RESEARCH NOTE

Use of pharmacoeconomics in prescribing research. Part 1: costs – moving beyond the acquisition price for drugs

J. Robertson BPharm MMedSc PhD, D. Lang BMath BEc PostgradDipHlthEcEv and S. Hill BMed PhD FAFPHM
Clinical Pharmacology, School of Medical Practice and Population Health, Faculty of Health, University of Newcastle, NSW Australia

SUMMARY

This paper addresses pharmacoeconomics in prescribing research and reflects the increasing use of techniques of economic evaluation to aid drug purchasing decisions in a variety of settings – for national drug subsidization programmes, provincial purchasing plans, insurance programmes, and for hospital and area health authority formulary decisions. First, we focus on the cost component of an economic evaluation and discuss methodological issues that are relevant to all pharmacoeconomic analyses.

Keywords: economic evaluation, pharmacoeconomics

INTRODUCTION

Key messages

• Drug cost is more than its acquisition price.
• Perspective of the analysis determines the range of costs included.
• Costing is a three step process.
  – Identification of costs to be included.
  – Measuring the number of units of each resource used.
  – Assigning a value to each item or resource.
• When comparing treatments only differences in resources used are important.
• Uncertainties in cost estimates should be explored in sensitivity analysis.

The term pharmacoeconomics implies the application of economic principles to the evaluation of pharmaceuticals. However, assessing the clinical data is the first part of an economic evaluation and judgements about the role of new and existing drug therapies will often be based primarily on the clinical evidence of benefits and harms. But, in an environment where new drugs often represent ‘me too’ drugs or modest advances on existing therapies rather than true ‘breakthrough’ drugs, the addition of cost data can help inform decision making. The question can be framed as, ‘Is it worth spending an additional $x or £y to achieve the additional benefits offered by the new drug compared with existing therapy?’ Where there are no additional benefits, an explicit consideration of costs can help determine an appropriate price to pay for a new therapy. It is important to recognize, however, that the decision to purchase a drug will often be based on more than economic information – it will be influenced by social values, ethical and political considerations as well (1).

Subsequently, we will address issues of the conduct and interpretation of different types of economic evaluations including cost-minimization, cost-effectiveness and cost-utility analyses, all of which relate costs to consequences or benefits. Here, we explicitly consider only the cost part of an analysis and focus on the need to move beyond simply a consideration of the acquisition price of a drug. As the analysis of comparative costs of alternative treatments is common to all forms of economic evaluation, the methodological issues discussed here will be relevant to all types of pharmacoeconomic analyses.
Cost vs. price

In economic terms, costs are a measure of the resources used or consumed in the production or delivery of a good or service (2). Hence by implication, resources used in one way are no longer available to be used in another, i.e. there is an opportunity cost of committing to the purchase of the product (3). Price is what is paid for the good or service. It relates to costs but will include profit margins and taxes, and in the case of pharmaceuticals, costs of drug research and development, patents, wholesaler fees, dispensing fees, container costs and the like. Out-of-pocket expenses to the patient may only be a small part of the price where there are national drug subsidization or insurance programmes in place.

Perspective

How much a drug costs depends on your point of view. From a patient’s perspective out-of-pocket expenses are the costs; to a hospital pharmacy department it may be wholesale drug purchase prices; to a national drug subsidy programme it may be the costs of drugs (including containers) plus professional dispensing fees minus any patient contributions via prescription charges; and to a national health programme it may be the costs of the drug, the costs of appropriate monitoring of therapy minus the savings in a reduced number of health outcomes that would incur costs. From a societal perspective, there may be additional considerations – the costs to carers, time lost from work due to treatment, illness or death, and travel costs to attend clinics or general practitioners.

What should be the perspective of a pharmacoeconomic analysis? A societal perspective is the most comprehensive, as it includes all costs and benefits irrespective of who pays and who benefits (4), but often more limited perspectives are adopted. The important point is that the perspective of the analysis needs to be clearly stated. The perspective determines the range of costs (resources used) that needs to be considered. In the economic evaluations presented to the Australian Pharmaceutical Benefits Advisory Committee (PBAC), submissions are required to adopt a societal perspective; however, sponsors are also asked to consider the financial implications to the Pharmaceutical Benefits Scheme (PBS) – the narrower perspective of a drug subsidization programme (5). The National Institute for Clinical Excellence (NICE) Guidance recommends that the clinical and health-related benefits are valued from the perspective of the National Health Service and Personal Social Services (PSS) decision-maker (6).

Boundary of an analysis

What happens if the use of a drug prolongs life? Should the costs associated with diseases that may develop later on in this extended life span be included? Usually costs and benefits are limited to the condition being treated, costs not associated with the underlying condition are excluded. This defines the boundary of the analysis. The time span or time horizon of the analysis should cover the time period over which the main health care effects and resource use occur (6).

Classifying costs

Traditionally, costs have been categorized as direct, indirect and intangible costs (7). Direct costs are those associated directly with the delivery of medical care. Indirect costs are those associated with lost production capacity, e.g. time lost from work due to illness or death. The arguments for and against the inclusion of indirect costs and the different methods available to assign a value to these costs is beyond the scope of this paper – for further details see References (8) and (9). Difficulties in the measurement and valuation of indirect costs have led the Australian PBAC Guidelines to recommend exclusion of indirect costs (5). If these are included in an economic evaluation, they need to be documented separately, so that the impact of their inclusion can be clearly assessed. NICE adopts a similar approach (6). Intangible costs are those associated with pain and suffering and are the most difficult to quantify and value, although these will be incorporated to some extent in the utilities assigned to disease states which reflect quality of life.

More recently, an alternative costing terminology has been proposed (7). Costs may be classified as health care sector costs (resources used in providing initial and continuing care), patient and family sector costs (out-of-pocket expenses, costs
associated with seeking care, time lost by patient and family), and other sector costs (e.g. home care and volunteer services). To date, this revised terminology has not been widely used in the literature.

Costs may have fixed and variable components. This is particularly relevant for hospitals, where overhead and capital costs are incurred regardless of the number of patients being treated. Although these are important to the overall hospital budget, they do not reflect the marginal cost of treating an additional patient. There are a number of approaches for determining and apportioning these fixed and variable costs across departments or programmes (10). However, for most pharmacoeconomic evaluations, treatments are being compared, e.g. two competing drug therapies, or new drug vs. standard medical care. In these circumstances, many of the costs will be similar in the two treatment options and can be ignored – it is the differences in costs that are relevant in assessing the merits of the competing therapies. Conceivably, there may be a new drug that enables outpatient treatment alone and is compared with resource intensive hospital care, where a detailed consideration of hospital fixed and variable costs may seem appropriate. However, often in such cases the clinical evidence is overwhelming or on other obvious grounds the new drug is preferred and a detailed costing exercise will not be needed to establish the value of the new therapy.

**Costing**

There are three aspects to costing (10): (i) identification of the items to be included in the analysis (which will depend on the perspective of the analysis), (ii) measurement or counting the number of units of each resource used and (iii) valuation of each of these resources.

*Identification of resource use.* The range of costs (resources used) included in an economic analysis of pharmaceuticals will depend on the perspective of the analysis. Some examples of items that might be relevant are shown in Box 1.

A recent Dutch study comparing etanercept with infliximab plus methotrexate in the treatment of rheumatoid arthritis (12) adopted a societal perspective and included direct medical costs, direct non-medical costs and indirect costs (Box 2). The cost analysis was based on the assumption that there were no differences in efficacy or adverse

<table>
<thead>
<tr>
<th>Box 1. Data collection on health care utilization [adapted from Harris 1997 (11)].</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Direct medical costs</strong></td>
</tr>
<tr>
<td>Drug (and comparator)</td>
</tr>
<tr>
<td>Drug monitoring</td>
</tr>
<tr>
<td>Medical consultations</td>
</tr>
<tr>
<td>Allied health consultations</td>
</tr>
<tr>
<td>Diagnostic tests</td>
</tr>
<tr>
<td>Procedures</td>
</tr>
<tr>
<td>Management of adverse effects of therapy</td>
</tr>
<tr>
<td>Hospitalizations (related to treatment effectiveness or side-effects)</td>
</tr>
<tr>
<td>Outpatient visits</td>
</tr>
<tr>
<td>Concomitant medications</td>
</tr>
<tr>
<td>Home visits by medical, nursing, allied health staff</td>
</tr>
<tr>
<td>Ancillary costs</td>
</tr>
<tr>
<td>(nursing care, dietary or other supplements)</td>
</tr>
<tr>
<td><strong>Direct non-medical costs</strong></td>
</tr>
<tr>
<td>Travel costs (ambulance, taxi, public transport, car)</td>
</tr>
<tr>
<td>Community assistance (meals on wheels, home help services)</td>
</tr>
<tr>
<td>Palliative care</td>
</tr>
<tr>
<td><strong>Indirect costs</strong></td>
</tr>
<tr>
<td>Time lost from work for patient</td>
</tr>
<tr>
<td>Time lost from work for carer</td>
</tr>
<tr>
<td>Informal (or non-paid) caregiver costs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Box 2. Identifying resource use [Nuitjen et al. 2001 (12)].</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Direct medical costs</strong></td>
</tr>
<tr>
<td>Drug costs</td>
</tr>
<tr>
<td>Other materials (equipment for infliximab infusion)</td>
</tr>
<tr>
<td>Personnel for preparation and administration of infliximab infusion</td>
</tr>
<tr>
<td>Personnel for administration of etanercept at home (10% of patients)</td>
</tr>
<tr>
<td>Monitoring for adverse effects of methotrexate (infliximab only)</td>
</tr>
<tr>
<td><strong>Direct non-medical costs</strong></td>
</tr>
<tr>
<td>Transport costs to hospital associated with drug administration</td>
</tr>
<tr>
<td><strong>Indirect costs</strong></td>
</tr>
<tr>
<td>Production losses due to working days lost</td>
</tr>
</tbody>
</table>
effects with the treatment options and therefore no difference in health outcomes. The analysis assumed no difference in monitoring for adverse effects of etanercept and infliximab as there were no clear protocols for monitoring these agents. Indirect costs as a result of working days lost were included in the analysis, but caregiver’s time was not, as it was thought to be insignificant in this case.

Measurement of resource use. Counting how many units of resources are used sounds a simple exercise. However, it may be one of the most challenging aspects of a pharmacoeconomic evaluation. One solution proposed is the collection of data on resource use alongside clinical data in a randomized controlled trial (10). However, there are a number of limitations to this approach, mainly related to how randomized controlled trials are conducted (13, 14). Do the patients in the trial resemble likely recipients of the drug in real life? Are there protocol driven costs that would not be relevant in routine drug use, e.g. more diagnostic and monitoring tests, more aggressive treatment of outcomes identified, more adverse effects identified and investigated? An alternative is the pragmatic trial (13, 15), i.e. data collection alongside a trial that more resembles real life, with more relaxed inclusion and exclusion criteria and longer follow-up.

Often there is no option but to use existing records such as patient notes or hospital records. The accuracy and completeness of the recording in these documents may be a problem. Sometimes surveys of patients or expert opinion (medical panels who define standard patterns of care) can be used to estimate the number of doctor visits, number and type of tests performed, number and duration of hospitalizations, levels of care provided, and need for community services. Each of these sources may introduce some biases. To some extent, these potential biases may be overcome in sensitivity analyses, which explore uncertainty and are a key aspect of any pharmacoeconomic evaluation. By using a plausible range of alternative values for key variables, sensitivity analysis examines the impact of changing parameter estimates on the study conclusions. Data sources used in an evaluation must be clearly identified (6).

In the etanercept–infliximab example, there were little or no published data available on resource use, so there was extensive reliance on expert opinion (Box 3). The views of a number of medical and nursing experts were combined with final agreement at a consensus meeting. The four clinical experts also validated each step of the study (clinical assumptions, data collection and sources used). A microcosting approach was adopted, i.e. each component of resource use was estimated and a unit cost derived (10).

Valuing resource use. Valuing should be performed separately to counting resource use. This means that if the methods of health care provision and likely resource utilization are sufficiently similar, alternative values from other countries or other settings (e.g. health maintenance organizations) can be substituted in the economic analysis to provide some general guidance as to the likely local costs associated with the use of the drug therapy. The currency and year of the cost values must be stated to facilitate this.

There are a number of possible approaches to valuing resource use (16). Micro-costing involves a detailed ‘bottom up’ collection of costs, gross costing approaches allocate total budgets to hospital stays or doctor’s visits according to rules. The important point is that to make comparisons, similar costs must be applied to similar resource use in any evaluation. The solution adopted by the Australian PBAC is the development of a standard list of unit prices which should be used in economic submissions to the Committee (5). Standard cost weights for hospital-based medical services developed as part of the National AN-DRG

Box 3. Measuring resource use [Nuitjen et al. 2001 (12)].

Expert opinion – Delphi panel/face-to-face interviews with rheumatologists, nurses
Administration materials and times, health care utilization
Published and unpublished literature, policy documents
Dependence on transportation, district nurse visits, estimates of employment status and potential lost production days
costing study are available on the Web (17), as are costs for medical services (18) and pharmaceuticals (19). NICE does not recommend a single source of unit cost data, although a standard cost manual for use in submissions may be a future development (6). At present, market prices (prices actually paid for goods and services) are considered satisfactory for most NICE appraisals.

Nuitjen et al. (12) used official Dutch price tariffs and lists and a costing manual supplemented with interview data from doctors and nurses (Box 4). The friction cost method (8) was used to calculate production losses. This more conservative method of estimating production losses recognizes differences in costs of a worker by location, industry and category of worker. The currency used (Netherlands guilders) and the year for the cost values (1999) have been specified and the conversion rate to $US noted, which facilitates a quick comparison of costs with other health care settings.

Incremental costs

In the Australian system, the first part of any pharmacoeconomic evaluation focuses on the clinical evidence and determining in absolute terms any differences between the competing therapies. This provides the estimate of ‘incremental effectiveness’ for any cost-effectiveness ratio. The cost component involves the determination of the difference in costs between the two therapies. This is the incremental cost of treatment with the new therapy compared with the alternative. What goes into this calculation varies with the perspective of the analysis, but the focus is on what is different between the two therapies rather than concentrating efforts on calculating the total costs of treatment with drug A and total costs of treatment with alternative B in detail.

It is important to recognize that any ‘cost savings’ identified may be illusory and not always realized in practice. For example, where hospitals operate near capacity and there are waiting lists, ‘savings’ in reduced hospitalizations will not translate into, for example, fewer nurses required. Resources freed up will be redirected towards treating other patients who will themselves incur costs to the system. However, as a society, we are likely to value the transfer of these benefits to others in the community.

Sensitivity analysis

Sensitivity analysis is proposed as a means of systematically exploring uncertainty and examining the influence of any assumptions used in economic analyses on the study conclusions (20). Several approaches can be used. A one-way sensitivity analysis examines the impact of each variable by varying it across a range of plausible values while holding all other variables constant; multiway analysis recognizes that more than one variable is uncertain. In extreme scenario analysis, variables are set to demonstrate the best and worst case scenarios. Probabilistic sensitivity analysis uses Monte Carlo simulations, where variables are simultaneously tested across plausible ranges of values. Threshold analysis (8) involves identification of critical values of parameters that are central to decision making (e.g. increases in costs that could be tolerated, acceptable cost-effectiveness ratio). Combinations of parameter estimates that would cause the threshold to be exceeded are identified and decision-makers can judge the likelihood that these thresholds would be breached.

Nuitjen et al. (12) use both one-way sensitivity analysis and scenario analysis in their etanercept–infliximab comparison (Box 5). The scenario analyses were based on modifications to the underlying therapeutic and health care management strategies of the model. In this study, the results were very sensitive to the number of vials of infliximab used in each infusion. Overall, the base-case analysis suggested that the annual drug costs per patient were not substantially different for
etanercept compared with the infliximab plus methotrexate treatment. However, total medical costs were substantially lower for etanercept than the combination treatment because of the costs of outpatient visits for infliximab infusions and the costs associated with coadministration of methotrexate, highlighting the importance of considering more than just the acquisition costs of the two treatments. Direct non-medical costs and indirect costs had a negligible impact on the results.

**Discounting**

When costs and benefits extend over a number of years, discounting is used to reflect the fact that values from today’s perspective depend on when costs are paid and benefits accrue. In many economic analyses of drugs, discounting is not really an issue as costs are incurred and benefits gained contemporaneously over a short period of time. However, discounting can be important when there are large up-front costs and potential benefits are not realized for many years, e.g. interferon-α for hepatitis C, where discounting has little effect on costs but a substantial effect on estimated benefits [for further details see Torger-son and Raftery 1999 (21)]. Typical discount rates applied range from 3 to 6%. Other rates can be tested in sensitivity analyses. In submissions to the Australian PBAC, costs and benefits are discounted at the same rate (a 5% rate is recommended in the base-case analysis). NICE Guidance recommends discount rates of 6% for costs and 1.5% for benefits, with equal discounting of costs and benefits (6% costs, 6% benefits) and no discounting of benefits (6% costs, 0% benefits) tested in sensitivity analyses (6).

Discounting was not applied in the etanercept–infliximab study as the stated time horizon (period of resource use examined) was only 12 months.

**Assessing a published economic analysis**

A number of guidelines exist for reviewing a published economic analysis (22–24). Some of the key issues to consider from a costing perspective are shown in Box 6.

**CONCLUSION**

In this paper, we have sought to introduce the basic elements of costing and the need to move beyond simply a consideration of the acquisition price of a drug. Approaches to the identification, measurement and valuation of resource use for the cost component of a pharmacoeconomic analysis have been described and these are applicable to all types of pharmacoeconomic evaluations. The next paper in this series will explore important issues in the conduct and interpretation of a cost-minimization analysis – the simplest form of evaluation.

**REFERENCES**
