- Economic evaluation studies can be conducted alongside a clinical trial or based on modelling of synthesised data from a number of sources. Both types of study have advantages and limitations, and methodological issues arise from both;
- Practical problems in undertaking economic evaluations of medicines include inadequate clinical data, timing of studies, differing perspectives, and variations among patients and settings;
- A number of issues and controversies remain around the generation of economic data and its use in prescribing decisions. The reliability of studies has been questioned and requires development, perhaps with the use of guidelines and/or regulation.
- If cost-effectiveness information is to be internalised to avoid individual clinicians faced with individual patients making difficult choices, clinical guidelines need to be developed by multidisciplinary teams, constructed as decision trees so that information can be updated and structures modified, and enabling development of computerised practice formularies;
- Prescribers require education about economic evaluation methodology if data is to be communicated directly to them, so that they become a more informed and critical audience for such studies. The approach needs to be taught in medical schools and postgraduate medical education, as techniques of statistical inference and not 'cookbook' rules;
- In economic evaluations, different assessments are possible at different times as more evidence becomes available. Evaluations are not a final answer: estimates should continue to be refined, and economics inform decision making rather than replacing it.

## Chapter 2

# Towards Effective Prescribing: Appropriate Research And Development Methods

Ian Russell

### Introduction

Health technology assessment incorporates a variety of technologies other than drugs. For the purpose of the UK National Health Service (NHS) health technology has been defined as “any method used by health professionals to promote health, prevent and treat disease, and improve rehabilitation and long-term care” (Standing Group on Health Technology, 1994). Thus the NHS regards drugs as technologies and thus eligible for health technology assessment; this has been defined as “the evaluation of the benefits and costs (clinical, social, economic and system-wide) of transferring the technology of interest into clinical practice” (Russell and Grimshaw, 1995). In this spirit the first part of this paper sets out some general principles of research design within health technology assessment and considers the relevance of these principles to cost-effective prescribing.

Although health technology assessment is relevant to cost-effective prescribing, it is only one of the programmes within the NHS Research and Development (R & D) Strategy. Research relevant to cost-effective prescribing will also arise from other programmes, for example those relating to cancer, to the interface between primary and secondary care, to specific conditions like asthma and diabetes, and to the implementation of research findings. Thus this volume should aim to facilitate the coordination of an explicit agenda for prescribing research, with particular reference to cost-effective prescribing, within the NHS R & D Strategy. Recognising the need to coordinate work from a wide range of sources if we are to achieve cost-effective prescribing, the second part of this paper addresses a development issue: whether clinical guidelines can help in the implementation of research findings. It is important to note that this paper focuses on effectiveness, leaving the other authors to focus on cost-effectiveness.

## 1. Choice of research design

### 1.1. *To randomise or not to randomise?*

The philosophy underlying both parts of this paper, and perhaps the symposium as a whole, may be summarised in a paraphrase from Professor Archie Cochrane’s seminal monograph:

“The development of cost-effective health care needs hard evidence, preferably from randomised trials, that the use of each clinical procedure or drug either alters the natural history of the disease or otherwise benefits many patients at a reasonable cost’ (Cochrane 1972).

It is worth reminding ourselves why Cochrane was so strong an advocate of randomised trials. Consider, for example, the problem of evaluating the best drug treatment for peptic ulcer. Suppose this had been addressed by an observational study comparing the clinical outcomes of patients treated by H<sub>2</sub>-antagonists with those of patients treated by antibiotics. It would have then been virtually impossible to attribute any significant difference in outcome to the difference in therapy rather than to the inevitable differences in the characteristics of these patients or their doctors.

While accepting the intrinsic weakness of the observational approach, many critics of randomised trials would argue that the fundamental problem of attributing differences in outcome to the true cause could be greatly ameliorated, if not resolved, by the adoption of quasi-experimental research designs (Cook and Campbell, 1979). In health technology assessment the most common rigorous form of quasi-experiment is the controlled before-and-after study. In the example of alternative therapies for peptic ulcer this would imply a comparison of patients treated before and after their doctors' preferred drug changed from an H<sub>2</sub>-antagonist to an antibiotic, controlled by other patients whose doctors' drug of choice remained an antibiotic throughout. While the risk of bias in such a study is certainly less than in the previous observational study, this risk can never be eliminated (Russell 1983). In this example there would be concern *inter alia* that the change of therapeutic strategy might itself have led to a change in the case-mix of patients being treated; and that such a change would be difficult to detect and even more difficult to correct with confidence during statistical analysis.

In summary, randomisation protects against selection bias in health technology assessment. Its other main advantage, less well known, is that it provides a sound mathematical basis for subsequent analysis. Two of the more common objections to randomised trials were cogently expressed by Professor Raymond Illsley (1982), at that time Chairman of the Scottish Health Services Research Committee. He argued that randomised trials are seldom feasible in health technology assessment. If drugs were not included within health technology, he was probably right at the time. However the number of trials for assessing health technology has been increasing ever since (e.g. Standing Group on Health Technology 1995), with the result that Illsley's first objection is no longer valid.

### **1.2. Fastidious trial or pragmatic trial?**

Illsley's second concern was that, even where randomised trials were feasible, the constraints of the experiment would limit the general relevance of the findings. With the continuing increase in the number of trials this concern has become increasingly relevant to health technology assessment, in particular the evaluation of drugs. To address this concern it is helpful to explore the distinction between explanatory and pragmatic trials, first proposed by Schwartz and Lellouch (1967) and now summarised in Table 1.

'Explanatory' or, as they are increasingly being termed, 'fastidious' trials are designed to draw conclusions about defined scientific hypotheses, while 'pragmatic' trials are designed to choose between two drugs or technologies in clinical practice. Hence this distinction is similar to, but not exactly the same as, the distinction between Phase II trials ["small-scale investigations into the (efficacy) and safety of a drug" (Pocock 1983)] and Phase III trials ["rigorous and extensive trials to compare a drug with the current standard treatment for the same condition" (Pocock 1983)].

The first implication of this distinction is that fastidious and pragmatic trials should be conducted under different experimental conditions. Fastidious trials, which are seeking information about defined scientific hypotheses, should be conducted under strict laboratory-like conditions to eliminate as many potential sources of bias as possible; in drug trials, for example, this desideratum is generally taken to imply that trials should be both double blind and placebo-controlled. In contrast pragmatic trials, which are intended to guide decision-making in clinical practice or resource allocation, should be conducted within normal clinical practice if those decisions are to reflect the real world in which they are inevitably taken, rather than the artificial world of the laboratory.

The second implication of the distinction between fastidious and pragmatic trials is that the therapies to be compared should be defined in different ways. Since fastidious trials are testing defined hypotheses about the intrinsic properties of those therapies rather than about any extrinsic psychosomatic or placebo effects, they must be governed by rigid protocols that both define the therapies precisely and equalise those placebo effects. Conversely pragmatic trials are designed to choose the better therapy in routine clinical practice, which spans a wide range of clinical circumstances in each of which health professionals aim to do the best for the individual patients who consult them, in particular by optimising the placebo effects of the therapies that they prescribe. It follows that pragmatic trials are governed by protocols that are explicit but flexible: explicit enough to ensure that those placebo effects are optimised, but flexible enough to permit professionals to adapt therapies to the needs of individual patients, as they do in the routine clinical practice to which the findings of the trial will be extrapolated.

This important difference between fastidious and pragmatic trials requires an example to illustrate its far-reaching effect on trial design. Consider a randomised trial to compare salmeterol, the recently developed long-acting bronchodilator, with salbutamol, the traditional short-acting bronchodilator. To equalise the extrinsic effects of the methods by which these two drugs might be administered, and thus to focus on their intrinsic pharmacological effects, the fastidious version of this trial would have to be double blind; if either the recruiting doctor or the recruited patient were to know for certain whether salbutamol or salmeterol had been prescribed, the placebo effect of the different intervals between doses would be activated. It follows that all patients would have to take some dose, either active or placebo, every four hours; while control patients randomised to

**Table 1 Differences between fastidious and pragmatic trials**

	<b>Fastidious</b>	<b>Pragmatic</b>
Objective	To acquire information relevant to defined scientific hypotheses and thus to draw conclusions.	To make a decision between two technologies in clinical practice
Experimental conditions	Laboratory conditions	Normal clinical practice
Definition of therapies	1. Rigid 2. Equalised (in particular) therapies are defined so that the psychosomatic or placebo effect is the same for each)	1. Flexible 2. Optimal (in particular, therapies are defined so that each makes the best of any psychosomatic or placebo effect)
Definition of patients	1. Patients eligible for the trial (ie for all therapies) are strictly defined a priori and may be redefined a posteriori 2. Patients who withdraw from a therapy are withdrawn from the trial	1. Patients eligible for the trial (ie for all therapies) are flexibly but irrevocably defined a priori 2. Patients who withdraw after the beginning of treatment remain in the trial for the purpose of analysis
Nature of criteria	Single or multiple	Single criterion only; multiple criteria must be weighted so as to form a single criterion
Method of analysis	Traditional significance test for each hypothesis (but no formal relationship between significance tests)	Select therapy which gives the best weighted criterion (no formal significance test)
Number of patients	Traditional calculation, based on type 1 and type 2 errors, for each hypothesis. Ideally, the eventual number of patients should be the maximum of these individual calculations	Calculation based on the weighted criterion and on type 3 error (concluding that therapy A is superior to therapy B when the opposite is true)

Source: Russell IT (1983). The evaluation of computerised tomography: a review of research methods. In *Economic and Medical Evaluation of Health Care Technologies*, eds Culyer AJ & Horsberger B. Springer-Verlag, Berlin.

salbutamol would receive the active drug within every dose, experimental patients randomised to salmeterol would receive the active drug only every third dose and a placebo drug within all other doses.

The pragmatic version of this trial would be far more natural, given the requirement that pragmatic trials be conducted in conditions as close as possible to normal clinical practice. Although control patients randomised to salbutamol would again receive the active drug every four hours, they would know this for certain, with the result that their doctors would have the opportunity to optimise its placebo effect by emphasising the benefit to them of receiving a drug whose performance was proven even if the interval between doses was short. Experimental patients randomised to salmeterol would also know this for certain, with the result that they would need no interpolated placebo and would take the active drug every 12 hours; their doctors would therefore have the opportunity to optimise the placebo effect of the long-acting drug by emphasising the practical and psychological benefits of leaving one's inhaler at home.

This example serves to highlight two methodological issues in the design of fastidious (or Phase II?) drug trials. First, how effective is the design of the fastidious trial just described likely to be in equalising the placebo effect between experimental and control groups? In particular, what proportion of patients in each group would become confident, if not certain, of the apparently concealed identity of the drug to which they had been randomised? To those who reply that this example is not typical of fastidious trials, which usually compare the experimental drug with a placebo drug, an analogous question may be posed: in a fastidious trial of salmeterol versus placebo what proportion of patients (who would either have experienced salbutamol or have some expectation of the effectiveness of bronchodilators in general) would become confident of the identity of the drug to which they had been allocated?

Secondly, why should control patients in a typical fastidious trial receive only a placebo drug? Whether or not patients in fastidious trials in general can deduce whether they have been allocated to active drug or placebo, there is a more fundamental problem with placebo-controlled trials. In focusing on the absolute efficacy and safety of a single drug they impede the study of the relative efficacy of pairs of drugs that are real alternatives to each other (for example salmeterol and salbutamol), a question that is far more relevant to the goal of cost-effective prescribing. To use a pair of placebo-controlled trials, one of salbutamol and the other of salmeterol, to infer the relative efficacy of these two drugs is essentially equivalent to using a quasi-experimental design for this purpose, a design that is inherently susceptible to bias (Russell 1983). The preceding example of a fastidious randomised trial that directly compares the relative efficacy of these two drugs shows that fastidious trials need not be placebo-controlled, at least in theory. Indeed the only patients in that hypothetical trial to receive a placebo drug would be in the experimental group, not the control!



The third implication of the distinction between fastidious and pragmatic trials is that the patients to be studied should be defined in different ways. The protocol for a fastidious trial should specify strict criteria to determine whether each patient is eligible for both drugs: criteria that are presumably easier to fulfil if one of the drugs happens to be a placebo. Furthermore patients who fulfil these criteria but fail to comply with the strict regime for drug therapy are deemed to have withdrawn from the trial because they can no longer contribute anything to the testing of the defined scientific hypotheses; in particular they are excluded from the definitive analysis. In contrast a pragmatic trial is intended to replicate normal practice, wherein the choice of therapy is based on clinical criteria and patients often fail to comply. Thus the protocol should specify explicit but flexible inclusion criteria, and patients who deviate in part or in whole from the recommended drug regime must nevertheless remain in their allocated group for analysis, because that is what happens in the real world where these studies of (cost-)effectiveness will be used.

The fourth implication of this distinction is that fastidious and pragmatic trials differ in the number and type of criteria that they use to compare the drugs under review. A fastidious trial can in principle test an unlimited number of narrow scientific hypotheses provided that they are all precisely defined in advance. However a pragmatic trial can in principle have only one criterion since the choice of the better therapy has to be unequivocal. Hence that criterion has to include and weight as wide a range as possible of the benefits and costs, both short-term and long-term, of the drugs being compared. Although it is easy to identify examples of such a criterion - cost-benefit ratios and, simpler but more controversial, cost per Quality-Adjusted Life Year (QALY) - it is less easy to derive and apply such a criterion in a real pragmatic trial.

The last two implications of the distinction between fastidious and pragmatic trials concern the statistical issues of analysis and trial size, and follow directly from the difference in the nature and number of the criteria that these trials use (Table 1). Since a fastidious trial typically has many well-defined hypotheses to test, it applies a traditional significance test to each. Each of these hypothesis tests will ensure that the theoretical concept of statistical significance has a meaningful basis in pharmacological or clinical terms only if the eventual number of patients available for analysis achieves a target identified in advance on the basis of a traditional sample size calculation; in lay terms the key feature of such a calculation is the specification of the size of difference between the two drug therapies that should be regarded as pharmacologically or clinically worthwhile. As each of these calculations gives rise to a different estimate of the sample size needed, the trial will achieve all its aims only if the eventual trial size is at least the maximum of these estimates.

In contrast, the corresponding pragmatic trial has but one comprehensive and therefore complex criterion by which to compare the alternative drug therapies. Since this trial is designed to decide between these two therapies, analysis is deceptively simple: the analyst

merely has to choose the therapy that performed better according to the single weighted criterion. To ensure that this choice is as robust as the conclusions of the traditional hypothesis tests, however, the planning of the pragmatic trial should be even more painstaking than that of the fastidious trial. As we have seen, the latter specifies the differences between the two drug therapies that are to be regarded as critical. It also puts limits on the probabilities of two types of inferential error:

- a) Type 1 error (concluding by chance that the two therapies differ when they do not); and
- b) Type 2 error (concluding by chance that the therapies do not differ when they do).

Although the process of trading off these two types of error receives widespread coverage in the statistical literature, neither type is relevant to the planning of pragmatic trials. Type 1 errors are irrelevant because, if the two therapies do not differ, it does not matter which is chosen; Type 2 errors are irrelevant because the requirement that one of the therapies be chosen ensures that one cannot conclude that they do not differ. Instead the planning of pragmatic trials depends crucially on the need to limit the probability of Type 3 error (concluding by chance that one therapy is superior to the other when the opposite is true). Although statistical tables linking the sample size needed (to limit the probability of Type 3 error) to the inherent variability of the single criterion are rare, they can be found in the text by Schwartz et al (1980) elaborating on the original paper by Schwartz and Lellouch (1967). However, the main difficulty in planning truly pragmatic trials lies, not in the paucity of relevant statistical tables, but in the near-impossibility of estimating the variability of the single comprehensive criterion: not only have there been few complete cost-benefit and cost-utility analyses of alternative drug therapies, but even fewer of these analyses have generated estimates of the variability of the resulting cost-benefit or cost-utility ratios.

### **1.3. Summary**

There is little dispute that the randomised trial is the method of choice for evaluating the effectiveness, and thus the cost-effectiveness, of alternative drug therapies. Although randomised trials have become the norm in this field, many problems remain: logical, practical and ethical. Many, but not all, of these problems could be overcome by the adoption of pragmatic rather than fastidious trials. Even though pragmatic trials create their own methodological problems, we are more likely to achieve cost-effective prescribing if we tackle these problems with a view to increasing the precision of our answers to the correct (pragmatic) questions rather than manipulate our relatively precise answers to the incorrect (fastidious) questions.

## 2. Implementing the findings of research

No matter how successful we are in resolving the methodological issues of designing drug trials and developing appropriate success criteria, no progress towards cost-effective prescribing will be made unless we can implement the findings of these trials. Rather than attempt to cover the growing body of research into methods of implementing the findings of research (Freemantle et al. 1995), this paper will focus on the most popular of these methods, clinical guidelines. Although the following definition originates from the US, it has already proved useful in the UK:

“Clinical guidelines are systematically developed statements to assist decisions about appropriate care for specific clinical circumstances” (Institute of Medicine 1992).

If clinical guidelines are to improve the cost-effectiveness of prescribing, at least three conditions must be satisfied. First guidelines have to be scientifically valid: when followed they should lead to the benefits (including reductions in cost) predicted by the evidence on which they were based. Since weak evidence is less likely to lead to benefit, the validity of the guideline is closely related to the rigour of the supporting evidence. Secondly guidelines have to be practically effective in changing medical practice in the desired direction; scientific validity is of no value if it is not associated with a change in clinical behaviour and thus with health gain. Finally there needs to be professional confidence, not only in the validity and effectiveness of guidelines, but also in their medico-legal basis (Hurwitz 1995).

### 2.1. *Scientific validity of clinical guidelines*

This issue has been addressed in a series of papers by Grimshaw and colleagues (Grimshaw and Russell 1993b; Grimshaw et al. 1993 and 1995). These papers drew not only on the general literature on systematic reviews (e.g. Chalmers and Altman 1995) and that on guideline development (e.g. Woolf 1992; Grol 1993), but also on a specific systematic review of clinical guidelines to be described in more detail below (Grimshaw and Russell 1993a). The authors identified four main factors that influence the likelihood that clinical guidelines will be scientifically valid, summarised in Table 2.

The second column of Table 2 is concerned with the first step in developing clinical guidelines - the identification and synthesis of all the available scientific evidence. Guidelines have the best chance of being valid if the developers begin with a (portfolio of) systematic literature reviews: the topics to be reviewed should cover the full range of scientific issues to be addressed by the guidelines, either explicitly or implicitly; for each of these reviews both the inclusion criteria and the data to be extracted from each paper that satisfies these criteria should be defined explicitly. When possible papers should be graded according to the rigour of their research methods; when they are homogeneous, in

**Table 2** Factors influencing the validity of guidelines

Likelihood of scientific validity	Method of identifying and synthesising	Composition of guideline group		Method of developing guidelines
		Proportion of guideline users	No. of key disciplines represented	
High guideline	Systematic	Low (eg 'national external' guideline group WITHOUT users)	All	Evidence linked development
Medium	Unsystematic review	Medium (eg 'intermediate' guideline group including SOME users)	Some	Formal consensus development
Low	Expert opinion	High (eg 'internal' guideline group)	One	Informal consensus development comprising ONLY users

Source: Grimshaw JM & Russell IT (1993b). Achieving health gain through clinical guidelines: I - developing scientifically valid guidelines. *Quality in Health Care*, 2, 243-248.

particular in the success criteria they use, they should be combined in a formal meta-analysis (Chalmers and Altman 1995). In contrast guidelines based on expert opinion rather than the carefully synthesised findings of rigorous research have the least chance of being valid.

Unfortunately, most clinical guidelines used in the United Kingdom fall short of these standards in two main respects. First, most are based on expert opinion or at best unsystematic reviews. Even the British Thoracic Society's (1993) widely acclaimed guidelines for the care of asthma are largely based on expert opinion. In particular there is very little scientific evidence to support the adoption of a stepwise approach to therapy (in which the potency of the drug prescribed is increased as the patient's pulmonary function deteriorates) in preference to a pre-emptive approach (in which more potent drugs like inhaled steroids are prescribed much earlier in an attempt to prevent deterioration). Fortunately the NHS R & D Strategy is taking steps to strengthen the evidence base for the drug treatment of asthma. More generally the Clinical Guidelines Subgroup of the NHS Clinical Outcomes Group is introducing a system of appraisal for clinical guidelines (Cluzeau et al. 1995) that has the potential to reinforce the welcome but incipient trend towards basing such guidelines on systematic reviews.

The second shortfall in the scientific content of clinical guidelines is more worrying, not only because it is even more widespread than the problem of reviews that are unsystematic or non-existent, but also because it is receiving much less attention. The problem is that very few guidelines address the issue of cost at all, let alone review the available evidence

about the economic cost or the cost-effectiveness, of the therapies they recommend. At first sight, the route to solving this problem is clear: the recommendation that guideline development groups should have technical support to identify and synthesise evidence (Grimshaw et al 1995) should be extended to specify that cost is an essential component of this evidence, and that economics is therefore an essential component of the technical support. To test the feasibility of this extended recommendation the team recently responsible for developing 'evidence-based guidelines' (ie guidelines based on systematic reviews of rigorous evidence) for the primary care of asthma and stable angina in the North of England (Eccles et al 1996a & b) have been funded by the NHS Health Technology Assessment Programme to extend their evidence base to include costs and to update their recommendations accordingly. However, success in this important task will depend on the ability of existing members of guideline development groups to work constructively with economists, and vice versa.

The third and fourth columns of Table 2 look more closely at the influence of the composition of the guideline development group on the validity of the resulting guidelines. When the proportion of that group who will actually use the guidelines is high (e.g. when guidelines are developed in a district general hospital or general practice), the likelihood of validity is low; it seems that people developing guidelines that they themselves will use tend to be influenced more by their current practice than by scientific evidence. In contrast groups with a low proportion of users (e.g. national or regional groups) have a high likelihood of developing valid guidelines. In similar vein the more key disciplines are represented in the development group, the higher the likelihood of validity.

Once formed the development group faces the task of assembling the evidence to formulate the guidelines. The final column of Table 2 offers them three methods of doing this. First they can explicitly link each recommendation in the guideline to the evidence that supports it, however flimsy; this gives the best likelihood of validity. If they adopt a formal procedure for consensus development without linking recommendations to evidence, however, that reduces the likelihood. Finally if their procedure is merely informal, with the result that consensus development is dominated by the loudest voices, this gives the least likelihood of validity.

## ***2.2. Practical effectiveness of clinical guidelines***

This section is based on a systematic review of rigorous evaluations of clinical guidelines (Grimshaw and Russell 1993a; Effective Health Care 1994). Thus it illustrates some of the principles of systematic reviewing summarised in the preceding section. In particular because the evaluations reviewed covered a wide range of clinical topics, the conclusions presented here are based on a qualitative synthesis (Grimshaw and Russell 1994) rather than a quantitative meta-analysis.

The review searched a total of five databases for published papers reporting rigorous evidence about the effectiveness of clinical guidelines as defined by the Institute of

Medicine (1992). Papers were excluded that evaluated: criteria for the appropriateness of individual items of care that had not been integrated into coherent guidelines (e.g. Hulka et al. 1979); educational programmes that had not generated guidelines (reviewed by Davis 1992 and 1995); and feedback on clinical performance that was not related to individual guidelines (reviewed by Mugford et al. 1991). From each paper that met these criteria we extracted information about: the methods by which guidelines were developed, disseminated and implemented; the context in which guidelines were used; and the estimated effect of the entire guideline process on both the performance of key clinical tasks specified in the guidelines and key patient outcomes associated with those tasks.

Table 3 shows how the 59 evaluations identified by Grimshaw and Russell (1993a) were distributed between the grades of research design discussed by Russell and Grimshaw (1992). 55 of these 59 studies showed positive effects of guidelines on the process of health care. Although it was disappointing that only 11 (19%) looked at patient outcome, nine of these identified positive effects. So at first sight guidelines can change clinical practice.

**Table 3 Grades of study design included in systematic review of guideline evaluations**

Balanced incomplete block designs (ie randomised trials strengthened by internal controls)	6
Trials randomised by doctor or team	23
Trials randomised by patient	13
Controlled before-and-after studies	9
Interrupted time series	8
	59

Source: Grimshaw JM & Russell IT (1993a). Effect of clinical guidelines on medical practice: a systematic review of rigorous evaluations. *Lancet*, 342, 1317-1322.

There are at least three potential threats to the validity of this conclusion, in addition to the obvious danger that invalid guidelines may change practice in the wrong direction! First, the authors of these 59 studies were sufficiently enthusiastic about the guidelines in question as to design and conduct a rigorous and time-consuming evaluation; thus it seems likely that the very high success rate represents the best that guidelines can achieve. The second threat lies in the possible incompleteness of the review; on this occasion, fortunately, the findings of an additional 32 evaluations identified by an updated review were entirely consistent with those of the first 59 (Effective Health Care, 1994). The third threat lies in the differential quality of the evaluations; on this occasion, fortunately, the findings were entirely consistent between the different grades of research design (Effective Health Care, 1994). Some critics would also regard the fact that the positive effects of guidelines showed enormous variation as a threat. However, this was treated as an

opportunity to undertake a qualitative synthesis and identify characteristics of the processes of developing, disseminating and implementing guidelines that were associated with larger changes in clinical process and patient outcome. The review attempted both to make (tentative) recommendations for the future use of guidelines and to identify priorities for future research.

The conclusions of that synthesis are presented in Table 4. The second column is in direct conflict with the third column of Table 2: although national guidelines were adjudged to have the highest likelihood of scientific validity, they also have the lowest relative probability of changing professional behaviour; conversely, although 'internal' guidelines (developed by putative guideline users) were adjudged to have the lowest likelihood of validity, they also have the highest relative probability of changing behaviour. It is also worth noting that national guidelines generally cost much more to disseminate and implement than to develop, again in direct contrast to internal guidelines. The Scottish Clinical Resource and Audit Group (1993) first advocated a compromise solution to this apparent impasse. This group suggested that guidelines setting out the general principles (of prescribing for a given condition) should be developed nationally, to ensure validity; and adapted to local resources and circumstances by internal groups, to give ownership.

**Table 4 Factors influencing the effectiveness of guidelines**

Relative probability of being effective	Development strategy	Dissemination strategy	Implementation strategy
High	Internal group (comprising ONLY users)	Specific education intervention	Patient specific reminder at time of consultation
Above average	Intermediate group (including SOME users)	Continuing medical education	Patient specific feedback
Below average	Local external group (WITHOUT users)	Mailing to targeted groups	General feedback
Low	National external group (WITHOUT users)	Publication in professional journal	General reminder of guidelines

Source: Grimshaw JM & Russell IT (1994). Achieving health gain through clinical guidelines: a systematic review of rigorous evaluations. *Lancet*, 342, 1317-1322.

The third column of Table 4 records that guidelines have a much higher probability of being adopted if disseminated by a specific educational intervention like a multi-disciplinary workshop to consider local implementation than if published in a professional.

The final column advocates, again on the basis of the synthesised evidence, that guidelines are much better implemented by a patient-specific reminder at the time of consultation, for example a summary of the main recommendations of the guidelines prominently displayed in the patient's notes, than by a general reminder, for example a notice on the wall of the clinic or surgery.

### **2.3. Summary**

Clinical guidelines are most likely to achieve health gain if they:

1. are based on a systematic and comprehensive review of literature that is relevant and preferably rigorous;
2. are developed by a national group including representatives of all key disciplines and with a remit to focus on general principles and ensure scientific validity;
3. are adapted to local resources and circumstances by a similarly representative internal group with a remit to ensure professional ownership without compromising scientific validity;
4. make explicit links between recommendations and the scientific evidence on which they are based;
5. are disseminated by an educational event designed for this purpose; and
6. are implemented by patient-specific reminders at the time of consultation.

## **3. Conclusion**

To complement the summaries of each of the main sections of this paper, this conclusion lists current controversies in this field:

1. Pragmatic trials that focus on effectiveness under normal clinical conditions are more relevant to the issue of cost-effective prescribing than fastidious trials that focus on efficacy under artificial laboratory-like conditions.
2. There are questions regarding whether the use of placebo-controlled double blind trials are consistent with cost-effective prescribing.
3. Clinical guidelines (which include prescribing guidelines) with recommendations linked to scientific evidence derived from systematic reviews are more valid than those based on professional consensus.



4. The hope has been expressed that the incipient trend towards such evidence-based guidelines will be accelerated by the impartial appraisal of national and regional guidelines before they are disseminated or implemented.
5. The absence of evidence about cost, and recommendations about cost-effectiveness, in almost all clinical guidelines is to be deplored.
6. Closer collaboration between health professionals and economists is required to fill this regrettable gap.

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## **Towards effective prescribing - appropriate research and development methods. Discussion**

### **Dr Sue Ibbotson**

There are four major reasons why health authorities need evidence of cost effectiveness:

1. For development of health strategy - as an aid to decision making. Evidence should be seen as informing the decision but is not sufficient to make the decision since value for money is not the only goal of clinical care. Evidence of effectiveness and cost effectiveness should be considered alongside local needs, resources, political issues and humanitarian aspects. Evidence is of particular use in assessing new technologies, enabling managed introduction into mainstream service provision.
2. In facilitating the effectiveness agenda, e.g. through the development of local guidelines.
3. To influence decisions across the primary / secondary care interface. A 1994 Executive Letter (EL(94)72) makes explicit the health authority's responsibility for enhancing appropriateness of hospital-led prescribing and for the managed entry of new drugs. The wording of that guidance suggests that cost effectiveness should be part of this.
4. To execute its monitoring role.

Health authorities require a number of characteristics of evidence:

1. Good quality' original studies, not only methodologically sound but addressing the 'right' (policy-directed) questions, which recognise that we operate in an imperfect world with many conflicting priorities. A broad understanding is needed of whether investment in new technologies is worthwhile, rather than 'proof' that a particular drug represents an economically efficient use of scarce resources. For this reason the pragmatic trial approach as outlined by Russell would seem to have many attractions. Health authorities also look for a relevant comparison. As Russell has outlined, placebo based comparisons are unhelpful. Comparisons of new treatments need to be made against existing standard treatments.
2. Methodology is clearly important. The guidance agreed between the ABPI and the DH would seem to be a fair start but this needs to be implemented and built upon. Prospective methodologies based on pragmatic trials would seem to be ideal because they make fewer assumptions (and are therefore more accurate and credible) than retrospective methodologies. This said, prospective methodologies are high cost and take a long time to conduct. In many respects they may also be incompatible with standard clinical trials which are protocol driven rather than 'real

world'. For this reason retrospective methods including modelling would seem to be relevant to complement prospective studies.

3. Evidence needs to come from an explicit and credible source. Rightly or wrongly, studies which are seen to be driven by pharmaceutical companies are viewed with some suspicion.
4. The design of the study and choice of outcomes is important. Ideally evidence of effectiveness should be based on randomised controlled trials; much less acceptable is consensus-based evidence. Outcomes need to relate to reductions in mortality and morbidity and /or improvements in quality of life.
5. Explicitness is also required regarding the costings used. Valuations used need to be credible and relevant, and evidence should ideally include all the drug costs, e.g. including costs of preparation and administration, relevant equipment and monitoring costs as well as the costs of treating side effects and complications.
6. Studies need to relate to a relevant context.
7. Ideally, evidence of cost effectiveness should be incorporated as an integral part of the effectiveness analysis of drugs. Clearly, different sorts of cost effectiveness information are likely to be available at different stages of the drug's development.
8. Studies should make realistic recommendations. This means credible evaluation of incremental costs/benefits of one therapy over another. Recommendations need to reflect the quality of the evidence.

Against these criteria many studies and reviews do not seem to meet commissioners' needs. The following problems tend to occur with current cost effectiveness information:

1. Lack of relevance. Studies often ask the wrong questions. In particular there would seem to be an obvious difference in the priorities of the NHS, the health economist, and the pharmaceutical company. Studies are often difficult to generalise, may isolate drug costs and may not use relevant outcomes or costs. From a public health perspective, relevant outcomes relate to health status and not to biomedical markers. For example, if there is a new drug for use in the management of osteoporosis, relevant outcomes would include reduction in the rate of fractured neck of femur. A much less relevant outcome would be any measure of increased bone density.
2. Lack of timeliness. Much of the evidence will become available after drugs have been launched. Nevertheless even the most basic cost effectiveness evidence derived from early studies may help, e.g. in relation to beta interferon, a very expensive drug in the management of multiple sclerosis. The debate which is beginning to unfold, particularly in the media, has focused on cost containment ('the

NHS cannot afford this drug'), rather than around a debate about whether the costs in relation to likely benefit are reasonable.

3. Poor communication. In the Department of Health's cost effectiveness register there are relatively few studies which consider drugs, and only about half of those in journals etc. are available to the average public health consultant. Economic analyses can be difficult to communicate because they are based on many assumptions and complex analysis. However, dissemination via peer review journals may not be the only answer. Concise, clear and timely summaries as well as freely available detailed reports to enable those who want to reproduce or adapt the analysis would help.

In terms of using cost effectiveness information locally, whether in original form or as part of guidelines from expert bodies, evidence is often criticised as being 'behind the game'. Many clinicians have not accepted the need for pharmacoeconomics or its relevance in the policy making process. There is also substantial confusion between cost-effectiveness and cost containment, added to by some of the central guidance which speaks about improving cost effectiveness whilst at the same time speaking about cost containment.

Locally, guidelines and evidence may be deemed to be unauthoritative. Russell's assertion that the most valid guidelines are those which are developed by independent experts who are not the people who will use the evidence should be accepted. That said, there is a problem with ownership at local level, and guidelines run the risk of being dismissed.

Finally, there are relatively few incentives to examine practice and to change built into the commissioning process. This is perhaps more so for secondary care clinicians, where costing for contracting is not sophisticated enough to allow virement of cost savings. The development of joint drugs budgets across primary and secondary care and the development of primary care-led purchasing could change this.

A number of potential solutions would seem attractive to commissioners:

1. That the existence of cost effectiveness evidence be made a criterion for inclusion of drugs in the National Formulary. Proof of cost effectiveness prior to inclusion is one step further on from this, but is perhaps unlikely in the UK.
2. Partnerships between health economists, pharmaceutical industry and the NHS in assembling the evidence.
3. A widespread debate about what we are trying to achieve and the notion of effectiveness as a legitimate part of the decision-making process.
4. Attention to communicating the evidence appropriately to the various audiences.

5. The emerging commissioner authority role may be of relevance at local level.
6. Greater attention needs to be paid to creating the right conditions for change.

### **Nick Barber**

Russell's call for the use of pragmatic trials in the assessment of health technologies is to be supported. The effectiveness of a drug in practice does not depend solely on its pharmacology, but also on the disease management process - how it is actually used in practice. Any judgement of cost-effectiveness needs to embrace this additional source of variability. The degree to which this matters varies to some extent according to one's perceptions of good prescribing and its relationship with cost-effective prescribing. Assuming that responding to patient's choices about therapy is part of good prescribing (Barber 1995), then a clinical trial will not be representative. Even taking the biomedical model, in which the patient is seen more as a condition than as a person, a clinical trial is unlikely to be predictive of the effect in general practice because it will exclude many of the types of patients who receive the drug in practice, and it does not reflect the different practices of the doctors with respect to dosage and monitoring of therapy.

To illustrate the effect of process a simple decision tree can be constructed, in which the choices are:

1. whether the prescribed drug is an effective one for the patient's condition
2. whether the patient adheres to the treatment regime
3. whether the patient's condition is monitored in such a way that patients receiving ineffective therapy (either because of inappropriate prescribing or non-adherence), start having effective therapy.

Assigning the probability of the first stage being correct as 0.9 (considering the difficulties of diagnosis in general practice this is conservative), a probability of 0.6 for the patient adhering to their regime (a consensus value from the literature), and 0.6 as the probability of a monitoring process being effective (conjecture), then the probability of therapy being ineffective is around 20%. If, however, the monitoring process is not present the probability of ineffective therapy becomes around 50%.

These probabilities are dependent on the drug in many cases. Beliefs that differ from research findings often grow up about the uses, doses and risks of a drug. The data available from clinical trials at the time of licensing, at present, is inadequate for the prediction of cost-effectiveness of a drug in practice - this is best done in pragmatic trials after the drug has been marketed.

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**David Henry**

In Australia, as a result of courageous formal policy moves regarding pharmaceuticals, the issue of how evidence is used as a basis for decision making has come very much to the forefront. There are four policy aims in relation to drugs:

1. Safety, efficacy and quality issues, which generally use placebo controlled trials;
2. Maintaining the viability of the local pharmaceutical industry in Australia;
3. Issues around equity of access and assessment of the cost effectiveness of drugs, which considers comparative clinical trials and the formulation of clinical guidelines for the use of drugs within this system;
4. A separate aim is concerned with how these drugs are used, and in particular with improving the quality of use of medications. Trials are used extensively in piloting new methods to change prescriber or consumption behaviour.

Some of the policy changes in Australia have worked, and some have not. This paper reports some of the experience of Australian policy makers in using comparative clinical trials and guidelines for informing decisions.

In Australia there is a two stage licensing procedure for drugs. The first stage is a classic licensing procedure, based on safety and efficacy, with no consideration of cost. The second stage is concerned with how new drugs compare with existing ones, and the comparative effectiveness and cost effectiveness of new products. This determines government reimbursement from the Pharmaceutical Benefits Scheme, a positive list of around 550 drugs (from the thousands licensed for sale). A license to market a new drug does not in itself confer a government subsidy - the drug has to pass a second test, on the basis of comparative effectiveness and cost effectiveness. This scheme is underpinned by powerful legislation, covers everyone in Australia, but does not cover all drugs - it is a limited list. The benefit scheme subsidises 90% of all important prescription drug use in the community, therefore tends to be a monopsony. The scheme also contains a complex system of co-payments and access. Co-payments are tied to economic status, and in some cases prior approval may be required for drugs, according to the condition being treated. Guidelines can restrict access for a particular drug to a particular defined group of people.

Experience with the Pharmaceutical Benefits Scheme in Australia shows that the great problem at the moment in addressing comparative cost-effectiveness is the quality of the clinical evidence, not the quality of the economic modelling or practice. In particular,

problems are created because companies do not carry out randomised controlled trials with useful comparators. This is primarily because these are not required by the United States Food and Drug Administration. This leaves a problem in estimating relative cost effectiveness, as there are a lot of placebo controlled trials, but many fewer trials of how the new drug compares with existing drugs.

Companies have tended to be reluctant to do head to head trials against an existing comparator. Logistically these have tended to be very large just to detect small clinical differences which can be important. Including economic differences may inflate the sample size even further, depending on the variance around the economic estimates. Unfortunately, this ambivalence about doing head to head clinical trials is not matched by marketing claims once the drug is licensed, which compare new drugs with existing formulations continuously, but not on the basis of evidence.

This is not entirely a criticism of the industry. Companies have to fit within a system, and the system has partly driven them this way. It is useful to consider how to start to pull away towards a more informative system where we can find out how new drugs compare with existing drugs already being subsidised.

The Australian Pharmaceutical Benefits Scheme uses a hierarchy of evidence. The preference is for randomised head to head trials of the new drug compared with an agreed comparator. If there are none of these, companies are required to submit placebo controlled trials of the new drug and placebo controlled trials of a comparator. This information is generally available and enables a transitive comparison to be made. These comparisons can be problematic, as placebo controlled trials of the comparator may have been done in the past and not done by the company. If the two control groups are different it may be difficult to assess the value of the two drugs in terms of comparing actual with relative differences. If placebo controlled trials for transitive comparison are not available, there can be other ways of trying to deal with non-randomised data. Some decisions, most recently reimbursement of a drug for treating breast cancer, have to be made in the absence of proper randomised trials.

Typically, there can be a number of problems with randomised data:

1. There are no head to head trials, in which case less robust data must be used;
2. Companies may not know they have head to head trials. In one instance, the agency was told that there were no head to head trials, but actually found two very quickly in a Medline search, and another three in the company's records. This was not intent to deceive, but a lack of awareness of the importance of finding and synthesising evidence;
3. Transitive data may be used, with associated problems;



4. There can be a lack of acceptance from the companies that although the trials show no difference, this actually means no difference and no higher price;
5. Technical problems of companies attempting to do meta-analysis of trials.

Guidelines are implemented in Australia at different levels. In the case of some expensive drugs there can be restricted access, with a requirements for prior approval before a drug will be paid for. Subsidy continuation may also be tied to clinical response, for example reimbursement of filgrastim and salmeterol.

Consensus or evidence based guidelines on their own have very little impact. These must be costed - when clinical groups get together it is not just cost effectiveness but the actual cost of implementing guidelines which needs to be estimated, and in Australian experience this is often not done. A set of evidence based guidelines on lipid lowering drugs formulated by the National Heart Foundation in Australian would have costed \$600 million if everyone complied with them. This would have wiped out a large part of the drug budget. The guidelines were well meaning and evidence based but uncostered, which can be very important.

One promising area of changing prescribing behaviour is preferred medicines lists, where groups of doctors are provided with information, and themselves decide what should be used. These lists may not be exclusively evidence based, but the fact that prescribers have some ownership of the issues and are enthusiastic can really change prescribing behaviour.

## **Adrian Towse**

### 1. Introduction

The paper by Ian Russell presents a three stage route to effectiveness:

collect evidence from pragmatic RCTs;

incorporate into clinical guidelines;

test the clinical guidelines for evidence that they are effective.

It is important to note that he is primarily concerned with establishing the effectiveness of non-pharmaceutical treatments within the NHS R&D programme rather than the cost-effectiveness of medicines. However, his paper raises a number of important issues for the collection and use of information on the cost-effectiveness of pharmaceuticals.

### 2. Issues arising from the paper

The most important issue raised is that pre-launch trials for medicines are likely to be of limited value in helping post launch effectiveness because they are experimental or

'fastidious', designed to establish high internal validity to meet licensing requirements for safety and efficacy. They do not measure performance in normal clinical practice and therefore have low external validity. How do we move from efficacy to cost-effectiveness?

Russell proposes pragmatic RCTs that would compare a new treatment against current therapy in normal clinical settings. They would be unblinded and take account of problems of patient compliance. The emphasis would be on achieving high external validity whilst retaining internal validity through randomisation.

This raises the question as to whether economic information should be collected as part of a pragmatic clinical trial. The guide prepared for the NHS R&D programme (Drummond 1994) set out four hurdles:

the trial has to be well designed;

- the economic implications have to be significant - is cost important?
- the study has to be of practical relevance. In particular is the comparator relevant, the setting typical and the end point the correct economic one (in both length of time and choice of outcome measure)?
- is it cost effective? The addition of economic analysis to clinical trials should itself be subject to economic assessment. It may substantially add to the complexity and size of the trial if significant economic results are to be obtained.

Even if we assume a pragmatic design meets the first and third of these criteria, it may well not meet the second and fourth. This raises the issue of the costs and benefits of collecting information. In particular Russell's strong argument for external validity may be more cost effectively met in many cases by post launch quasi experimental or other observational studies, or by adjusting pre-launch trials with modelling to move from efficacy against placebo to effectiveness against current treatment. Interactive modelling can be used to enable prescribers to enter local data to estimate the impact of a treatment choice on health outcomes and costs.

Russell's case for assessing the effectiveness of clinical guidelines is also a strong one. He points out that most are based on expert opinion and few address the issue of cost. There is an assumption, for example, in asthma treatment that stepwise approaches to therapy are preferable to pre-emptive approaches. This may or may not be true. He also notes the importance of local ownership.

In short, Russell's approach to trials and guidelines makes a powerful case for the collection of relevant evidence for local decision makers. Expected costs of collection and scientific validity have to be traded off against the expected value of the knowledge

obtained. There can be no doubt, however, about the strength of the case he makes for post-launch pragmatic trials to establish the effectiveness and cost-effectiveness of pharmaceuticals. NHS and industry should work together that non-ethical obstacles to these studies are overcome.

### **Reference**

*Drummond MF. Economic Analysis Alongside Clinical Trials. Department of Health, London; 1994.*

### **Andrew Herxheimer (chair)**

Russell's paper and the comments on it have raised a cluster of ideas focusing on the evidence needed for cost effective prescribing. However, so far nobody has focused on the most expensive resource in health services, which is the brains of the professionals in health services. The amount of brain use involved in different choices has to be measured and valued. This comes out in the learning process: when a new technology or drug is introduced, it is essential that practitioners learn how to use it. For example, in surgery it is accepted that the first 50 operations carried out by a surgeon will have worse results than the tenth 50. The same is true of drug use but this is not yet taken account of. The costs involved in learning are a hidden cost of innovation, and if an innovation is indifferent, the brain work in learning to use it will be wasted, resulting in a net loss of resources.

Another omission from these discussions has been that of serious and rare adverse reactions. Evidence for these never comes from RCTs, and there are no good methods for combining data on these adverse reactions with evidence from RCTs. They can however be extremely expensive in human and monetary terms, and analysts need some way of taking account of them.

A related point is that it seems to be a general rule of human behaviour that good things come early and bad things later. This is true of alcohol, tobacco, drugs, and new surgical procedures. When a new intervention is introduced, the level of certainty of benefits is higher than that of disbenefits. This means that an unknown must be included in the cost effectiveness equation, representing uncertainty. This takes us into parallels with the insurance market, where risks are unknown but nevertheless insured against.

Barber's response referred to the decision to use or not use a therapy. This is addressed in most guidelines and in the inclusion criteria of RCTs, where the idea of a threshold intensity for an indication applies. However, in normal practice there is often no agreement about whether or not a drug should be prescribed. The intensity of a condition before a general practitioner intervenes with drug or non-drug therapy depends on negotiation between GP and patient, the insistence of the patient etc. This influences the outcome of a new therapy and it needs to be considered. Once a drug is licensed for use in one or more indications, manufacturers naturally want it to be used for all patients with

this indication, regardless of intensity, but the balance of benefit and disbenefit varies greatly with intensity of illness. Therapeutic guidelines should try to define the threshold intensity of the problem, below which use of a treatment is not adequately effective and is not recommended.

Barber's paper also referred to monitoring, which among other things relates to stopping rules for treatment. It is a fact of prescribing behaviour that it is always easier to start a prescription than to stop a prescription. If a stopping rule were built into the prescribing decision at the time of prescription, and agreed with the patient, this could save considerable adverse effects and expenditure, and this is relatively simple in principle.

### **Audience discussion**

David Henry suggested that there is not necessarily a tension between pragmatic (post launch) trials and the need for prior approval. These are not alternative approaches, but approval processes recognise that there is always a need for a decision now, with the evidence available even if this is imperfect. Prior approval decisions in Australia have some requirement to consider cost and to relate this to benefit from trials. This is not a tension, but just an acceptance of reality.

Allan Detsky commented that there are groups of pharmaceutical products: those which can easily be abused and those which cannot. For example, drugs such as (seradase) for Gaucher's disease, which costs \$200,000 per year, (pulmozon) for cystic fibrosis, which costs \$14,000 per year, g-CSF and t-PA are 'large ticket' items which frighten hospital budget holders and governments, but are in many ways economically safer than smaller ticket items. These drugs are used only in very specific conditions, and it is difficult to use them inappropriately. This makes expenditure on them much smaller than other lower priced but more common drugs. For a new therapy, cost effectiveness in one situation is a small piece of the budgetary decision, and a much bigger challenge to governments and budget holders is how to use smaller tickets such as omeprazole appropriately. The Ontario government spends approximately \$15 million per year on omeprazole and only \$1m on seradase, as omeprazole is available for use and abuse by Astra and by clinicians. Similar smaller ticket items, such as ace inhibitors, lipid lowering drugs and H<sup>2</sup> antagonists are often more widely abused than more expensive drugs and represent more of a challenge for utilisation control. Guidelines must be viewed as a replacement for the price mechanism and for market forces. The first step for cost effective prescribing is getting cost effective products on to a formulary for optimal use, but a far bigger monetary problem is appropriate utilisation of these products.

David Taylor (Audit Commission) pointed out the difference between discussing aggregate data about cost effectiveness, and criteria for 'macro' appropriateness (affordability), as opposed to decisions of 'micro' appropriateness such as whether an

individual really does have this condition. Russell's paper makes assumptions about how decision makers react to new information, and how this can be regulated to change behaviour. Taylor questioned whether or not changing medical behaviour and the medical culture is the most effective way forward.

Deborah Khudabux suggested that the patient can often be forgotten in these prescribing decisions. For example, haemophilia patients are increasingly asking to be prescribed recombinant factor 8, which may not be available because of cost constraints. The change in medical culture could mean these types of conflict occur more frequently, as patients will want to know why they cannot receive expensive drugs. How are patients to be brought into prescribing decisions and policy?

Allan Detsky responded to this point, stating that there are two very different objectives of 'good' prescribing. Cost effectiveness analysis is a replacement for price signals and markets, attempting to maximise net benefits for a target population within a fixed budget. Clinicians undertaking direct patient care wish to maximise outcomes for the individual patient, within financial constraints and subject to availability. He argued that cost effectiveness analysis should not be applied at the bedside to make individual patient decisions, but guidelines should be set by policy makers deciding that a pharmaceutical product will or will not be used for certain patients. This takes the clinician off the hook in terms of making that decision for an individual patient, as society has expressed the way it wants to pay for health care. The alternative to patients is exit from the public health system, and paying for their treatment.

Adrian Towse suggested that in the UK this explicit difference is not made, and too often physicians at the bedside have to make both decisions: the policy rule and doing the best for an individual patient. These two functions are not sufficiently separated. However, the alternative to exit is voice - doctors are entitled to change policy rules, and this creates a more mixed debate in the UK. Deborah Khudabux agreed that doctors are in some cases faced with conflicts of policy and patient, and pointed out that cost effectiveness is recognised by the British Medical Association as an ethical issue.

## **Session 2: Towards Effective Prescribing: Appropriate Research and Development Methods. Key Points**

- Economic studies informing cost-effective prescribing need to be based on sound clinical evidence, ideally from randomised controlled trials;
- Randomised trials can be carried out in 'explanatory' or 'fastidious' conditions (designed to draw conclusions about defined scientific hypotheses) or 'pragmatic' conditions (designed to choose between two alternatives in clinical practice). Pragmatic trials are more relevant to the issue of cost-effective prescribing, as the effectiveness of a drug in practice does not depend solely on pharmacology but also on the disease management process and the utilisation of the drug;
- Pragmatic trials are conducted in normal clinical practice, and governed by flexible protocols. Control group patients generally receive the normal clinical alternative, (not placebo), and results should be analysed on an intention-to-treat basis (including patients who deviate from recommended drug regimes);
- No progress towards cost-effective prescribing will be made unless the findings of trials are implemented. Clinical guidelines may improve take-up of research and cost-effectiveness of prescribing. However, they must be scientifically valid, practically effective in changing medical practice and have the confidence of professionals;
- Clinical guidelines are more scientifically valid when they link recommendations to evidence derived from systematic reviews. Unfortunately, most guidelines used in the UK are based on expert opinion. Also, few guidelines address the issue of cost and review available evidence of the cost-effectiveness of the therapies they recommend. These problems need to be addressed by collaboration between health professionals and economists;
- Evidence based clinical guidelines are most likely to achieve health gain if they are developed by a national group but adapted to local circumstances, make explicit links between recommendations and their evidence base, are actively disseminated by an educational event and are implemented by patient-specific reminders;
- Many studies of effectiveness and cost-effectiveness currently do not meet the needs of health care purchasers, due to lack of relevance, lack of timeliness, poor communication and lack of incentives to examine and change practice;
- This issue of how evidence is used as a basis for decision making is essential. In the Australian drug reimbursement process, problems of submitted economic evaluations tend to centre around the quality of the clinical evidence rather than the economic methodology;
- The use of guidelines based on evidence from pragmatic trials fits well with the philosophy of a decentralised and consent based NHS

## Chapter 3

# Initiatives to Improve Prescribing and Promote Cost Effective Prescribing

Tom Walley

### Introduction

To suggest that prescribing can be improved implies that there is something wrong with prescribing at present, and that we can measure good prescribing. Good prescribing is usually defined as appropriate, effective, safe and cost conscious - in that order (Parish 1973). It is often easy to detect bad prescribing - grossly excessive use of drugs, or use of interacting drugs. But these are relatively rare, and identifying quality of prescribing outside this involves consideration of the whole prescribing process. This cannot be done by reviewing only what is prescribed. 50-60 per cent of patients attending a general practitioner (GP) defy physical diagnosis, yet a GP may appropriately prescribe for them based on his best formulation of the patient's problem (Reilly and Marinker 1994). Good prescribing can really only be defined at the level of the individual patient, considering the diagnosis and other factors.

One cannot have appropriate prescribing without appropriate diagnosis, and medical practice variation follows in large part from medical diagnostic variation, which can be seen in many morbidity surveys. Prescribing variation (costs per person per year ranging by a factor of three to four between practices) is not explained simply by morbidity, and may suggest that there is waste in prescribing.

To partly resolve the semantic difficulty, 'improvement' is defined here as improvement in the cost-effectiveness of prescribing. We might correct waste in prescribing in two ways - firstly addressing the decision to prescribe or not prescribe, and secondly by addressing choice of what to prescribe. Many of the initiatives to improve the cost-effectiveness of prescribing only address the second issue, which is very easy to measure. Such initiatives are unlikely to improve the broader quality of prescribing, although they may reduce expenditure and improve cost-effectiveness in a limited way.

### 1. Background

Prescribing in the NHS cost £2.9 billion in 1991-2; primary care prescribing alone cost £2.6 billion in 1992-3. This is around 11 per cent of the total costs of the NHS. The drug bill has increased on average at a rate of 4 per cent above inflation over the last ten years. The annual drug bill for primary care in the UK rose by 14 per cent between 1991-2 and 1992-3, but the rate of rise fell to 11 per cent between 1992-3 and 1993-4, and still further to 8.3 per cent in 1994, suggesting perhaps that some of the initiatives described here are succeeding (Walley et al. 1995; Anon, Scrip 1995).

The factors behind this rise include an ageing population with increased morbidity, new products at higher costs and perhaps new benefits, patient demand from a better informed public, drug company promotion, government encouragement and payment to GPs to screen for asymptomatic disease in health promotion clinics, and a move to treating patients in the community rather than in hospital. These may reduce overall costs to the NHS, but increasing the primary care drug bill.

## **2. The initiatives**

### **2.1 Information**

Doctors have traditionally depended for drug information on the pharmaceutical industry, which may promote poor prescribing practice. The government funds the respected *Drug and Therapeutics Bulletin* (sent to every doctor in England since the mid 1970s), and a specific primary care drug bulletin by the Medicines Resource Centre (sent to every GP since 1990). Nevertheless, the volume of noise from the industry is vastly greater than from independent or NHS sources. The promotional activities of the industry have increased and changed in response to attempts to control the drug bill.

Provision of literature alone makes little difference to doctors' prescribing behaviour, although it does improve their knowledge. More influential is face to face contact supported by literature. Medical and pharmaceutical advisers to health authorities, responsible for managing primary care in an area fulfil this role and greatly reinforce the messages of the literature (Walley and Bligh 1992).

Detailed information about a doctor's prescribing is provided by the Prescription Pricing Authority which collates all GP prescriptions dispensed in the NHS to authorise the payment of pharmacists. Harris used this data, coupled with specific discussion of their prescribing with groups of doctors, to encourage prescribing review. This produced substantial benefits in prescribing costs (Harris et al. 1984), but a prolonged intervention would be required to achieve long term effects (Harris et al. 1985).

PACT (Prescribing Analyses and CosT) data at a superficial level are now sent to all doctors, and more detailed reports are sent on request, or to those who are prescribing markedly differently from their peers. PACT data is also sent to the health authority prescribing advisers. The combination of face to face contact using independent information on therapeutics and feeding back to doctors details of their prescribing is a powerful tool for influencing prescribing. Parts of this have been the mainstay of drug company promotion for years.

### **2.2 Generic prescribing and formularies**

The development of formularies and generic prescribing have been successfully promoted as good practice and likely to improve cost-effectiveness.



A formulary is a personal limited list of drugs, effectively used by every doctor, but not always written down. Attempts to produce health authority formularies to which GPs would subscribe were unsuccessful, since formularies without GP ownership and without incentive will not be followed. Constructing a practice formulary affects choice of drug and is of great value as a learning exercise for the doctors, improving familiarity with dosage, side effects and interactions of a limited range of drugs. Although not their primary aim, formularies may influence prescribing costs (Beardon et al. 1987). Health authorities now encourage and support the development of practice formularies.

Generic prescribing, using the approved name for a drug, may be substantially less expensive than prescribing the branded equivalent. It is encouraged for educational reasons, and as good professional practice. Nationally the rate of generic prescribing has risen from 15 per cent in 1977 to 54 per cent by 1994, with considerable cost saving.

### ***2.3. Indicative prescribing and other incentive schemes***

#### ***2.3.1. The Indicative Prescribing Scheme (IPS)***

The aim of the indicative prescribing scheme was to encourage doctors to consider the cost of their prescribing and so eliminate wasteful prescribing (Walley et al. 1995; Bligh and Walley 1992). The scheme began in April 1991; general practitioners were set an indicative (theoretical) prescribing amount (IPA), to cover their prescribing costs for the following year. The IPA was based on the previous year's spending, modified by an 'uplift' factor determined by central government, and adjusted locally to meet special needs by a health authority prescribing adviser. These advisers were appointed to each health authority specifically to administer the scheme and to provide advice on prescribing to both GPs and to the health authority; in practice their role has been substantially wider than this.

GPs receive monthly statements showing their actual spend compared to their predicted spend; in theory, if they find themselves overspending, GPs would modify their prescribing to keep within their overall IPA. The monthly statements are also sent to the health authority, whose prescribing adviser might intervene in 'overspending' practices.

#### ***2.3.2. Results of the IPS***

The IPS has suffered from many problems, including the use of historic prescribing costs to calculate the IPA, so penalising previously careful prescribers and rewarding the profligate; unrealistic uplift factors, resulting in unrealistic low IPAs; a lack of practical penalties for 'overspending' practitioners or until 1994, real incentives for reduction in prescribing costs (Walley et al. 1995). As a result, many GPs largely ignored the IPS; in 1991-2, 85 per cent of GP practices overspent their IPA, while in 1992-3, the total overspend among non-fundholding practices was 7.5 per cent of the predicted budget. The scheme "has been somewhat discredited to date as a means of controlling expenditure" (Audit Commission 1994).

### *2.3.3. Incentive schemes*

Incentive schemes were intended to encourage non-fundholding GPs to save money on their IPA. Such schemes initially were unpopular, but have been revitalised by the Department of Health. Now, the aim for the GP is to achieve savings of 1-3 per cent on the practice IPA (or 'target budget' - see below). The exact target saving will be more "challenging" for high prescribing practices, and is set by the health authority. The targets may be purely financial, or may for example include a level of generic prescribing, or use of a formulary. A practice achieving its targets may keep up to 35 per cent of savings, up to a maximum of £3,000 per GP, to be used for patients' benefit.

In many areas, up to half of non-fundholding practices are participating in such schemes. In one area, the annual rise in prescribing costs was 5.6 per cent in practices participating and 9.45 per cent in non-participants (personal data). In another area, participants limited the overspend in their prescribing budgets to 2 per cent, while in non-participants, the overspend was 9.1 per cent (Paris et al. 1994).

The changes in prescribing which bring about such savings include eliminating or reducing unnecessary discretionary prescribing, minimising cost by moving to generic prescribing or by altering their choice of drug within a therapeutic class on cost grounds (eg cimetidine for rantidine).

### *2.3.4. Incentives for authorities*

Controlling prescribing was a new task for health authorities. Many managers could not see the relevance of prescribing since any savings were made centrally and did not directly benefit the authority. Health authorities are therefore set 'corporate contracts', under which they must produce quantifiable targets in improving prescribing. These targets could include rates of generic prescribing, use of formularies, visiting of high-spending practices by prescribing advisers, or prescribing policies for specific drugs. Failure to meet targets might affect the performance-related pay of authority officers.

### *2.3.5. Capitation-based funding*

Prescribing budgets based on the needs of the health authority or practice population would be preferable to crude historical spending. Budgets for Regional Health Authorities may in the future be set according to size and age/sex distribution of the population (NHSME 1994). For a Regional Health Authority with a population of several million, this is reasonable, but not for a general practice (population 2-12,000) where individual patients needing high cost drugs may drastically distort the budget. In health authorities (population around half a million), the major determinants of prescribing costs are the age/sex structure of the population, the standardised mortality ratio (used as a crude indicator of morbidity) and the number of GPs. Refinements to this such as the mobility

of population and other surrogates of morbidity have been suggested (Forster and Frost 1991; Morton-Jones and Pringle 1993).

Attempts to use practice demographics to predict costs within individual practices have also been made. New weighting for prescribing costs according to the age/sex structure of a practice population and the number of temporary residents seen by the practice have been derived. This gave rise to the age, sex and temporary resident originated prescribing unit (ASTRO-PU) which is now used in calculating practice budgets (Roberts and Harris 1993). This model explains only 25 per cent of the variations in prescribing costs between practices, and other factors, such as morbidity, are of greater importance.

The Department of Health had intended to use weighted capitation for allocating prescribing funds to regions from 1995/6 but failure to develop a suitable formula has delayed this (NHSME 1994).

### *2.3.6. The future of the IPS*

In the absence of any formal evaluation of the IPS, it is unclear to what extent the drug bill might have risen without it. Despite its apparently disappointing performance, the Department of Health has not abandoned the IPS. The term 'indicative prescribing amount' was replaced by 'target budget' in 1994, although the principle of an indicative rather than a true cash limited budget remains. The purpose of this semantic change is said to be to emphasize the link between prescribing and other areas of health expenditure. The initially loose mechanisms for setting amounts have been tightened up, and the budgets are set with less importance given to historical spending and more to demographic factors (Walley et al. 1995).

The most recent guidance on setting prescribing budgets (NHSME 1994) opens up the opportunity for incentive scheme-type payments to all non-fundholders, without necessarily participating in a formal scheme. Target budgets are now set as an upper and lower range - effectively the target budget and incentive targets previously set. Any savings between the two ranges may be eligible for incentive payments, if other conditions such as generic prescribing are met. The funding for these extended incentive payments comes largely from fundholding prescribing budgets, which will be effectively reduced. Whether this will reduce the incentive for fundholders to control their prescribing will be seen over the next year. The final setting of the budget remains in the hands of the health authority adviser, who must take into account a variety of practice factors, including local morbidity, while ensuring that the sum of the upper range of the target budgets, fundholder budgets, and any contingency reserve, does not exceed the total permitted health authority budget.

### **3. The 1991 health care reforms**

#### **3.1. *The purchaser/provider split and prescribing***

Purchasers, primarily district health authorities (DHAs) and fundholding GPs buy services on behalf of their population from providers (usually Trust hospitals), who compete for business in an internal NHS market. The resulting competition is expected to promote efficiency.

Purchasers may influence prescribing in hospitals and by hospital consultants. Hospitals have a major influence on choice of drug in the community, and this has led to 'loss leading', whereby a hospital may accept cut-price deals on drugs from pharmaceutical companies, who make their profits from the subsequent community sales. Another problem is cost shifting of expensive drugs from hospitals, which have a limited drug budget, to the non-cash limited primary care drug bill, with consultants asking GPs to take on the prescribing of such drugs. The GP has little clinical responsibility for the prescription which he is writing, although apparently retaining legal responsibility (although this has still to be tested in court). This is clearly poor prescribing practice.

Purchasers now often include prescribing in their contracts with hospitals, and may require the hospital to consider the costs of drugs in the community, and not just in hospital. when making formulary decisions. Combined primary and secondary care therapeutics committees are now being established within health commissions to address these issues.

In the future, the remit of the purchaser may expand, perhaps, to include purchase of primary care services including prescribing. The purchaser could then largely dictate a formulary or practice protocols to its contractors (Laing 1994).

#### **3.2. *Prescribing by GP Fundholders***

In fundholding, GPs in large practices hold budgets for services such as elective surgery, outpatient care, prescribing and staff costs. They can move money between parts of their budget as they wish for their patients' benefit. Fundholding has expanded in annual "waves", so that by April 1996, 50 per cent of the population of England were registered with fundholding practices. The uptake is patchy, with some suburban areas reaching 100 per cent while in inner cities there may be very little.

Unlike non-fundholders, who prescribe within a non-cash limited budget, GPs fundholders have a fixed cash budget for prescribing, and any overspend is taken from other parts of their budget. They therefore have a clear incentive to contain their drugs bill (Glennerster et al. 1994). Savings made are to be used for patient benefits, although there has been concern that some fundholders may have blurred the distinctions between the practice (essentially a small company) and its patients. Closer monitoring by health authorities has

largely resolved these concerns and early anomalies which may have led to overfunding, including loose budget setting because of lack of accurate information, particularly about hospital referral rates and costs, have now been largely eliminated. The budgets for fundholders are broadly set in the same way as the IPA for non-fundholders; however the ability of local advisers to use their discretion allowed the setting of generous budgets for fundholders in at least some areas, and hence facilitated making savings on the drugs budget (Keeley 1994). This has now been addressed by the Department of Health (NHSME 1994).

Two studies of prescribing in small numbers of first wave fundholders and non-fundholders found that while prescribing costs rose in both, the rise was lower in fundholders largely due to the prescribing of lower cost items rather than less prescribing (Bradlow and Coulter 1993; Maxwell et al. 1993). However, these effects may not be sustained (Stewart Brown et al. 1995). A report by the Audit Commission (1994) included data on prescribing by a large number of fundholders (249, out of approximately 1400 fundholding practices at the time of the study) and non-fundholders (3,120 out of approximately 9,800). Fundholders prescribed at lower cost per patient, and the rate of increase of prescribing costs in fundholders (10 per cent in first wave fundholders but only 7.7 per cent in second wave) was less than in non-fundholders (12 per cent); nationally, the rate of rise of costs in fundholders was 4 per cent lower than in non-fundholders. Generic prescribing was higher in fundholders, and rates of prescribing for asthma were similar in both, suggesting no diminution of quality of care. Clearly, the incentive of fundholding had influenced prescribing more than the IPS.

First wave fundholders of the type often studied were generally well organised and motivated enthusiasts for the reforms, and were traditionally low prescribers (unpublished data). The effectiveness of later waves of fundholding practices, including less, many less, ideologically dedicated, in restraining drug costs may therefore be less than that of the first wave. Furthermore, as fundholding expands, the benefits to the individual practice of being a fundholder diminishes. The future of fundholding remains uncertain. No formal independent evaluation has yet been conducted, and in particular, it has not been compared to other models of GP involvement in purchasing (Ham and Shapiro 1995). Although very attractive as a cost containment measure, in prescribing (although one health authority is said to have achieved better results in non-fundholders than fundholders even in prescribing (Ham and Shapiro 1995)) and in other areas, the main opposition Labour party are pledged to remove it if they come to power. Even within practices, fundholding seems unstable; the impetus to fundholding often comes from one individual. In a survey of fundholding GPs, where only two thirds of responders said that they supported the scheme. A development of fundholding is total GP purchasing, whereby fundholders hold budgets for all services for their patients, and not just the limited budgets currently held. This is currently being piloted, and may have interesting effects on prescribing.

#### **4. Other measures to control the drug bill**

Government has made other attempts to control the drug bill over the past three years in addition to the IPS and GP fundholding. That such measures are thought necessary reflects government disappointment at the IPS in particular.

##### **4.1. *The selected list***

In 1985, the government introduced a 'limited list' of drugs in seven therapeutic categories - e.g. benzodiazepines, minor analgesics. Drugs from this list are not reimbursed by the NHS in these categories. This allegedly saved £75 million in its first year. The profession regarded it as a limitation of clinical freedom, largely since there was no consultation with doctors, but in practice few found difficulty in applying it.

The government announced an extension of the list into ten new categories in 1992 (Bateman 1993). This alarmed the pharmaceutical industry, but was accepted by the British Medical Association. Unlike the original list, the extension involved prolonged discussion with interested parties, including the company whose product was at risk. The first category addressed in the new list was topical non-steroidal anti-inflammatory gels, widely prescribed but perceived to be of limited therapeutic value. The review committee considered that £7 per 100 gms was an appropriate price to pay for such drugs; manufacturers promptly reduced their prices. The selected list therefore acted as a reference pricing system. In addressing further areas, the committee has been hampered by complaints from the pharmaceutical industry about lack of transparency, and a veiled threat of legal action in European courts as a result. The selected list has progressed very slowly, and the government are clearly disenchanted with it.

A review by the House of Commons select committee on health suggested that there should be a positive prescribing limited list (House of Commons Health Committee 1994). The government declared that such a white list would be considered in the next major review of prescribing controls, including PPRS which is due in 1998 (Department of Health 1994): this may be a way of letting the proposal die quietly (Walley 1995).

##### **4.2. *POM to P and prescription charges***

The regulatory status of some drugs, previously available as prescription only medicines (POM) have been changed to pharmacy (P) or available over the counter (OTC), i.e. available in selected doses for short term use without prescription through pharmacies (Ferner 1994; Anon, Lancet 1994). Although the decision to change is made on safety grounds by independent experts, such deregulation is in keeping with government policy to encourage patients to exercise choice in self-medication, and discourage prescribing by GPs. Drugs deregulated include H<sub>2</sub> antagonists and topical aciclovir. Deregulation may decrease the use of the H<sub>2</sub> blockers on prescription, or may actually increase it as patients realise that such drugs are available at less cost to the patient on prescription.

This increases the role of the community pharmacist in drug supply and advice, and might in part represent an encroachment on the traditional preserve of the doctor, and perhaps the source of the doctor's power, the ability to provide access to medical technology, most often in the form of drugs. Nurse prescribing is currently being tested in a limited form. The effects of both these initiatives remain to be seen.

The prescription charge is a tax levied on under 20 per cent of all prescriptions, currently £5.50; children, elderly and poorer patients are exempt. The charge is not related to the cost of the drug; in about 50 per cent of all prescriptions on which prescription charges are paid, the drug costs less than the charge. This raises tax revenues of £300 million per year. Increased charges may influence uptake of prescribing and deter patients from consulting, increasing non-compliance as patients fail to have their prescriptions dispensed, and does seem to reduce utilisation of NHS drugs (Ryan and Birch 1991). The unpopular prescription charge has been consistently increased ahead of inflation.

Private prescriptions do not attract a prescription charge. GPs were formerly not permitted to issue a private prescription to NHS patients, even if the drug cost less than the prescription charge. The Department of Health have now allowed this, and this will decrease the national drug bill slightly, especially in the more affluent parts, where most patients may pay charges. In other areas, the numbers exempt from prescription charges are so large that it will make little difference (Heath 1994).

#### **4.3. *Pharmaceutical Price Regulation Scheme (PPRS)***

The PPRS (Department of Health 1993) is a voluntary agreement between the pharmaceutical industry and the Department of Health to regulate the profits made in sales to the NHS. The Department of Health in the UK has two partly contradictory roles, as the patron of the pharmaceutical industry (encouraging investment and exports), and as purchaser of drugs (trying to constrain the drug bill). PPRS covers about 86 per cent of the NHS drug bill (generic products are excluded).

Under the PPRS, a target profit for a pharmaceutical company is set, between 17 and 21 per cent of the capital employed in the UK in providing these drugs. The target profit is not guaranteed: if a company exceeds the target by 25 per cent or more, the Treasury may reclaim the excess profit, while if a company underperforms by 25 per cent (much rarer), the company will be permitted price rises in the following year. The negotiations with individual companies within the PPRS are confidential; the contribution of the company to the UK economy as a whole, export earnings, and spending on research and development will be considered.

The PPRS was renegotiated in 1993 (Department of Health 1993; Anon, Drug and Therapeutics Bulletin 1993), and included an overall drug price cut of 2.5 per cent, and then a price freeze for the next three years; this explains part of the recent fall in overall

drug spending (Anon, Scrip 1995). The new PPRS suggests that within government and the Department of Health, control of the drug bill (both on the supply as well as the demand side) is currently more important than promotion of the pharmaceutical industry.

#### **4.4. Economic evaluation of pharmaceuticals**

The principle of pharmacoeconomics, the weighing of all the benefits and costs of drug therapy to decide best practice, was specifically supported by the government. But the government suggested that the pharmaceutical industry should be responsible for producing economic evaluations of new products, so that doctors could consider the value of drugs, in terms of health gain for patients and not just acquisition cost, and in comparison with alternatives. The industry had already begun to do this for promotional reasons in response to the developing climate of cost limitations in the health service. Such evaluations have had little impact so far, in part because of the difficulty in realising savings identified in academic studies due to organisational difficulties - for instance an increase in spending in primary care on inhaled steroids may reduce hospital admissions with asthma, but there is currently no easy way to transfer money between the separate budgets which fund each (Walley and Edwards 1993, 1994).

Recently, the ABPI and the Department of Health have agreed guidelines for economic evaluations which are conventional and represent only the minimum of good practice (ABPI / DH 1994). These are not formal regulations, but any claim in drug advertising to cost-effectiveness or other economic advantage will be expected to be based on studies conforming to the guidelines. This will be policed by the self regulation of the ABPI code of practice committee. These guidelines will also apply to any study conducted or funded by the Department of Health itself. These guidelines have recently been criticised as inadequate by health economists who wish government to adopt a more centrist approach, and who compare the UK unfavourably with Australia and Ontario in the respect (Freemantle et al. 1995), but this fails to recognise the complexities of the role of government as promoter and as regulator of the pharmaceutical industry (see below), concerns which scarcely exist in either Australia or Ontario.

The guidelines will provide only limited support for the purchaser or prescriber in interpreting economic studies; if economic assessments are to influence clinical practice, much more will have to be done to make them practically applicable within the NHS. The UK government has no intention to introduce mandatory economic evaluations as part of the reimbursement or licensing procedure in the foreseeable future. Purchasers of health care however are likely to demand evidence of cost-effectiveness, and a fourth hurdle will exist *de facto*, regardless of legislation. Purchasers will need to develop their ability to critically examine economic evaluations of health care, and need the ability to move money freely between primary and secondary care budgets to implement the results of such studies.



## **5. Perverse incentives**

There are a number of factors which act against these measures. Many are suspicious that the PPRS shields companies from the effects of a reduction in their sales due to the other initiatives, by guaranteeing their profits. In practice the limits of the PPRS within which a company's profits may lie are so wide (17 - 21 per cent of capital investment) that the PPRS can only provide a safety net for companies in danger of completely failing, and local savings are of value.

The pharmaceutical industry has considerable influence on government and GPs. It is a major employer, with over 70,000 employees, and overall UK exports of pharmaceuticals exceed imports by over £1 billion. No government can ignore such a powerful lobby, but some argue that the relationship between industry and government is too cosy; the PPRS has been criticised for its lack of transparency by the House of Commons committee (House of Commons Health Committee 1994).

Dispensing doctors work in rural areas and prescribe and dispense drugs. They may have an incentive to prescribe those drugs on which they have achieved good discounts, so enhancing their profits as they charge the NHS full price. The payment structure for such doctors needs to be revised, but in general the Department of Health has tolerated this, accepting that without additional payment, some of these practices would not be viable.

Perhaps the major disincentive to cost-effective prescribing is the division of budgets, as described above, so that while increased spending in one budget may reduce costs in another, there is no readily available means of transferring money between these budgets. This problem may be resolved in the future by the unification of drug budgets within health authorities or the extension of GP fundholding, which will create a single budget for drug therapy within primary and secondary care and the ability to move funding into or out of prescribing as considered most appropriate.

A final example of perversity in incentives to control the drug bill lies in the poor coordination between central and local attempts to encourage good prescribing, such that the two seem to be acting sometimes in opposite directions. Often, new central initiatives or relevant decisions are made known to local prescribing advisers by the medical media before they hear about it from the centre. This is a source of great frustration and undermines the morale of local prescribing advisers.

## **6. Conclusions**

There are many ambivalent attitudes in all players in prescribing: government wishes to contain the drug bill while supporting the pharmaceutical industry; prescribers wish to treat the patient, and retain professional freedom, but recognise that at times resources could be better used; the public wants treatment, and new innovative drugs, but is reluctant to pay either directly or in taxation.

These tensions contribute to the apparent failure of the IPS; in contrast, providing direct incentives to doctors to modify their prescribing has been a more successful approach. However, this might carry risks of harming patients if professional values slip. Ways of defining and measuring quality in prescribing need to be developed and used to feed back to prescribers alongside cost data.

The possibilities for moving from consideration of drug costs to drug value and value for money seem limited in the near future, but the purchaser/provider split may offer some hope in the long term. Perverse incentives seem likely to continue.

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## **Existing initiatives to improve prescribing: Discussion**

### **Colin Pollock (chair)**

Since 1990 the Department of Health has invested significantly in developing the role of professional advisers in health authorities as one means of controlling spiralling prescribing costs. As yet there is little or no research evidence evaluating the cost-effectiveness of these advisers in their role as either simply controllers of cost or facilitators of improved prescribing quality by GPs.

Initiatives for improving the quality of prescribing have focused almost exclusively on GPs and not on hospital clinicians, although the latter is said to have an influence on the former's prescribing activity (Audit Commission 1994). Evidence is balanced as to the relative importance of this influence but the Pharmaceutical Industry considers it important enough to target hospital doctors at the launch of new drugs. Training and education in the principles and application of cost-effectiveness need to be targeted at hospital doctors as well as at GPs.

The Indicative Prescribing Scheme for GPs has been in operation since 1991. Initially, Department of Health policy guidance to health authorities on setting Indicative Prescribing Amounts (IPAs) for GPs changed significantly each year, together with often long delays in releasing the guidance. This resulted in IPAs being set in very short timescales and close to the start of the financial year, thus depriving fundholding practices of the necessary information to plan and manage their funds appropriately. This led to confusion among, and criticism from, many GPs. Apparently the direct involvement of the Treasury in deriving policy on budget setting lay behind much of this vacillation. With the Treasury driving national policy on these issues, the Department of Health is unable to take longer-term strategic policy decisions to enable better consistency and clarity in the NHS. More recently, however, some stability and earlier notice of guidance has been forthcoming.

Barton (in preparation) has usefully adapted Maslow's Hierarchy of Need at a practice level, e.g. by transforming the concept of 'self-actualisation' to that of optimal clinical practice and behaviour. He suggests that as workload in primary care increases and practices resort to basic day-to-day survival and coping mechanisms, so the ability and motivation of GPs to address and improve the quality of their care (e.g. prescribing) diminishes. Without the luxury of spare capacity in primary care (time and personnel) achieving better quality of care in prescribing is limited.

Increasingly, the role of the pharmacist (both community and hospital) in achieving improved cost-effectiveness is being promoted in many parts of the country. Over the next ten years as more pressure is brought to bear on clinical prescribing decisions, this role may develop even further with pharmacists becoming involved after the clinical diagnosis stage in advising doctors and patients on appropriate treatment regimes.

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### **John Howie**

#### *The theory of prescribing*

A useful theory of clinical behaviour of general practitioners places illness factors, doctor factors (including knowledge, skills and culture) and patient factors (again including knowledge and culture) at the three points of an equilateral triangle, and the concept of family (which includes 'community') in the centre. Clinical decisions (including prescribing decisions) should be able to be explained on the basis of combinations of these four factors and of relationships between them. Clearly absolute rules become progressively less appropriate as precisely definable pathology which threatens life or well-being becomes diluted by the more common and less specific presentations of health problems, which may be self-limiting, and where management decisions are complicated by issues of belief, choice and risk.

However, the theory of professional behaviour is further complicated by another literature, that of institutional behaviour. In the setting of general practice this includes the influences of work stress and issues that cause or flow from stress, of which pressures on time and the provision of inappropriately brief consultations are the best documented components.

'Good' prescribing may be best defined as any decision which can be defended by an analysis based on the influence of the professional and institutional behaviours referred to above. 'Right' and 'wrong' quickly become at best, relative concepts.

#### *Practical issues*

Four issues must be addressed if prescribing is to improve:

1. Quality of information

Feedback to prescribers (and indeed audit of prescribing generally) is still based on the prescribed item as the measure of prescribing volume. Although partly acceptable at area level, this is uninformative at the level of the individual prescriber or the group practice. Changing to use of the defined daily dose (DDD) as a method of analysing volume seems

an essential part of the debate on what is actually happening in prescribing and how it should develop.

## 2. Political rhetoric

The prevailing rhetoric of politicians (in particular) and some managers suggests that doctors are prescribing irresponsibly by allowing prescribing volume to rise unchecked. If the recent literature based on DDD information is studied, it is however apparent that the only drugs where volume has increased have been those where medical consensus has advised this ( $H_2$  antagonists, inhaled steroids and antidepressants) and that the principal reason for rising costs is due to pricing strategy, an issue in which the government has the lead opportunity and responsibility. A more supportive press is deserved and would be highly appreciated.

## 3. Fund-setting and incentives

The health service reforms have introduced new ways of setting budgets for practices to use for patients and new targets for doctors to achieve to maximise or to maintain income. Fund setting remains insufficiently rational to achieve ethical acceptability, and incentives bring winners and losers to the contextual issues already referred to above as influencing consistent or ideal prescribing. The health service reforms and the contract target requirements for general practitioners may be combining to form a perverse incentive for general practice prescribing.

## 4. Education and marketing

The paper by Russell has referred to the relatively low impact of published work on knowledge and practice. Publication is however an important driver of academic activity. Altering dissemination activity towards other interventions in the field of continuing medical education (such as academic detailing) has the potential to improve prescribing. But those best able to do this are driven by state policies to work to different performance indicators. Should these be re-thought too?

In conclusion, it seems that if a broad view is taken about what 'good' prescribing is, then variation will be more tolerable, and problems of achieving 'goodness', may be less substantial than often imagined. Some relatively simple policy initiatives could improve the setting in which the prescribing debate is presently taking place. In summary, as suggested by Walley's paper, the removal of features that institutionalise bad prescribing is as important as introducing new interventions that will promote good prescribing.

**Richard Hobbs**

The paper by Tom Walley raises a number of questions:

1. Does consideration of prescribing costs hinder prescribing quality? Unfortunately the answer is yes if prescribing costs are taken in isolation of overall care costs. For example, the cost benefit of drug therapy may be very long term (such as the reduction in strokes and myocardial infarctions through antihypertensive therapy). High drug expenditure may also reduce costly hospital utilisation (such as asthma or heart failure therapy). Such cost savings will appear in another budget. There is clearly an expectation that aggressive prevention will reduce disease incidence and prevalence, so that aggressive secondary disease prevention through drugs which demonstrate effective suppression. Such a dynamic might ironically increase the pressure on GPs to be less aggressive in disease monitoring, since tight control may raise pharmaceutical expenditure.

Measuring the quality of prescribing remains very difficult. There will always be a balance to be struck between volume prescribing and individual drug high cost prescribing, although some authorities suggest that efforts should be concentrated on high volume prescribers initially. Prescribing remains such a significant area of clinical practice that a more realistic target for measuring quality might be through the selective investigation of prescribing within a number of limited clinical indications, which performance is then taken as a proxy for overall prescribing quality.

2. What drives doctors to respond to initiatives to contain prescribing costs? The stimuli are complex. Conceivably the least important issue is the maintenance of a practitioner's 'expected' remuneration, since in the UK at least, practitioner income is not linked to scale of health service utilisation. However identifying resources to fund the time needed to improve a clinical activity remains a pertinent issue (i.e. funding the time practitioners need to spend on implementing initiatives to reduce prescribing).

3. What drives doctors to respond to initiatives to contain prescribing costs - professionalism or purely financial gain? Examples of beneficial initiatives are the routine feedback of personalised prescribing audit information, enabling a comparison to be made between personal activity and local and national peer activity. Such data are available through PACT and are probably even more powerful if accompanied by prescribing 'detailing' from FHSA professional advisers (although there is no evidence of their effectiveness as yet).

4. To what extent does the ambivalent attitude of the Department of Health to the pharmaceutical industry negate any local attempts to save money on the drug bill? This macro-institutional relationship is not an issue to individual prescribers. Most are unlikely to be particularly aware of the nature of the relationship. However, the disparity between hospital and community prices of drugs, which is a centrally enabled factor, is a major

issue for primary care clinicians. The potential for hospital driven high cost primary care prescribing of drugs (which are low cost for in-patients) has produced considerable irritation amongst general practitioners and further clouded the other important interface question related to prescribing - the primary care prescribing of essentially specialist drugs. The main problem for the Department of Health will be to balance the clinical objectives of Health of the Nation targets against the rationing objectives of the Treasury.

5. What will be the effect of unified care budgets? These ought to improve the consistency of prescribing and may present better opportunities to influence the quality of prescribing also. They should certainly drive primary and secondary prescribers to greater dialogue.

6. Can we have a reasoned public debate on level of resources for the NHS? It is important in any public debate to recognise that in almost any international comparison of health and pharmaceutical expenditure, the UK remains highly conservative in terms of overall spend and, with regard to prescribing, in terms of innovation. The public will also benefit from the availability of more cost-effectiveness studies, which may enable a greater degree of comfort amongst professionals and the public with the concept of unifying budgets and of virement between headings.

### **Ian Watt**

In attempting to improve prescribing there is first a need to identify what constitutes good prescribing practice. Whilst a number of academic definitions and discourses on this topic exist it is also important to embed these in the reality of everyday practice. From a straw poll of general practitioners a number of elements were identified as constituting good prescribing:

- patient safety, the need to avoid hazardous side effects and drug interactions
- a need to respect patient decisions and wishes
- a need to avoid the abuse of therapeutic drugs and preparations. This may include avoiding such bad practice as providing individuals with a supply of blank signed prescriptions, leaving completed prescriptions at unsupervised collection points, prescribing inappropriately large amounts at any one time.

Whilst cost-effective prescribing is clearly an important issue the points outlined above serve to indicate that it is only one element of what might be referred to as 'good' prescribing practice. Whilst economists and others involved in health policy initiatives might immediately identify issues of cost and effectiveness when asked to define good prescribing, clinicians (particularly general practitioners) might point to the other issues. Therefore, any initiatives to improve prescribing need to reflect the variety of views held by the different perspectives and backgrounds held.



Whilst the above may represent the professional views on what constitutes good prescribing, it is important to take account of the patient perspective. Again many individual patients might identify elements of good prescribing that were not picked up on by professionals. However, taking into account the views of individual patients will on occasions come into conflict with an approach more geared towards improving the health of the population. This tension between the individual and population perspective of health is not a new one and some clinical specialties, such as general practice, are familiar with the conflicts that it can present. However, this is not the case for all specialties.

Even if a consensus could be reached as to what constitutes good prescribing there remains the problem of changing professional behaviour to reflect this. The pharmaceutical industry spends large amounts trying to influence prescribing practice, and it is doubtful whether the National Health Service could compete in terms of a similar expenditure to promote cost-effective prescribing. Whilst a number of methods of changing professional behaviour have been shown to work at least in some circumstances, it is not clear what the costs and benefits of using such methods in the NHS would be. For example, whilst academic detailing has been shown in a relatively small number of studies to be a promising intervention through which prescribing could be improved, it is not clear who would take on this role within the NHS. Medical and pharmaceutical advisers of health authorities reflect elements of detailing in their work, but there is no professional body taking this on in a systematic way, nor is there any evidence of the necessary training and resources being made available if this were thought to be a desirable approach to adopt. Similar concerns could be seen to be reflected in many of the other behaviour change strategies that might be used to influence prescribing. Whichever methods are used, it would seem important that the cost-effectiveness of such approaches is fully evaluated.

### **Conrad Harris**

One of the most noticeable features of Tom Walley's paper was how little it discussed initiatives to improve the quality of prescribing. The paper discussed PACT reports, which conscientious GPs can use for the purpose as long as they already have a clear idea of what good prescribing is; written information from MeReC, the DTB and elsewhere; and such education as is provided by medical and pharmaceutical advisers on practice visits - about whose content we know little and about whose effects we know less.

The problems with initiatives to improve the quality of prescribing lie in defining and measuring quality. 'Good' prescribing has meaning only in terms of individual patients, so we cannot know how often it happens; and in any case it depends on a cultural context. Looking at the wildly different patterns of prescribing found even in advanced European countries makes it tempting to believe that therapeutics is a branch of anthropology rather than of clinical pharmacology. The best we have been able to achieve in this country in relation to quality indicators is to define limited areas of bad prescribing, e.g. the use of

barbiturates, and to look for these drugs in a practice's prescribing data. Eliminating such areas will improve quality, but only by default.

Walley defines improvement as an increase in the cost-effectiveness of prescribing, but said little about this either. Here the problem lies in defining an end-point directly attributable to the medication given, and the choice of endpoint in the context of the undifferentiated illness so characteristic of general practice, and so unlike that of the RCT, is very difficult. It can be anything from patient satisfaction to return to normal of a laboratory value, to time off work, to the subsequent hospital admission rate, or to mortality; all of them capable of being influenced by an infinite number of life-events. It would be a brave economist who would assume any correlation between these outcomes. Cost-effectiveness in many contexts tends to mean the use of the cheapest drug that may be expected to produce a desired effect. This is properly termed cost-minimisation. GPs are given plenty of cost comparisons of similar drugs, particularly in relation to generics. This is part of cost-effectiveness, but there is a lack of information about well-defined circumstances in which the use of an expensive alternative makes sense. Often these well-defined circumstances are unknown, but they are an integral part of proper cost-effectiveness.

Even where doctors have the necessary facts, they are not necessarily used. The most commonly used paediatric antibiotic has a dose of 15 ml a day, and there is no evidence that a course of this antibiotic need last for more than 5 days. The amount needed is therefore 75 ml. If a GP prescribes 75 ml, the chemist will dispense 100 ml and claim for 100 ml, and that is the amount that will appear on the doctor's PACT report. This is true whether the prescription is for a generic or a proprietary formulation. So how much do we really believe in cost-effectiveness?

There may be three main ways of trying to contain costs. The first is education, and here there is a great deal of activity. The best documented success has been one that has increased prescribing costs: the reduction in asthma mortality that seems to have occurred since the British Thoracic Society guidelines persuaded GPs to prescribe steroid inhalers more liberally. The rising percentage of generic prescribing must have resulted in savings, but the fact remains that prescribing costs go up relentlessly every year and not all of the increase is likely to be justifiable on pharmacological grounds.

The second way of containing costs is by the imposition of sanctions on GPs, and this would work if the sanctions were tough enough. Every GP in the country could reduce his costs by 30% overnight if he knew that he would be shot if he failed to do so. The Department of Health has so far seen sanctions as appropriate only for persistent extremely high cost prescribers, but the decision when to impose them is essentially political, and any government or health authority will do whatever it thinks it can get away with.

The third way is by giving incentives to cut costs. Despite their new popularity these are in my view immoral - to use a quaint old-fashioned term. If GPs were prescribing

properly, incentives would encourage improper prescribing. No-one offers a bonus to the surgeons who cut off the fewest wrong legs. Incentives can destroy the trust a patient has in his doctor, even when there is no justification for this. That we appear to be accepting incentives reflects a serious lack of professional pride, and is to be regretted.

Both sanctions and incentives rely on ways of measuring prescribing and its costs that are of very dubious validity because they lack proper standardisation. The difficulties of standardising for demography, morbidity and drug volume are substantial, but until they have been resolved what is being rewarded or penalised remains unknown.

Three proposals may improve prescribing:

1. As far as costs are concerned, the current approaches of 'hit them on the head' or 'offer them a bag of gold' are far too crude. GPs are almost all well-intentioned people, and far more likely to respond to a challenge than to devices based on donkey psychology. Why doesn't the Department of Health try to make a fresh start, going to GPs and saying "Look, we have a real problem here and we don't know that to do about it. Can you help? What do you suggest? Is there anything we can do that would be useful?" - and listening to the answers. Perhaps too, the pharmaceutical industry has some psychology to teach. A recent article in *Scrip* magazine categorises GPs into four types - reactionaries, conservatives, entrepreneurs and progressives. A sales representative marketing a drug needs a different approach for each of the four types, based on their differing psychologies. Is there a message here for prescribing advisers?
2. Improvements are also required in medical education. Medical students learn a little about pharmacology, less about therapeutics and nothing about prescribing. In their early postgraduate years in hospital they learn several sets of habits, and vocational trainees in general practice learn new sets of habits. They have no strong and principled educational structure giving them internalised standards to support them when they are subjected to the many powerful pressures they find in general practice. Prescribing is a low status activity suddenly thrust into the limelight by its cost. This situation could and should be changed, and the resources required could be a very good investment.
3. If GPs are subjected to social pressures in their prescribing, should society be altered as well GPs? If we want a public more educated about medicines we have to start young - putting up notices in the surgery saying "Prepare to leave here empty-handed" is pathetically inadequate. Starting in the primary schools, children could be taught about how the body works, how it can go wrong, how it often cures itself, what can be expected of medicines and what risks they entail. This is a long term initiative and would have its own costs, but the pay-off could be huge.

These three simple and practical initiatives: the Department of Health humbly asking GPs for help, medical schools changing their curricula, and long-term co-operation between the

Department of Health and the Department of Education and Employment, could considerably improve the quality of prescribing. So it's easy, really.

### **Audience discussion**

Andrew Herxheimer put forward the equation that a medicine is a drug with information. Information should come with the drug from the doctor and from other sources such as the pharmacist and the package leaflet. This information and the way it is received and used by patients makes a crucial difference to the quality of a prescription, and it needs to be built into the prescription process. In response to the view of Professor Hobbs that the relationship between the Department of Health and the pharmaceutical industry is not an issue to individual prescribers, Dr Herxheimer pointed out that the Department pays no attention to abuses of marketing and promotion by the industry, which is left to self regulate. If companies break the Medicines Act, this is dealt with by the industry regulators, meaning that there are almost no prosecutions when there should be lots. This can be viewed as absolute collusion.

Dr Jonathan Cooke raised the issue of cost shifting between hospitals and primary care. This is very complex, as hospitals are subject to discounting, and also pay VAT on medicines. However, hospital Drug and Therapeutic Committees in Manchester do have GP members and, for a number of years have considered the full cost (hospital and community) before including a drug on the hospital formulary. Also, following the publication of an executive letter relating to costs between primary and hospital care (EL91-127), meetings were arranged with local FHSAs, LMCs, the Regional Health Authority, Trust hospitals and a selection of GPs to devise a hospital proforma, where a hospital consultant could provide GPs with a diagnosis and offer suggestions of therapy within a broadly based group of medicines. This has shown GPs to be happy to take on prescribing, even of high cost medicines, when they have a rational shared care protocol, which offers clear guidelines for prescribing, monitoring and reviewing therapy.

Dr L Kamal thought that the role of community pharmacists should be more carefully considered, and this is impossible while large chains of pharmaceutical outlets remain in the high street to sell over the counter products. His view is that GPs and community pharmacists should work together, in whatever form (not necessarily all dispensing GPs), but forming a beneficial working relationship.

### **Professor Nick Barber made three points:**

- controlling prescribing has worked well in the hospital setting because of the dynamics between prescribers and pharmacists, with frequent initiatives by clinical pharmacologists. The primary successes have been in the ability to control access to drugs, and in monitoring by ward pharmacists. Prescriptions often change on the

advice of pharmacists, and big savings have been made. Some pharmacists are employed on the understanding that their contract will be renewed if they save twice their own salary in one year, which is a possibility that practices may wish to consider.

- pharmacist prescribing may possibly be beneficial in very constrained circumstances, where the diagnosis is clear, and the prescription is protocol driven and generally poorly done, for example in orthopaedic and other areas of surgery.
- with regard to the role of the high street community pharmacist, we need to think whether pharmacists should act as a form of triage system. If so, they need to think in the same way as prescribers, so that they are a true gatekeeper, rather than thinking in a different mindset, as they do at the moment, around recommending drugs available over the counter.

Professor Conrad Harris emphasised that pharmacist prescribing does work best where the issues are clear cut and protocol driven, but pointed out that this is the opposite end of the spectrum to general practice. If this is introduced it should be done very carefully, and based on a personal relationship between pharmacist and GP, and not some separate activity that results in criticism from on high.

Professor Richard Hobbs suggested that this also works best when it is positive, i.e. when it adds to practice, for example the use of inhaled steroids for asthma. UK prescribers are conservative, which suggests that the influence of marketing may be lower than generally implied.

David Taylor initiated a debate about incentives, suggesting that people do respond to incentives, and it is important to consider how these incentive schemes are working, and what are the real dangers in them. If there has been an 8% reduction in the volume of prescribing, yet GPs are still prescribing more H<sub>2</sub> antagonists etc., what has been cut, and is this beneficial or are incentives perverse?

Richard Hobbs suggested that it may be 'back pocket' incentives which people find objectionable, whereas other incentives such as more time may be more acceptable.

Conrad Harris agreed that if you have incentives you need to know whether they work and how they work, but continued to object to the very idea of them.

### **Initiatives to Improve Prescribing and Promote Cost-Effective Prescribing. Key Points**

- Improving cost-effectiveness in prescribing requires addressing the decision to prescribe or not prescribe (often neglected) as well as choice of what to prescribe;
- Doctors have traditionally depended for drug information on the activities of the pharmaceutical industry, now supplemented by government funded sources such as the Drug and Therapeutics Bulletin and the Medicines Resource Centre. PACT data are sent to all GPs, informing them of cost and volume of prescribing locally;
- Provision of literature may not change behaviour, and face to face contact from medical and pharmaceutical advisers is designed to reinforce literature (although this remains unevaluated);
- The development of formularies and generic prescribing have been successfully promoted as good practice and are likely to improve cost-effectiveness;
- The indicative prescribing scheme aimed to encourage awareness of costs and eliminate wasteful prescribing, but this has had problems including the use of historic prescribing costs and a lack of real incentives to reduce cost;
- In future, the indicative prescribing scheme may be developed using incentive schemes and basing budgets on the needs of practice populations, using practice demographics and weighted capitation;
- The 1991 health care reforms included initiatives which had an impact on prescribing, including the purchaser-provider split, which can influence hospital prescribing (and may create incentives for cost shifting to primary care) and GP fundholding, gives incentives to contain prescribing costs and use savings for other patient services;
- Other measures to control the drug bill include the selected list, changes some drugs from prescription only to pharmacy or over-the-counter status, increasing prescription charges, the pharmaceutical price regulation scheme (PPRS) and encouraging economic evaluation of pharmaceuticals;
- Perverse incentives remain with some of these measures, particularly PPRS which can guarantee company profits, payment of dispensing doctors, division of budgets enabling cost shifting and poor coordination between central and local attempts to encourage good prescribing. Prescribing costs must be analysed with overall health care costs, not in isolation;
- The role of the pharmacist in achieving improved cost-effectiveness is being promoted, and may develop further in future, in collaboration with GPs;
- If a broad view is taken of what 'good' prescribing is, variation may be more tolerable. Good prescribing includes taking account of patients' wishes as well as cost-effectiveness. Initiatives to improve prescribing need to reflect the variety of views and perspectives involved;
- Improvements are required around education of prescribing, both in medical schools and in the population more generally.

## Chapter 4

# Cost Effective Prescribing: Is There Only One Way To Heaven?

Alan Maynard, Karen Bloor and Nick Freemantle

### Introduction

In recent years there has been increasing effort around the world to link prescribing decisions with information about cost. UK attempts have been considerable, including aspects of the internal market reforms, the limited list, PACT data and indicative prescribing budgets. However, despite these initiatives to contain the cost of pharmaceuticals, the drugs bill has grown rapidly. Although both the relative and absolute cost of pharmaceuticals in the UK NHS is lower than in many other developed countries (notably the US), the trend continues to rise. What can the UK learn from the experience of other countries in implementing policy initiatives to improve prescribing behaviour?

Three primary objectives of any policy initiatives in health care are equity, efficiency and cost containment. Linking prescribing decisions with cost data can assist with two of these goals: it may increase efficiency by increasing the cost effectiveness of prescribing, allocating resources to produce greater benefit to patients; and it may facilitate cost containment (although reducing expenditure on drugs must be used with caution and evaluated, to avoid simply shifting costs to other budgets such as hospital care).

It is important to clarify the goal of initiatives to improve prescribing behaviour. The aim is not simply to minimise the cost of drugs, if this were the case the optimal policy would be to spend nothing. The evaluation of costs and benefits of medicine can be used to inform and review prescribing choices. The full costs of such prescribing options should be considered, not simply the drug price. Reducing expenditure on drugs can in some cases increase expenditure elsewhere in the health care system (e.g. reducing expenditure on psychotropic drugs can increase mental health care hospital admissions (Soumerai et al. 1994)). Drugs may also generate other health care costs, e.g. the side effects of drugs which may be costly. The overall aim of a rational prescribing policy would be to ensure that any additional benefits from expensive pharmaceuticals are worth the additional costs involved (Freemantle et al. 1995).

Whereas the primary goal of policy might be to improve the efficiency of prescribing, taking into account a broad range of costs and benefits, policies are often initiated in response to the 'system panic' induced by increasing drug budgets, and therefore the architects of most policies focus on cost containment rather than efficiency. There have been widespread trends towards discussion of cost control in pharmaceuticals, but much less progress on increasing the efficiency of drug use, despite advocacy by some individuals over many years (e.g. Williams 1974).

This paper outlines some drug policies from outside the UK which attempt to link information about cost effectiveness with prescribing decisions. This includes supply side initiatives (Section 1) such as reimbursement policies and positive and negative lists, and demand side initiatives (Section 2) such as co-payments and behavioural change. The extent to which these initiatives have been evaluated is discussed, along with the results of those evaluations where they are available. The impact on innovation, research and development within the pharmaceutical industry is considered (Section 3), and finally conclusions and areas for debate are outlined (Section 4).

## **1. Supply side initiatives**

### *1.1. Registration and reimbursement*

Registration procedures for pharmaceutical products are broadly similar in most countries. Procedures generally require evidence of efficacy and safety of new products, but as Hutton et al (1994) point out, registration is “ultimately the most powerful economic control as it can exclude products from the market”. In many countries, governments also restrict the registered drugs which will be reimbursed by the public health care system, either by positive or negative lists. These decisions are made on the basis of information on safety and efficacy, professional opinion and, sometimes, on cost effectiveness information. Increasingly, the provision of economic data and evidence of the cost effectiveness of new pharmaceutical products is being encouraged by governments. Two countries have been at the forefront of this trend, Australia and Canada.

#### *1.1.1. Australian guidelines for the reimbursement of pharmaceuticals*

In Australia there are two tiers of drug regulation. Drugs must be approved for marketing by the Therapeutic Goods Administration (TGA) on the basis of safety, efficacy and acceptable quality. In addition, for reimbursement by the health care system, new drugs must be part of the Pharmaceutical Benefit Scheme (PBS), a positive national formulary. From 1 January 1993, pharmaceutical companies have been required to include an economic evaluation of their drug products in their applications for reimbursement through the PBS. Guidelines for the preparation of applications to meet these requirements were released in 1990 (Commonwealth of Australia 1990) and revised in 1992 (Commonwealth of Australia 1992).

A company requesting subsidisation for a new drug, or changes to current prescribing restrictions on existing drugs, is required to state the clinical claims of the drug, substantiate these claims with good quality data, and perform an economic evaluation that is consistent with this evidence (Aristides and Mitchell 1994). The Australian guidelines are described as ‘outcomes-based’: they focus on comparative outcomes of therapy and then the economic evaluation. This evidence is used to assess any benefits from reimbursement under the PBS, and then to negotiate the price at which products may be reimbursed.



The guidelines are intended to be pragmatic (Henry 1992), for example by recommending the use of cost effectiveness analysis (CEA) rather than cost benefit analysis (CBA) in recognition of the difficulty in estimating values of broad costs and benefits required for CBA.

The Australian guidelines are the first legislative requirement for economic evaluations in the world. This has elevated economic evidence to a status similar to the results of tests for efficacy and safety, which are required prior to government approval of new pharmaceutical products. The lead taken by Australia has since been followed by action in other countries, which are discussing guidelines prior to implementation.

The application of economic analysis is having an impact on listing decisions and drug prices in Australia. New drugs that have no demonstrable advantages over existing products are offered the same price. Those that are superior, on the basis of clinical trial data, have their incremental cost effectiveness assessed in order to determine whether they represent 'value for money' at the price being sort by the sponsor. While the deliberations of the advisory committee are confidential, some recommendations have received press coverage, such as the failure to agree prices for sumatriptan and salmeterol, and the rejection of applications to list finasteride for prostatic hypertrophy and DNase for cystic fibrosis. There have also been instances where good data and competent economic analyses have been used to justify higher prices than would have been achieved using a more arbitrary approach (Freemantle et al. 1995).

#### *1.1.2 Canadian & Ontario guidelines*

In October 1991, the province of Ontario in Canada also provided draft guidelines for preparation of economic analysis to be included in submission to its Drug Programs Branch, for listing in the Ontario Drug Benefit Formulary/Comparative Drug Index (Ontario Ministry of Health 1991). These guidelines are being discussed as part of a continuing debate on the topic in Canada (Detsky 1993), and have been revised (Ontario Ministry of Health 1994).

The Ontario guidelines state that the Drug Quality and Therapeutics Committee (DQTC), which advises the Minister of Health about public funding of pharmaceutical products in Ontario, has always considered cost in addition to effectiveness. The request for information on cost-effectiveness is not therefore reflecting new criteria, but offering guidelines to manufacturers on how to address economic issues to satisfy the information needs of the DQTC.

During 1992 the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) determined that it would be useful to develop a set of Canadian guidelines, that each Province in Canada could adopt as they saw fit. The Canadian guidelines (CCOHTA 1994), similar to those developed in Ontario, have been developed through a process of broad input and wide consultation. The process included a workshop in June

1993 to lay the foundations for the guidelines, attended by 73 representatives of the major Canadian stakeholders including the pharmaceutical industry, the provincial and federal governments, academic experts from Canada and other countries, and relevant national agencies, associations and organisations. Based on the results of the workshop, a steering committee of 10 members, again broadly representative, developed draft guidelines, solicited wide input and finalised the guidelines in June 1994 (Freemantle et al. 1995).

Health is a provincial responsibility in Canada. The plan is for the guidelines to be maintained by the Canadian Coordinating Office for Health Technology Assessment, a national agency funded by, and acting on behalf of, the provinces and territories. Further, the plan is to develop a periodic process to evaluate the guidelines and to make amendments as appropriate. As of December 1994, the guidelines have been accepted by CCOHTA as guidance for studies that they undertake or fund, and have been submitted to the provinces for consideration. It is anticipated that most provinces will endorse the guidelines as representing the type of studies they wish to see when new drugs are submitted for funding approval for their provincial drug plans (Freemantle et al. 1995).

The CCOHTA guidelines state that pharmacoeconomic studies should be used to inform rather than to replace decision making. The guidelines aim to leave scope for innovation and creativity within each study, to deviate from the recommended set of methods when justified, and to add additional analyses to those suggested in the guidelines.

### *1.1.3. UK Department of Health/ABPI guidelines*

The UK government has not mandated guidelines, but is encouraging the use of economic evaluation of new pharmaceutical products, given the changing economic environment in UK health care. The UK Department of Health (1994) has released "guidelines for the economic evaluation of pharmaceuticals", endorsed by the Association of the British Pharmaceutical Industry.

The UK guidelines, unlike those in Canada and Australia, were derived with a minimum of consultation among those working in the field, with no evidence of the scientific rigour exemplified by the Canadian guidelines development process. They were disseminated through a Department of Health Press Release (DH 1994), with no attempts to promote actively their use. It is not clear who, if anyone will monitor and 'police' the advisory UK guidelines: as yet they are a voluntary code of practice. Manufacturers are not required to submit economic evaluations to a Department of Health committee, and the capacity of NHS purchasers to monitor and police the guidelines is not evident.

Decision makers in purchaser and provider units may have neither the skills to synthesise economic analyses nor the ability to evaluate them. A response of the UK government to these problems has been to centralise research and development (R&D) and thus create problems of an absent client group for their work and major problems of dissemination. Without changed attitudes in the users of such R&D, which requires systematic training to

ensure management is research led, the benefits of the DH-ABPI guidelines may be limited. It has been suggested that their creation was rhetorical, aimed at cooling the Treasury's anxieties over the increasing NHS drugs bill (Freemantle et al 1995)

#### *1.1.4. Overview*

There are a number of tasks in these guidelines which are common, and which are agreed to by most health economists. These include:

- i) use of a recognised form of analysis (cost minimisation analysis, cost effectiveness analysis, cost utility analysis, cost benefit analysis);
- ii) careful and justifiable choice of comparators for analysis;
- iii) careful and critical use of high quality clinical evidence as the basis for economic evaluation, using prospective randomised controlled trials (RCTs), and meta-analyses of RCTs where possible;
- iv) use of marginal analysis;
- v) use of discounting and sensitivity analysis.

There are however some elements of these guidelines that are contentious, either because of debate about methodology within the health economics community, or because of differences in the policy approach of different countries. Differences include:

- i) choice of study perspective. The UK and Ontario guidelines encourage a societal study perspective, including consideration of a broad range of direct and indirect costs and outcomes, although these should be disaggregated to enable identification of the recipients of costs and benefits. The Australian guidelines however focus on direct medical costs of the alternative therapies, including non-medical costs where relevant, but concentrating on the more limited perspective of the health care purchaser. This difference reflects debate within the economics community regarding the appropriate inclusion and measurement of indirect costs (e.g. see Drummond et al. 1988).
- ii) choice of discount rate. Australian guidelines recommend consistent discounting of costs and outcomes over time, whereas the UK guidelines require discounting of non-monetary benefits at both the Treasury rate and at a rate of zero, an approach which favours health promotion investments. Again this reflects debate within health economics (Parsonage and Neuburger 1992, Cairns 1992). The choice of discount rate may be examined empirically, and research has been carried out regarding people's actual rates of time preference for health (Olsen 1993, Cairns 1994).
- iii) emphasis on cost utility analysis. The Australian guidelines take a pragmatic approach, allowing a range of intermediate and final clinical outcomes. The majority of

economic evaluations submitted to the PBAC so far have used cost effectiveness analysis, with a single natural outcome measure. This approach facilitates choice within but not between therapeutic categories. In previous drafts of the Ontario guidelines there was advocacy of the calculation of quality adjusted life years (QALYs), and it was proposed that a number of 'grades of recommendation' based on the incremental cost per QALY gained from the adoption of a new medicine be used (Drummond 1992). The most recent guidelines however permit more narrow outcome measures, provided the approach taken (cost effectiveness analysis, cost utility analysis etc.) is justified. The differences between the sets of guidelines reflect debate in health economics, and provide challenges for future research (for example see Mehrez and Gafni 1992 on QALYs versus Healthy Year Equivalents (HYEs)).

### **1.2. Price regulation**

Price regulation is used to control pharmaceutical expenditure in a number of countries in Europe and elsewhere. In Belgium and Switzerland prices are negotiated with the government on all products sold. In most other countries, e.g. France, Italy, Sweden and Australia, this applies only to products reimbursed through public programmes. A system of product price control is in place in France, Italy, Portugal and Spain, whereas in Germany and the Netherlands, reference pricing systems are in place.

A reference price system uses the prices of comparable products as a guide in determining the appropriate price for a new product. Recent initiatives for price regulation of pharmaceuticals include:

#### *1.2.1. The Netherlands*

In the Netherlands, the rate of consumption of medicine is low compared to other European countries, but expenditure is high because of a high price level (Rigter 1994). This has prompted the government to direct most cost containment policies at price rather than volume. In 1991, a 'Medicines Reimbursement System' (MRS) was introduced, under which reimbursement for groups of medicines that are interchangeable in terms of clinical effect, with the limit set based on the average price of the drugs in the particular group. Medicines that are more expensive than the reimbursement limit may still be prescribed, but the patient has to pay the difference. Innovative medicines that cannot be grouped because of their uniqueness are fully reimbursed (Rigter 1994).

Experience with the MRS has been mixed. Overall expenditure on pharmaceuticals has continued to increase considerably (e.g. 11.1% from 1991-1992) but the government feels that the MRS has had a cost containing effect. The increase in costs for medicines falling into one of the groups with a reimbursement limit has been smaller than predicted, but costs of innovative, non-classifiable drugs have been soaring, with annual increases of more than 20% since 1988 (Rigter 1994). This had led the government to tighten the

MRS, in July 1993, by limiting the wholesalers' margin, and barring new drugs from the list of fully reimbursed medicines unless it can be proved that they provide a remedy for which there is no pharmacological alternative. These policies have been opposed by the pharmaceutical industry, wholesalers and pharmacists.

### *1.2.2. Germany*

In Germany there is also a reference pricing system, in place since 1989 which has forced companies to lower prices for products without patent protection. For example, all ACE-inhibitors in Germany are to be given fixed level reimbursement with captopril in April 1995, when captopril becomes off patent. This decision categorises the 'me-too' ACE-inhibitors as non-innovative, despite previous patents (Scrip, 10 March 1995).

Individuals are charged a basic co-payment of 3-7 DM, depending on the size of the prescription, but also any additional amount by which the retail price exceeds the reference price. A drug's reference price is essentially the average of the prices of that drug and similar products (products with the same or therapeutically similar active ingredients, and/or therapeutically comparable effects, adjusted for variations from average strength and pack size) (Gross et al 1994). About 50 per cent of all sales in Germany are regulated with reference prices (Schulenburg 1994). In addition, further cost containment measures were introduced in January 1993 under the 'Health Structure Act', including price controls, a national pharmaceuticals budget and co-payment changes (Munnich & Sullivan 1994).

A 'price decree' was introduced in January 1993, stating that prices of non-reference priced products be reduced by 5 per cent and over the counter (OTC) products by 2 per cent. In addition, the prices of these products were to remain at their May 1992 price level until the end of 1995, and products introduced after May 1992 were to remain at their market introduction price during this period. This policy was introduced at the same time as other policies such as budgetary restriction, which will be considered in later sections. The price freeze appears to have had a considerable impact on pharmaceutical costs, but it is a short term measure.

### *1.2.3. France*

In France, price regulation is direct, with product by product price controls. Both new product prices and price increases are regulated. New product prices emerge from negotiation between the government and each drug manufacturer. There is a three tier process for the introduction of new drugs. First a new drug must receive marketing authorisation on the basis of efficacy and safety. Second, the Transparency Commission recommends a 'technical price' based in part on whether the drug represents a major or minor advance in therapy and on the number of drugs in the same therapeutic class (or, if no other drugs are available, by comparing it to the average price of treating the disease

without the new drug). Finally, the Economic Committee reviews the technical price and the manufacturer's suggested price, and proposes an 'economic price' for the drug. The economic price may be higher than the technical price if the new drug is expected to benefit the national economy, for example by increased exports, job creation, increased investment or more R&D. The economic price effectively becomes the dug price after negotiations (General Accounting Office 1994). The Transparency Commission also distributes information regarding indication and daily treatment cost of drugs with the same pharmacological action (Pelc & Castan 1994).

Health economics studies appear to be used in one in three dossiers for a new drug (Pelc & Castan 1994), but there is no formal requirement for this at any stage of the approval process, and no study guidelines are available.

From April 1993, new pharmaceuticals have been awarded reimbursement for three years only, after which the Health and Social Security Ministry may decide not to renew reimbursement, justifying its decision in accordance with the recommendation of the Transparency Commission. Later in 1993, a new cost containment plan was introduced, with some demand side measures to reduce pharmaceutical costs, which will be examined in Section 2.

#### *1.2.4. United States*

The United States has traditionally allowed the free market to determine drug prices. However, drug prices in the US are considerably higher than in other industrialised countries, and the high and rising cost of pharmaceuticals has resulted in proposals for Federal regulations limiting prescription drug prices. Critics of regulation have asserted that reducing drug prices would cripple US pharmaceutical companies' ability to develop new lifesaving and life improving drugs. Considerable debate is underway in the US, fuelled by media attention to vulnerable groups who can't afford essential therapies, and stories of price gouging (for example claims that one company charges \$1.75 for 36 tablets of a drug when used to treat sheep and \$230 for the same amount when used to treat humans (Volkers 1991, in Lyons & Larson 1992)). The debate has increased US interest in European and other policies to control pharmaceutical prices (Gross et al. 1994, GAO 1994).

The lack of federal pharmaceutical cost control has created a variety of cost control measures at the level of States, insurers and health maintenance organisations. The majority of these measures concentrate on cost control rather than cost effectiveness. For example, Medicaid's cost control programmes (generally supply side) have included caps on the number of drugs allowed per patient per month. However, limiting reimbursement to three drug prescriptions per month in New Hampshire has been estimated to cost 17 times more than it saved (Soumerai et al. 1994). Their analysis showed that the cap resulted in substantial reductions in the use of psychotropic drugs with coincident

increases of one or two visits per month to community mental health centres and a sharp increase in the use of mental health services and partial hospitalisation. After the cap was discontinued, the use of medication and most mental health services reverted to pre-cap levels. This illustrates the importance of using cost effectiveness rather than simply cost control of one budget as a criterion for policy initiatives.

Other cost control programmes introduced by Medicaid have included a restrictive positive formulary, emphasising use of generics; a list of pharmaceutical companies whose products are covered depending on their agreement to pay rebates on their products used by Medicaid to match the lowest price offered in the larger market; prior authorisation requirements for coverage of drugs not listed in the formulary; and denials of early refills of drug products (L Wilson, personal communication, February 1995).

#### *1.2.5. Price regulation and cost effectiveness*

Price regulation devices appear to be relatively unrefined measures of cost control. There are very few attempts to encourage cost effectiveness by using price regulation of pharmaceuticals. Price negotiations in France, and the use of reference pricing systems in countries such as Germany and Sweden may begin to do this, by allowing a premium price only if there is evidence of significant therapeutic benefit. However, without the use of carefully monitored economic evaluation (such as in Australia) price regulation remains crude.

#### *1.3. Profit regulation*

Only two countries in Europe use profit control in the place of price regulation of pharmaceutical: the UK and Spain. The British 'Pharmaceutical Price Regulation Scheme' is a voluntary agreement between the Department of Health and the Association of the British Pharmaceutical Industry. Companies are given target profit rates to be achieved from sales of drugs to the NHS. This rate is between 17 and 21 per cent rate of return on historic capital. Firms set their own prices and can negotiate prices upwards to achieve this target rate. However, companies earning excessive profits can be forced to cut prices to the NHS, such as the recent negotiated price cut for fluoxetine. Spain introduced a similar scheme in 1991 but with target returns to investment in the 12-18 per cent range.

The advantage of profit regulation is that it avoids the need to identify separately the R&D and other overhead costs for each individual product and recognises the characteristics of the innovation process in terms of many products being developed but very few contributing to overall profit at any one time (Hutton et al 1994). However, PPRS also results in some perverse incentives. It can be perceived as reducing the incentive to control costs within companies: if costs increase, the rate of return decreases and can justify a negotiated price increase. In addition, there is a potential conflict with other UK Department of Health cost containment measures such as encouraging generics, PACT

data and other demand side measures. PPRS may, at least partially, negate policies to contain pharmaceutical costs by allowing companies to increase prices when profits are threatened by demand side measures. It is important to consider the objectives of the UK government as a whole rather than separating the demand and supply sides of the market for pharmaceuticals.

Profit regulation measures such as PPRS make no attempt to link prescribing with cost effectiveness: products that are cost effective and those that are not are treated equally under the scheme. It would in principle be possible to link profit returns to some form of cost effectiveness 'score' for new products, but in practice this is not attempted. Profit controls are crude measures of expenditure control, and can conflict with other measures and undermine cost effectiveness.

## **2. Demand side measures**

Demand side measures can be split into those aimed at the three individuals concerned with demand for pharmaceuticals: doctors, pharmacists and patients (Hutton et al. 1994).

### **2.1. Policies to change patient behaviour: co-payments**

Co-payments are the main influence upon patient behaviour, and a number of countries have co-payment systems. In the UK, the prescription charge covers around 40 per cent of the average prescription cost, but only around 17 per cent of prescriptions are chargeable. Exempt prescriptions include patients with certain chronic diseases (e.g. diabetes), certain therapeutic categories of drugs (e.g. oral contraceptives), all elderly people and low income groups. In Germany, the Health Structure Act of 1993 extended patient co-payment to cover all pharmaceuticals. The legislation introduced a co-payment of DM3, 5 or 7 based on the package size of a prescription item, as well as any difference between the reference price and the retail price for prescription pharmaceuticals that were priced higher than the reference price for their group (as noted above) (Munnich & Sullivan 1994, Gross et al. 1994).

In France, co-payments are based on the drug reimbursement rate (assessed by the Transparency Commission). Drugs for serious and chronic conditions and exceptionally expensive drugs are fully reimbursed. Other reimbursable drugs are reimbursed at 65 per cent apart from drugs used mainly for treatment of minor pain, which are reimbursed at 35 per cent. Around 10 per cent of the population with health insurance are exempt from co-payment, including patients with a serious chronic disease and pregnant women. However, most of the population who are not exempted from co-payment are covered by a supplementary health insurance that pays for most of the difference between the price of the drugs and the reimbursed value by the statutory health insurance (Pelc & Castan 1994).



There are many reasons why health policy makers may require patients to pay co-payments for health care. In places such as the former Soviet empire and in developing countries, tax revenues are uncertain and co-payments are a useful way of raising revenue: i.e. co-payments are a disguised tax. However, in Western Europe and North America, taxes can be raised more easily. Policy makers use co-payments for ideological reasons, and because some of them believe that co-payments reduce 'misuse' of health care services. This is a problematic argument: given the technical complexity of diagnosis and therapy, if health services are misused this is the result of inappropriate decisions by providers rather than patients. In addition, evidence from the RAND insurance experiment demonstrates that cost sharing (user co-payments) reduce utilisation of all types of service (Newhouse et al. 1993). This reduces cost effective and less cost effective services, and does nothing to increase efficiency.

The influence of prescription charges on patient demand for pharmaceuticals and utilisation of health services for the rich healthy minority that pay them in the UK is significant. Lavers (1989) analysed data from the UK from 1971 to 1982 and concluded that demand for prescriptions had been responsive to price, with a price elasticity of between -0.15 and -0.20. This means that a 10 percent increase in the prescription charge could lead to a 1.5 - 2 per cent decrease in the demand for prescriptions. Ryan and Birch (1991) analysed data in England for the period 1979-85 for the non-elderly patients who were subject to prescription charges. They found that the policy of increasing NHS prescription charges has been associated with a significant reduction in the rate of utilisation of prescribed drugs among non-exempt patients.

The appropriateness of the UK policy of increasing charges has been questioned by some authors as being contrary to the aim of the NHS and representing a regressive tax on the sick (O'Brien 1982). These equity issues are partially addressed by exemptions, but as a policy for reducing costs of prescribing, co-payment obviously has drawbacks (Bloor & Maynard 1993). Economists Barer, Evans & Stoddart have argued (1979 and 1994) that user charges are "misguided and cynical attempts to tax the ill and/or drive up the total cost of health care while shifting some of the burden out of government budgets" (Barer et al. 1979, Stoddart et al 1994).

## ***2.2. Policies to change pharmacist behaviour***

The use of generic pharmaceuticals, while encouraged in most countries, is rarely mandated. Generic substitution by pharmacists is permitted by some countries, including the Netherlands. However, it is specifically forbidden in France and the UK, and allowed in Germany and Denmark only if specified by the doctor on the prescription. In Belgium and Italy it is allowed with the consent of the doctor. The use of generics is encouraged by many policy makers, and generic substitution has been suggested in the UK (e.g. Greenfield 1982, Royal Pharmaceutical Society 1992), but this is resisted by the pharmaceutical industry. Despite this resistance the use of generics has grown

considerably, from approximately 16 per cent of prescriptions in 1977 to 37 per cent in 1993, (OHE 1995), and this proportion has continued to rise, to around 54 per cent in 1995.

Generic substitution may reduce expenditure on pharmaceuticals, but it can only tackle part of the cost containment problem, as new drugs are patent protected and their increased use will not be affected by generic substitution.

The wide variation in prices of branded drugs has led to parallel importing by the wholesale pharmacy sector. In the European Union, the absence of trade barriers has meant that firms cannot prevent the movement of products from one market to another (Hutton et al 1994). Parallel importing is actively encouraged by some countries, e.g. the Netherlands (Rigter 1994), and this is likely to have a major impact on pharmaceutical prices.

### ***2.3. Policies to change doctors' behaviour***

In the UK, a number of initiatives have been introduced to improve the efficiency of GP prescribing behaviour. These include provision of PACT data, indicative prescribing budgets and GP fundholding. However, the impact of these policies on prescribing expenditure appears to have been limited (discussed by Tom Walley, chapter 3).

In Germany budgetary restrictions have been introduced, effective from January 1993, with a ceiling on pharmaceutical expenditures. This meant that the first DM280 million spent above a physicians' target must be paid for out of their income. This amount represents about 1 per cent of total physician income earned in the treatment of statutory health insurance patients, a tiny proportion of total physician income. This was not expected to have a dramatic effect on physicians' prescribing behaviour (Munnich & Sullivan 1994). However, the drug budget appears on preliminary evidence to have had significant consequences. Expenditure for drugs fell in 1993 by 25 per cent in comparison to 1992 (Schulenburg 1994). In addition, the number of referrals to specialists increased by 9 per cent and the hospital admission rate rose by 10 per cent. These percentages were much larger for 'drug intensive' indications such as Parkinson's disease, hypertension, asthma, ulcers and cancer (Schulenburg 1994).

This policy again highlights the possibility of cost shifting between sectors when cost containment measures are implemented, and it reinforces the need for initiatives to encourage cost effective prescribing, taking account of patient benefits and a broad range of costs, rather than simply cost cutting in one area of the health care budget. However, the initiative does demonstrate "the ease of controlling drug costs by forcing physicians to work within a national drug budget, with personal financial penalties for failure to stay within that budget" (Lasagna 1994).

In France, action to curb healthcare expenditure has been implemented at the level of the physician through a national contract, from a bill enacted in January 1993. This introduced National Medical Guidelines for doctors with respect to diagnosis and treatments, including antibiotic prescriptions, NSAID prescriptions, medication for elderly patients, surveillance of oral contraceptives and other health areas (Pelc & Castan 1994). 147 guidelines are currently in force, covering a total of 47 areas of medicine, and approximately 12 of these relate to the prescribing of pharmaceuticals. Surveys indicate that 75 per cent of French doctors are abiding by the new treatment guidelines (Scrip 10 March 1995). 17 doctors are to be fined for repeatedly failing to observe the treatment guidelines in 1994, with a maximum fine of Fr 15,000 (\$3,000) (Scrip 14 March 1995).

The use of guidelines to inform professional behaviour, including the cost-effectiveness of prescribing is also taking place in other countries, for example the Agency for Health Care Policy and Research guidelines released by the US Department of Health and Human Resources, and the Effective Health Care Bulletins commissioned by the Department of Health (e.g. on the treatment of depression, EHC 1993). However, in most cases these are only advisory, whereas the French guidelines are more binding, with fines for non-compliance.

There have been a number of attempts to influence prescribing through behavioural interventions aimed directly at doctors or other relevant health professionals. In a recent rigorous review of this literature, Soumerai et al (1990) concluded that it was possible to influence prescribing through a variety of means (most notably the use of educational outreach visits modelled on the activities of drug reps), but the effects of such interventions are likely to be small (Soumerai et al. 1990). An overview of 91 attempts to increase the uptake of clinical practice guidelines found that changes in practice almost never led to changes in practice over 30 per cent measured in natural units (Effective Health Care 1994). Although it is likely that such behavioural approaches may contribute to policies encouraging the cost effective use of pharmaceuticals, they may not represent solutions in themselves, and the cost effectiveness of such interventions in the UK remains to be established. Advice in itself is unlikely to be a cost-effective method of changing professional behaviour, and regulation is likely to be required. This must be designed and implemented to include effectiveness and cost effectiveness, not simply cost containment.

### **3. Impact of policy initiatives on innovation, research and development**

The pharmaceutical industry opposes legislation and policy initiatives to control prescribing costs on the grounds that it discourages research and development in the pharmaceutical industry and therefore restricts innovation. The market for pharmaceuticals is risky and subject to unusual forms of competitive pressure (Maynard 1993). The search for a new chemical entity has been likened to the search for a needle in

a haystack. The process is expensive and lengthy as most potential new chemical entities (NCEs) are discarded during development due to toxicity and lack of efficacy. When NCEs are brought to the market they are marketed intensively in an environment where price competition is muted and replaced by 'quality competition' which emphasises the apparent therapeutic merits of the product. The market requires regulation to encourage research and development and the control of marketing and costs of drugs sold. This forms the justification for patent protection to reward innovation, and schemes such as the UK Pharmaceutical Price Regulation Scheme, which effectively guarantees companies a much higher rate of return than that obtained by most companies in other areas of manufacturing.

Pharmaceutical regulations vary greatly between countries, and are changing rapidly. In the UK there is an ad hoc maze of often conflicting demand and supply side rules created by separate, apparently isolated and competing departments of government. In the UK Department of Health "the finance division (cost containment) and the medicines division (safety and efficacy) pursue policies separate from their PPRS colleagues and often, it seems, with little liaison with officials in the Department of Trade and Industry who have antitrust and balance of trade goals" (Maynard 1993). The UK Department of Health can learn from the experience of other countries in encouraging cost effective prescribing, but it would then have to reform PPRS and other regulatory mechanisms which inhibit the efficient use of pharmaceuticals.

#### **4. Conclusions: areas of agreement and controversy**

##### **4.1. Areas of agreement**

1. There has been a world wide move towards increasing regulation of the pharmaceutical industry, with demand and supply side measures aimed at controlling expenditure on pharmaceuticals. However, some of this interest appears to be at least in part rhetorical, or even contradictory.
2. There are considerable similarities in some approaches. For example, many countries use patient co-payments, and price (or profit) controls of the industry. Use of generic alternatives to branded drugs is encouraged, and this is expanding significantly. However considerable resistance to the use of generic substitution by pharmacists remains, and in any case this would do little to affect the costs of increasing use of new and patent protected drugs.
3. There is also a trend towards use of economic studies in the registration and reimbursement mechanism of new pharmaceutical products. This is a legal requirement only in Australia, but other countries have released guidelines for the economic evaluation of pharmaceuticals, and still more are encouraging firms to submit these with the overall application package.

## 4.2. Areas of controversy

1. Government policy initiatives have tended to concentrate on controlling pharmaceutical expenditure rather than encourage cost effective use of drugs. This has led to considerable debate: in Germany there may be some cost shifting to the hospital sector, and in the US, the RAND study (Newhouse et al. 1993), and Soumerai et al. (1994) showed that budgetary control led to reductions in all interventions, those that were cost effective as well as those that were not. How can policies be targeted to identify and reduce inefficient and inappropriate prescribing while encouraging that prescribing which has been demonstrated to be cost effective? Perhaps only the Australian initiative offers this potential? However, will this contain costs?
2. A number of policy initiatives have been advisory rather than including any legislative 'teeth'. A good example of this is the contrast between the Australian guidelines for the economic evaluation of pharmaceuticals and those released in the UK. In Australia guidelines have been well researched, derived with extensive consultation, piloted for a year before their formal introduction and modified according to experience with them. When introduced, they became part of the legislatively required process of reimbursement, and agencies were set up to monitor the quality of studies and infer appropriate pricing and reimbursement policies based on their results. The UK guidelines however were derived with minimal consultation, and promoted through a press release (DH 1994). There have been no attempts to promote their use, and it is not clear who, if anyone will monitor and police them (Freemantle et al. 1995).
3. There are questions regarding whether or not the methodology of economic evaluation is "ready for its enhanced status" (Drummond 1992). The quality of many studies remains poor (Udvarhelyi et al. 1993, Freemantle & Maynard 1994, Mason & Drummond 1995), despite acceptance of agreed standards in economic evaluation (e.g. Drummond et al. 1988). The practice of economic evaluation must be improved if attempts to link prescribing and cost effectiveness (such as the Australian and Canadian guidelines) can be implemented and maintained.

## 4.3. Overview

In most countries expenditure on pharmaceuticals is high and continues to grow rapidly. The evidence base, in terms of both effectiveness and cost effectiveness, is generally poor and merits careful appraisal. Such appraisal will identify under-use of drugs (e.g. the prophylactic use of antibiotics in caesarean section) and over-use (e.g. the rapid growth in the use of SSRIs such as Prozac despite their uncertain cost effectiveness). Global budgets (cash limits) in Germany appear to have reduced drug expenditure at least in the short term (the law expires at the end of 1995) but it is unclear whether the reduced activity is equal

across drugs which are cost effective and those which are not. Similar uncertainty is evident with most other policies: the effects may be short term and of undemonstrated efficiency due to lack of systematic evaluation. This may be the purpose of policy: most interventions are to mitigate short term cash crises, do so and then are rescinded and/or overwhelmed by consumer and producer perversity. If the long term aim is to target scarce resources to produce health, economic evaluation, though difficult and sometimes flawed, is unavoidable. Williams' advice from over 20 years ago should now be followed:

'In contemplating cost benefit analysis, I prefer the philosophy embodied in the answer Maurice Chevalier is alleged to have given to an interviewer who asked him how he viewed old age: "Well, there is quite a lot wrong with it, but it isn't so bad when you consider the alternative", (Williams 1972 p224)

Economic evaluation, carried out in a principled and thorough fashion, may be better than the alternative policies outlined here, and may be the only way to get to the 'heaven' of economic efficiency in health care.

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## **Cost-Effective Prescribing - Is there only one way to heaven?**

### **Discussion**

#### **Allan Detsky (chair)**

In Ontario a committee advises the Ministry for Health about reimbursement for out-patient pharmaceuticals, there is a formulary, and everybody who is over 65 or on social assistance (35-40% of the market) receives free drugs. Also, if a household spends more than 4.5% of their gross income on drugs they receive them free, removing price constraints for about half of the market. In the past, this committee has typically put anything that is safe and effective on the formulary. In 1991, I was asked to inject some modern economic thought into the pharmaceutical formulary. In response to this, a set of guidelines was drafted in 1991 and widely distributed across the industry, academics and other interested parties throughout the world. Useful comments were incorporated into the guidelines.

At this time there were discussions in Canada regarding whether these guidelines should be implemented nationally or provincially. There is no national formulary in Canada and health is a provincial responsibility. This debate led to two years of delay, during which the industry objected to the guidelines on the grounds that more requirements inhibited development of new drugs. The most powerful argument against this is the alternative: a simple comparison of unit prices. For example, a new product such as Imigran costs \$14 per tablet in Canada, compared to paracetamol at 20c a tablet. If the nature of an economic argument is simply a comparison of unit prices, new products will lose every time, and no expensive new drugs will be reimbursed. Old, generic old products will always be cheaper, and companies must therefore present value for money in a logical way. This should incorporate cost savings elsewhere in the health care system, reductions in morbidity and mortality, indirect benefits, cost of monitoring, and, most importantly, the denominator - incremental effectiveness. Unit price comparisons are in the formulary now, and the guidelines (not regulations) simply tell companies what information large third party payers want to convince them to buy the product. Marketing pharmaceutical products in Canada in 1990s is not about marketing to physicians in an agency relationship with patients, but marketing to the large third party payers who are making decisions to purchase the new drugs.

The Ontario guidelines are relatively broad and permissive, and they acknowledge the problems of the 'science' of measurement but they move beyond a simple unit price comparison. The two year delay was helpful in convincing companies of this. Arbitrary restrictions (e.g. expenditure caps) do restrict new innovatory products and procedures. These decision rules can maintain ineffective and unproven procedures while excluding cost effective new procedures.

Companies receive a subsidy for investment in research, and a patent (17 years in Canada). The consumer is largely removed from price sensitivity - in Ontario no consumers pay for their drugs out of pocket. This is very far from the free market, and regulations attempt to simulate the free market, because of issues of social equity and health as a merit good. Incentives work, but free market incentives are completely removed from health care, and need to be replaced. The pharmaceutical market is distorted, and information is required beyond unit price comparisons to support the use of products that are effective and efficient, and to get rid of anything else.

### **David Henry**

The 'closed door' policy in the Australian process of review of economic evidence is not the choice of the regulatory authority. This is insisted upon by the pharmaceutical industry - everything in the process is marked 'commercial in confidence', even if it is made up of published papers.

There is a strong case for a central regulatory decision that sets prices, and bases prices on the performance of the drug. It is ludicrous to set prices on anything other than how good the drug is, and other systems produce distortions in pricing that creates an industry trying to correct it. Without price setting based on performance, drugs that are the same on the basis of performance, with 2, 3, or 4 fold differences in prices. Activity is then required to encourage doctors not to use these expensive drugs, and spending money to prevent it. If a company cannot demonstrate superiority it should not get a higher price. Other agencies can then deal with more central issues - the decision to prescribe cimetidine or ranitidine is unimportant, whereas the total level of H<sub>2</sub> antagonist use is a reasonable question. This is highlighted in the UK Audit Commission report, where many of the potential savings suggested in the report could not be realised (and would not be necessary) under a system where price setting based upon performance of drugs had been applied. A strong central price setting mechanism should be based on a careful assessment of the relative performance of the products, and after that it is possible to deal with the real issues of who best should receive these drugs and how they should be used.

### **Jeremy Grimshaw**

Alan Maynard's paper summarising the various approaches of promoting cost-effective prescribing appears to favour central regulatory and financial interventions. Whilst these

strategies are likely to be a powerful way of ensuring that newly registered drugs are cost-effective, they do not address a number of key issues suggesting they will be insufficient by themselves to ensure cost effective prescribing. These issues relate to:

1. Pre-registered products - there are many pre-registered products available which may not be cost-effective. The relatively slow change in professionals' prescribing practices suggests that there would be a considerable lag in the uptake of products registered using cost-effectiveness criteria.
2. Proprietary vs generic prescribing - in most cases, generic drug substitution would improve the cost-effectiveness of prescribing.
3. Acts of omission - cost-effective prescribing can only occur when cost-effective medicines are prescribed appropriately. There are many examples where failure to prescribe may limit cost-effective prescribing. For example, in the management of depression, there is considerable evidence of under diagnosis and under treatment of depression leading to some patients not receiving treatment or inadequate dosages or inadequate lengths of treatment. Thus strategies to promote cost-effective prescribing should address acts of prescribing omission.
4. Therapeutic drift - cost-effectiveness registration policies can be undermined if registered drugs are prescribed for indications other than those for which they were registered or in different dosages or for different patient groups.
5. Entrepreneurial skills of pharmaceutical companies - pharmaceutical companies have a vested interest in ensuring that their drugs are registered and prescribed. Whilst working within a regulatory structure, pharmaceutical companies will use their considerable entrepreneurial skills to promote prescription of their products irrespective of cost-effectiveness issues.

Professional behavioural change strategies are required to overcome these threats to cost-effective prescribing. A variety of strategies have been used or proposed to promote appropriate prescribing behaviour (including drug formularies, audit and feedback, educational outreach visits, local opinion leaders, reminders and anti-marketing). In the United Kingdom, the main approaches adopted have been drug formularies and audit and feedback (involving feedback of PACT data to general practitioners). However, there is little rigorous evidence on the effectiveness of drug formularies to promote cost-effective prescribing and only limited evidence of the effectiveness of audit and feedback in fields other than prescribing. Other strategies which have been rigorously evaluated in North America including the use of educational outreach visits and reminder systems have not been evaluated or widely adopted in the United Kingdom. Despite the considerable resources spent on the drug budget surprisingly little research has rigorously evaluated interventions to promote cost-effective prescribing.

In summary, there are many ways to heaven: a variety of approaches are required to promote cost-effective prescribing, including regulatory, financial and professional behavioural change strategies. Within the United Kingdom, further research is required to determine the relative effectiveness of these different strategies.

### **Martin Backhouse**

Maynard's paper was intended to describe and evaluate models for the UK NHS which link information about cost-effectiveness with prescribing decisions. However his approach mainly involves a description of some aspects of regulatory policies in place in selected European countries, North America and Australia. The policies reviewed are castigated as either 'crude', 'unrefined' or 'conflicting' cost-containment tools which allegedly do not encourage economic efficiency in prescribing. One exception to criticism is the Australian national reimbursement process which mandates cost-effectiveness data. Maynard clearly holds the Australian model as exemplary no doubt because it has 'legislative teeth'. Thus the proposition for the UK appears to be that the existing regulatory policies (in particular the PPRS system) should be overhauled. Apparently a prominent feature of reform would be a mandatory requirement for economic evaluation, presumably along the lines of the Australian model.

Few would disagree with the proposition that the focus of policy - and incentive - mechanisms should be on economic efficiency rather than cost containment. However, whilst the paper provides a useful (yet highly selective) starting contribution to the debate about alternative models for efficient prescribing in the NHS, it is somewhat sparse in a number of critical areas which clearly require further research. Firstly, little empirical evidence is provided to support the contention that existing mechanisms do in fact lead to inefficient prescribing decisions, and if so on what scale. Secondly, alternative non-regulatory models, such as the possibilities within the NHS internal market with decentralised budgetary and prescribing responsibilities, are (perhaps conveniently) largely ignored. This implies that a centralised mandatory requirement for economic data for new medicines is the single most effective route to cost-effective prescribing. Thirdly, the scope of the paper is confined to medicines (which is understandable given the theme of the symposium) although we should not overlook the question whether subjecting medicines to a level of formal evaluative scrutiny not being applied elsewhere is the most cost-effective use of scarce health research resources. Fourthly, the content of the Australian, Canadian and UK DoH & ABPI economic evaluation guidelines are not subjected to comparative critical appraisal. For example, Maynard does not discuss whether he agrees with the Australians' puzzling (to economists) discouragement of cost-benefit analysis. Lastly, no practical recommendations are presented on how the process of 'reform' should proceed on matters such as further research required, how the possible models for cost-effective prescribing should be identified and what criteria should be used for appraising them.

A number of factors are critical to the achievement of cost-effective prescribing. Firstly, robust methods of economic evaluation are needed. However, the paper presented by Drummond suggests that the methodological foundations are probably not yet firm enough to build new regulatory mechanisms upon them, as favoured by Maynard. Secondly, incentive mechanisms will need to be established which encourage efficient (and deter inefficient) prescribing practices. Even if the case for a regulatory approach was accepted as a necessary condition for cost-effective prescribing (and it is currently a weak case) it would probably not be sufficient. Thirdly, explicit thresholds of 'acceptable' levels of cost-effectiveness are required to guide decision-making. These have proved elusive to economists. Fourthly, thorough and objective research is required into all possible models to achieve cost-effective prescribing (not just regulation of the pharmaceutical industry). Finally the agenda for achieving efficiency in the NHS should be broadened to ensure that research effort is directed towards those aspects of health care provision where there are greatest potential efficiency gains to be made.

### **Peter Clappison**

This paper responds to some of the points made in Maynard's paper about a number of UK Government policies.

#### *DH economic evaluation guidelines, May 1994*

These guidelines were not, and are not, meant to have anything whatever to do with with licensing or pricing. Maynard may believe that they should, but that is not our policy. The guidelines:

- aim is to provide a basis for high quality information from the companies to the doctors (or whoever makes a prescribing decision). That information can guide the choice of drug, but the choice rests with the doctor;
- are for use by the companies, to provide a standard for their studies to achieve.

The resulting studies will be collated and held at the new NHS Centre for Reviews and Dissemination set up in 1994, at York University, which will only accept those which do achieve the standard set. Those which do will have a cachet and prestige in the eyes of doctors which others will lack; to talk of 'policing' the guidelines is quite misplaced. As they are not meant to be a requirement for either licensing or pricing decisions the need to 'police' them does not arise. The NHS Centre for Reviews and Dissemination will maintain standards.

The guidelines were discussed in a joint industry-government working party. That was appropriate for what are not legal requirements. But they could certainly be amended and

improved if new ideas such as those of Maynard are put forward - but would such ideas be to improve the achievement of the current objective, or to propose a radically different objective?

Certainly the Department of Health does take health economic evaluation seriously. For example *Economic Analysis Alongside Controlled Trials*, written by Drummond, was published by the Department in 1994 - and a reprint of 5,000 copies has recently been ordered.

#### *The Pharmaceutical Price Regulation Scheme*

The 17-21% rate of return on historic capital permitted in PPRS was negotiated in the light of the average profitability of all UK industry. There is also a 'margin of tolerance' for additional profits of an extra 25%, matched by a parallel threshold that price increases may not be awarded until a company is over 25% below target.

If sales are below the projected level which would give the target level of return, the allowable working capital on which the profit margin is calculated is also reduced. When even after such adjustments profits fall below the tolerance or grey area, price rises will by no means be automatically granted and with increasing cost consciousness among GPs might not be in the company's best interests.

There is also the current price cut of 2.5% for three years, which effectively reduces the present levels of return on capital by over 2 percentage points: this recognises the lower levels of general industry profits in 1993.

It is over-simplistic to argue that the PPRS "reduces the incentive to contain costs". The PPRS includes a commitment by the industry to cost reduction where possible, which DH negotiators use as the basis for rigorous examination and challenges to company figures, when the details are assessed and negotiated. The industry certainly does not like that, and does not feel that it gets an easy ride.

Therefore to suggest that the PPRS negates other government policies is to misunderstand how things work. In the application of the PPRS, we seek to ensure that we do not undermine other policies. That was made explicitly clear to the industry in the 1993 PPRS settlement.

It is indeed true that all UK policies need to be considered as a whole, rather than separating demand and supply side policies. The short answer is that there are, of course, discussions between different parts of DH to examine the interaction of the PPRS with other policies. We have realised the need to do so! Just as we have recognised that one policy alone on the drugs bill would be insufficient, and that a package of supply and demand side policies is needed.

Linking profit returns to some form of cost effectiveness score begs a lot of questions about how to make such judgements, the costs of running such a system, and the broader picture.

### *Other Issues*

To illustrate what I mean by the ‘broader picture’, consider the Australian guidelines for the reimbursement of pharmaceuticals, which Maynard finds attractive. There is within them an element of compromising the clinical freedom of doctors if drugs are not marketed, or if doctors are told what not to prescribe. There are also industry points to consider.

The Australian initiative has had substantial effects on international drug companies. It has led some to be reluctant to invest there, and the approach discourages new R & D - because companies are reluctant to invest in a project when there is an additional hurdle on top of all the other uncertainties of drug development. It is accepted that it is usually not possible to predict at the start of a R & D project whether it will work, even less so whether it will be a major advance on existing therapies. The UK has a valuable pharmaceutical industry, with a balance of trade surplus of nearly £1.5 billion, and nearly 80,000 skilled jobs. Not things to be lost lightly.

Underlying all these thoughts is the fact that it is always possible to seek to cut drug costs and make present health services cheaper or more efficient. But lower prices mean lower profits to pay for future R & D. A balance has to be struck between good prices for the NHS and supporting an industry capable of developing new or improved drugs. Where should that balance be struck? How much importance should be given to R & D? Isn't the ability to provide better drugs in the future also part of overall cost-effectiveness? Especially so when it has been argued that too many government policies (world-wide) are short-term and ignore the need for true cost-effectiveness?

Lastly, several times we have heard the phrase “the pharmaceutical industry opposes...”. The industry is not our enemy. New drugs are not usually found by civil servants, practising doctors or even health economists, but by the pharmaceutical companies. The industry has a role to play, and the government recognises that and seeks a partnership with it.

## **Audience discussion**

Allan Detsky described the Canadian system of three levels of listing in the registration procedure: full listing, partial listing (for a limited use, which is however unaudited and unpoliced), and a very small number of drugs for which a letter to government is required for special control of utilisation. Products can be on the market and not on the provincial formulary: patients can buy such drugs themselves. The Ontario guidelines are only for reimbursement.

David Henry commented that in Australia new drugs such as omeprazole can be restricted by a prior approval scheme, to encourage cost containment. A doctor has to supply justification for prescribing omeprazole, and only two common conditions are acceptable justification: severe ulcerative oesophagitis, endoscopically demonstrated, or peptic ulcer which has failed to heal after 12 weeks with other ulcer healing drugs. This is tightly restrictive, and was prior to the implementation of the mandatory economic evaluation guidelines.

Questions of incentives were again raised. Richard Hobbs pointed out that incentives, e.g. indicative prescribing/fundholding scheme - are monetary incentives to practices to improve patient care and not to the back pockets of GPs. One GP stated that these incentives illustrate UK government policies working one against another. The policy of shifting GP remuneration on to a capitation basis gives a clear emphasis being that you are rewarded for having more patients on your list. This also means you have to keep patients satisfied and gives a clear incentive to try and meet patient expectations (including prescribing omeprazole if this is desired).

Another delegate suggested that this presumes that the patient expectation is to receive a prescription, whereas good research has shown that this perception is flawed, and that patients do not necessarily want this.

Andrew Herxheimer supported Detsky in the suggestion that users want information in the way that they are going to use it, and that companies should provide this. This has been demanded in clinical trials for some time and is now required evaluations. The companies that understand this shared need for information will benefit. At present we are moving (too slowly) from a research agenda driven by independent marketing of companies to a shared research agenda between users and manufacturers of drugs.

Martin Backhouse questioned where decisions about cost effectiveness should be made, with price setting at the centre or a decentralised system? In Australia a central price setting mechanism was in place, and it made sense to look at economic effectiveness as well as international comparisons. In Canada there is also central price setting, but a local decision whether or not to reimburse drugs. This can influence prices, and there is some negotiation. Information should be directed at the people who make key decisions. The issue in the UK is therefore whether the NHS internal market, which is essentially devolving budgets and decision making, is the appropriate model. Should the decision maker be a GP fundholder, should it be the Department of Health formulary committee - how should it be organised. In a centralised pricing system doctors are then free to prescribe as they like, whereas in the UK policies are trying to link price and utilisation decisions by giving a budget to the person who has to make that decision. We have to be clear that centralised price setting may have benefits (and costs), but is not a panacea, because problems of utilisation may remain.



### **Cost Effective Prescribing: is there only one way to heaven? Key Points**

- UK attempts to link prescribing decisions with cost information have been considerable, but the drugs bill has grown rapidly. UK policy-makers may learn from other countries' experience of policy initiatives to improve prescribing;
- The goal of initiatives is not to minimise cost but to increase efficiency of prescribing, despite a policy focus on cost containment rather than efficiency;
- Registration procedures for drugs are broadly similar in most countries, but some have positive lists for reimbursement. The reimbursement procedure can incorporate economic data and evidence of cost-effectiveness, as is legally required in Australia. Australia and Canada have been at the forefront of development of guidelines for the economic evaluation of pharmaceuticals. UK guidelines have been provided but without attempts to promote actively their use, and they have no link with registration;
- Price regulation is used to control drug expenditure in a number of countries, particularly reference pricing systems where the prices of comparable products guide the price for a new product. Price regulation may not encourage cost effectiveness, although reference pricing can begin to do this by allowing a premium price only with evidence of therapeutic benefit;
- The UK pharmaceutical price regulation scheme (PPRS) regulates prices indirectly through monitoring profits. However, the 17-21 per cent allowable rate of return may result in perverse incentives, lessening incentives for companies to control costs and at least partially negating Department of Health cost containment measures and undermining cost effectiveness;
- Co-payments and prescription charges influence patient demand for pharmaceuticals. However, these reduce utilisation of all drugs, including those that are cost-effective, and may be viewed as a regressive tax on sick people;
- Policies to influence doctors' prescribing behaviour have also been introduced in a number of countries. In Germany, budgetary restrictions considerably reduced expenditure. In France, national guidelines have been introduced, some relating to prescribing;
- Pharmaceutical regulations vary greatly between countries and are changing rapidly, but tend to not only regulate health care expenditure but also encourage innovation, research and development in the industry. Health policy and industrial policy may conflict, in the UK a valuable pharmaceutical industry exists;
- Lack of systematic evaluation of policies may result from short term policy goals. If the long term aim of improving prescribing is to target scarce resources to produce health, economic evaluation, though difficult and sometimes flawed, is unavoidable;
- There is a strong case for a central regulatory decision that sets prices based on the performance of drugs. However, this may not be sufficient in itself to ensure cost effective prescribing because of existing products and particularly because of potential problems of utilisation

## Chapter 5 Overview

Martin Buxton

It is important to remind ourselves why we are focusing on prescribing. From the amount of policy attention devoted to prescribing, it would be reasonable to presume that it is one of the biggest problems facing the NHS. In fact, prescribed pharmaceuticals account for approximately 10 per cent of NHS expenditure: an important element, but the proportion of total NHS expenditure for which they account has remained broadly the same over the past 30 years (OHE, 1995). Rather than because of the magnitude of expenditure on prescribing, it is the focus of much attention because it is easily identifiable, separately budgeted and drugs are commercially supplied. Discussion in this volume has vividly illustrated some of the ways in which the relationships between the NHS and the pharmaceutical industry are different to other relationships with the NHS. The pharmaceutical industry is already subject to a variety of regulations, and these attempt to strike a difficult balance between the sometimes conflicting objectives of regulating the industry as a major supplier to the NHS, and promoting the industry as a major employer and exporter. Given that drugs account directly only for 10 per cent of spending, we should perhaps be considering whether or not some of the issues discussed here relating to prescribing can, and should, be generalised. Indeed, one of the issues discussed in this symposium has been whether we want to focus simply on the prescribing of drugs, or whether it is more appropriate to focus on the broader issues of patient management, within which prescribing is but one factor.

I would like to highlight four statements, one from each of the main papers, that seem to me to be key elements in the debate.

First, Drummond suggests that “it may be best to view many of the current economic evaluations of drugs as preliminary assessments.” This highlights the issue of the evidence available for, and the timing of, economic evaluation. Sometimes it is implied that an imperfect initial exercise in economic evaluation, based on short-term measures of clinical efficacy from a phase III clinical trial perhaps with some modelling of the longer-term implications, and a systematic review and meta-analysis of a series of long-term pragmatic trials, are alternatives, between which choices have to be made. Clearly they are not alternatives, because they relate to quite different time frames. The latter ideal will never be available at, or near to, the time of the launch of a new drug. But this is not a problem introduced by the desire to consider economic factors. David Henry noted that the problem in the operation of the Australian guidelines has tended to be the poor quality of the underlying clinical evidence rather than worries about the economic analysis. The timely availability of appropriate data is a problem which cannot be avoided.

Russell stated that “clinical guidelines require scientific validity, practical effectiveness and professional confidence.” This encapsulates the complexity of turning evidence into

advice that doctors are likely to follow, and there has been much discussion of the best ways to present information and influence behaviour. Good guidelines require more than simply good science.

Walley argued that “most of the initiatives focusing on GPs tend to focus on the choice of therapy, rather than the more important choice of whether to prescribe at all.” This emphasises again that the choice between alternative drugs is but a small part of the broader question of appropriate patient management, but as yet most economic studies have simply looked at ‘head to head’ comparisons of drugs.

Finally, Maynard noted “there has been widespread discussion of cost controls, but much less progress in increasing the efficiency of drug use.” This distinction between cost-saving measures, and measures that increase cost-effectiveness is one that is still too often ignored. Maynard’s comments raise the question as to which of the two in reality is the more pressing policy objective. Unfortunately, but perhaps inevitably, constraints and incentives still focus too much on cost-saving and too little on increasing effectiveness within a given budget.

These four quotations highlight some of the many important issues which were discussed at the symposium and the very lively discussion reflected some rather different reactions to the papers from the audience, drawn from a wide variety of relevant backgrounds. What important conclusions emerged?

One was a plea for realism. It was suggested that commissioning agencies want a broad understanding of whether investment in new technology is worthwhile, rather than precise estimates of cost-effectiveness. Certainly, a local commissioner for acute care, in response to a discussion of meta-analysis and related techniques, suggested to me recently that commissioners do not expect to be 95% confident that they are doing the right thing. “Generally, if a decision is based on better than even odds, it is better than many I will have to make.” We need to continually bear in mind whether the information is better than what would otherwise be available, rather than whether it is perfect.

We need to remember the potential conflict between individual and social interests. Effectiveness is about individual patient outcomes, as has been echoed a number of times. There is clear friction in the system being created in the UK. Patient choice is being encouraged, but patients may have different perspectives on what they consider to be effective and certainly their perspective of cost-effectiveness, given that they do not pay the full cost of treatment or of drugs, may be at odds with what is cost-effective for the NHS as a whole, or even for a group of patients.

The concern that physicians are being left to make both policy rules on behalf of society and specific decisions on behalf of individual patients, leads to the issue of how to improve public understanding and how to involve the public in a meaningful debate. UK policy-

makers have tended to be very reluctant to do this, and tend to stifle public debates as soon as they are opened-up. Although a number of specific, well-publicised cases have provided the potential opportunity for an intelligent public debate about rationing issues, health authorities and hospital providers have tended to avoid this. In particular, they tend to fudge the issue as to what should be done when treatment may potentially be marginally effective for the individual, but is unlikely to be cost-effective for society.

Discussion often came back to the question of the most appropriate target for cost-effectiveness information and its usefulness at the 'coal-face' of medicine. Should cost-effectiveness information be directed at the individual prescriber? It may well be that prescribers are not seeking this kind of information and cannot reasonably be expected to make appropriate use of it. Economists tend to forget how off-putting economists' language can be. Information to GPs must be accessible, understandable, and relevant. More fundamentally, if even an economically-sophisticated audience, such as was represented at this symposium, find it difficult to interpret the implications of some economic evaluations and continually stress the need to interpret cost-effectiveness data very cautiously, can we expect individual GPs to make good use of it?

With any system of incentives and regulations to promote public policy objectives, there needs to be transparency. Some of the discussion reflected the lack of transparency regarding many of the detailed incentives influencing GPs, and particularly the opaqueness of the workings of the PPRS. The Department of Health's formal restatement that it does all make sense and it is straightforward once you understood it, may still leave a public credibility gap when there are so few people who understand it. It is not a good advertisement for a major element of regulation when the relevant minister clearly indicates in public, in front of a parliamentary committee, that he doesn't understand it either! (Health Select Committee, 1994)

Where does responsibility for good or cost-effective prescribing or treatment lie? A large number of bodies have been mentioned as having a role, and the situation becomes potentially quite complex. Discussion in this volume has centred around two extreme models:

**The regulator focused model.** This centralised model focuses on national (or provincial) decisions relating to the funding, reimbursement or inclusion on limited lists of specific pharmaceuticals. It has the advantage that decisions can be based on cost-effectiveness data, taking account of all relevant costs. Decision-makers can subject the data to rigorous analysis to test the validity of the cost-effectiveness claims, and can reasonably be expected to use the evidence intelligently. The Australian and Canadian systems exemplify this model. Typically in this model, the system produces a central blanket decision, although the Australian system incorporates some subtleties. The system is relatively easy to enforce, but actually it gives no encouragement to the prescriber to

consider costs or cost-effectiveness. Indeed this model may effectively discourage such considerations by the prescriber: once a product has demonstrated its cost-effectiveness, jumped the hurdle and obtained a seal of approval, it may seem inappropriate and may be difficult to justify not using the product on grounds of its relative cost-effectiveness in particular situations. This model therefore does very little to ensure appropriate use of reimbursed pharmaceuticals.

**The prescriber orientated model.** This points in the direction of prescribing based on guidelines, which can be locally owned, and fine-tuned to local circumstances. These guidelines can encourage the selective use of new drugs, but are not restricted to the choice of drug, and can consider a variety of issues about when to start, how to monitor, when to change, when to stop. However, building in cost to these decisions becomes constrained by the inevitably arbitrary budgetary boundaries that exist in any health-care system. In addition, there may be problems of how well doctors' practice will conform to guidelines. The evidence suggests that guidelines can work, but alone they do not work particularly well.

At present the policy emphasis in the UK is firmly on the prescriber orientated model. Of course, it may be artificial to regard these models as necessarily separate. A system of regulation, information and incentives combining characteristics of the two models, with the better attributes of both, would be attractive. However, the appropriate combination is unknown. The following research agenda may assist formulation of such a system:

1. Whilst there has been much discussion of the guidelines in Australia and Ontario, there now needs to be a formal analysis of their impact. This assessment could then inform UK policy.
2. There is concern about whether false judgements are made by economic evaluations carried out at an early stage of product development. It is important to examine the historical evidence, and establish to what extent initial cost-effectiveness views, based on the limited data available close to launch, have subsequently been changed radically, or should have been changed, in the light of later evidence. This would give some indication of the value, or danger, of these 'preliminary assessments'.
3. It would be useful to look at how much GP prescribing is inappropriate when compared to good existing cost-effectiveness evidence. This would give an indication of the size of the problem of non-use of economic evidence. Is it the case that the evidence is simply not there, or is available evidence not being used?
4. There are a number of issues about how best to communicate cost-effectiveness information to GPs. A careful examination of how the pharmaceutical industry approaches communication could provide some useful ideas - the feeling is that the industry is rather good at conveying its messages.

5. We need to consider how far we can get with simple cost-minimisation. It is uncontroversial to adopt an intervention that offers lower cost with equal or greater benefit. If there are many instances when that is not happening, then a major opportunity exists. Of course, this may not be as intellectually challenging to economists as grappling with ways of meaningfully handling the situations where extra benefit is obtained at extra cost.
6. Where opportunities to reduce cost at no loss of benefit do not exist, the only way that something new, that has an attractive incremental cost-effectiveness ratio, can be introduced into the NHS within an essentially fixed budget, is if something can be removed from the system that has a less attractive cost-effectiveness ratio. Where evidence is good, and it is politically possible to reduce services, such circumstances must be highlighted. The concept of an acceptable maximum incremental cost-effectiveness ratio (how much we are prepared to pay for a life year or a QALY gained) must depend on how much are we currently paying that we could save to transfer the resources to a more attractive alternative. Much greater debate about this is required at a number of different levels.
7. Finally, the emphasis of economic evaluations should be switched from 'either/or' 'head to head' comparisons of drugs, to broader issues of good prescribing and appropriate patient management protocols. Only with such broader focuses can we hope to begin to persuade prescribers that cost-effectiveness information, rather than being simply another set of factors they need to juggle, can be integrated into guidelines that can genuinely aid them in their decisions about patient management. This implies a major investment in cross-disciplinary collaborative research.

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