The Use of State of the Art Methods in Pharmacoeconomic Evaluations

Keith Tolley[1] and Francis Pang[2]

[1]Health Economist, Glaxo-Wellcome UK, Uxbridge
[2] Centre for Health Economics, University of York

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Correspondence: Francis Pang, Centre for Health Economics, University of York, York, YO10 5DD. E-mail: fp4@york.ac.uk or pharmacoeconomist@yahoo.com

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1. Introduction

In recent years there has been a large increase in the number of economic evaluations of pharmaceuticals, in response to increasing demands by payers, health authorities and reimbursement agencies for information on the cost-effectiveness of new and existing drugs. The majority of pharmacoeconomic evaluations have been cost-effectiveness analyses (Medical Care, 1998). Compared to cost-benefit analyses they are relatively easier to conduct, obtain data for and for the construction of economic models using decision analysis techniques. In addition, cost-effectiveness analysis (CEA) is the only technique regarded as acceptable in the key reimbursement guidelines for pharmacoeconomics produced in countries such as Australia, Canada and the UK (Commonwealth of Australia, 1992; CCOHTA, 1994; ABPI/DOH 1994).

The focus of this paper is on the sophistication of the methodology and approaches employed in recent pharmacoeconomic analyses using CEA. We have extended the review to cover cost-utility analyses (CUA) as this is considered by many to be an extension of CEA and there is much interest from researchers and decision makers in the generation of cost per QALY evidence to enable wide comparisons across different health care interventions (Loomes et al. 1989).

There are two associated questions we hoped to address. Firstly, what might be considered to be the current "state of the art" methodological and analytical approaches in CEA? "State of the art" is defined as the use of methods and approaches that go beyond established basics that might be expected in any pharmacoeconomic evaluation (such as the use of sensitivity analysis, discounting future costs). Some SOA methods may be new or innovative, some long established but rarely applied. They do not necessarily have to be highly technical methods.

Secondly, through a review of recent literature, are there signs from published studies that the SOA methods have diffused into empirical pharmacoeconomic research? To

help express how a method might evolve to become an accepted and useful technique for practical pharmacoeconomic evaluations we have developed a conceptual model for the diffusion of innovation, based on similar models available from the marketing literature.

2. Pharmacoeconomic Techniques of CEA/CUA: A Brief History

The foundations for the use of CEA in the evaluation of health care interventions were set out in a seminal article by Weinstein and Stason (1977). The term' pharmacoeconomics' was coined by Townsend in an article on post-marketing research and development to describe the application of microeconomics to pharmaceutical products and services. Pharmacoeconomics has emerged to gradually develop as a health science discipline by the pharmaceutical industry, academic economists and pharmacy and medical practitioners worldwide. Table 1 outlines some of the main landmarks in CEA and pharmacoeconomic application.

Table 1: Important Landmarks in Pharmacoeconomic Analyses

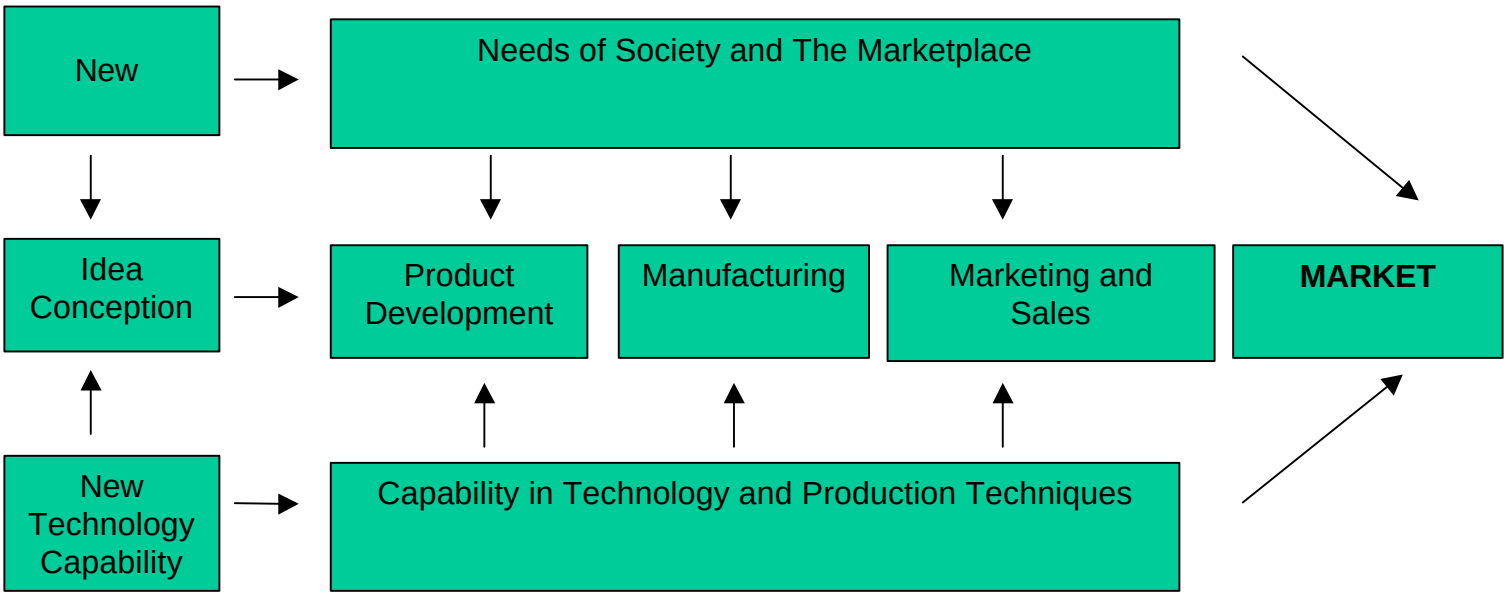
1968	Klarman et al. publish first cost-effectiveness analysis for the treatment of chronic renal disease
1972	Williams provides an interesting discussion on the use of cost-benefit analysis in healthcare
1973	Pioneering work in the development of QALYs for an analysis of phenylketonuria screening by Bush et al.
1976	Use of the QALY in an analysis of the cost-effectiveness of hypertension treatment by Weinstein and Stason.
1977	Foundations of CEA set out by Weinstein and Stason
1987	Drummond et al. publish their leading textbook 'Methods for the Economic Evaluation of Healthcare Programmes'
1990	Black et al. introduce a graphic representation of cost-effectiveness in their cost-effectiveness plane
1992	Laupacis suggest the most widely cited magnitude of a ceiling ICER with reference to the Canadian healthcare system. Drummond et al. consider cross-national issues in cost-effectiveness analyses
1993	Johannesson et al. outline the decision rules of cost-effectiveness analyses
1994	Briggs et al. review the issue of sensitivity analysis in cost-effectiveness analyses O'Brien et al. pioneer research for addressing stochastic issues in cost-effectiveness analyses.
1996	Gold et al. publish findings of the Washington Panel in their book 'Cost-effectiveness in Health and Medicine'
1997	Drummond et al. publish the second edition of their leading textbook.

3. The Diffusion of Innovation: The Marketing Model

Conceptual models of the diffusion of innovation are available from the marketing literature. These models are used to describe the steps a new product or service might take to progress from idea conception through to become a marketed product. These involve physical inputs in terms of the research to develop the product, the manufacture of the product and the commercial strategy to introduce potential customers to the product. However, a product reaching the market is also dependent on the need being identified in the first place and that need in society and the market place being realised in practice (demand factors). In addition, the diffusion process is also dependent on their being sufficient technological capability and sophistication in the production facilities available (supply factors).

Figure 1 represents a marketing model of innovation diffusion for new products or services that capture these processes and dependencies (Gardiner and Rothwell, 1985). Not all new products will make it through the diffusion process. For example, the Sinclair C5 electric car (an invention conceived by Sir Clive Sinclair in the 1980's) failed despite being a bright idea to produce a cheap, affordable to run vehicle in the face of a perceived need brought on by decreasing fuel stocks and measures to minimise environmental pollution. However, limits in the state of the art of production techniques meant the C5 looked akin to a dry land toboggan, contributing to its failure in the market. Many other products may fail earlier in the production process. For example, many new drug compounds fail during the development part of Figure 1 due to early evidence of a lack of safety, efficacy or commercial attractiveness (i.e. insufficient need).

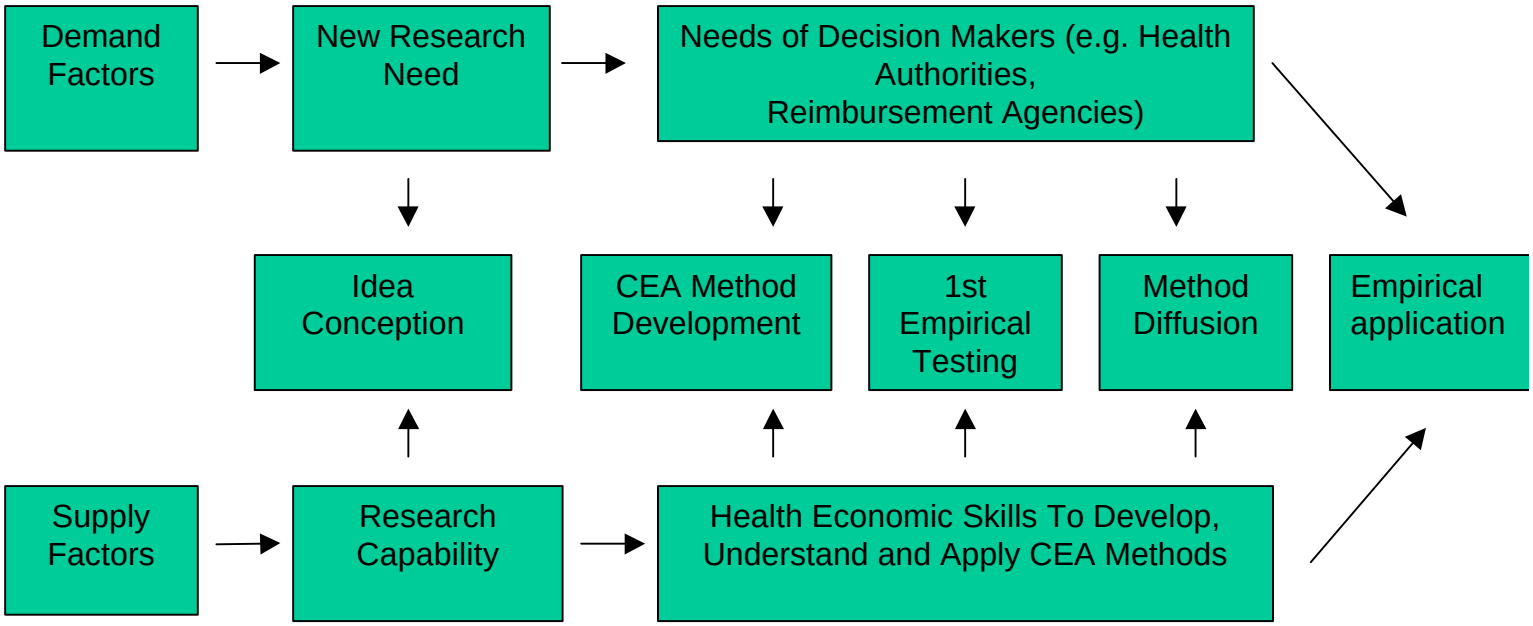
Figure 1. Innovation Diffusion model



4. Application to Pharmacoeconomics

The marketing model in figure 1 can be adapted to reflect the process involved in the development and diffusion of new methods and analytical approaches in cost-effectiveness analysis as applied to pharmacoeconomic evaluations. Dependent upon a need (demand), and the research capability and skills available to apply new methods, the diffusion of a CEA method into widespread empirical application goes through the process described in Figure 2. Therefore, the method is hypothesed to move from idea conception, development and initial empirical testing, diffusion into practice through, for example, inclusion in economic evaluation textbooks (e.g. Drummond et al., 1997, Gold et al., 1996), academic guidelines such as Drummond et al. (1996), and reimbursement agency guidelines, and finally widespread empirical application in pharmacoeconomic studies. As an example, the discounting of costs beyond one year has completed the process (although the choice of appropriate discount rate has not) and is accepted empirical practice, whilst the idea of hyperbolic discounting has not progressed beyond the first box (idea conception).

Figure 2: Diffusion of Innovation Model Applied to CEA of Pharmaceuticals.



As with new products and services, not all CEA methods will make it through the whole process. Failure could be due to a lack of methodological/scientific rigour in the development and empirical testing of the new method or for supply/demand reasons if their is a lack of perceived need by decision makers, or a lack of research capability to apply the technique.

On the demand side, the "needs" in the long box at the top of figure 2 are those of decision makers such as health authorities and other payers of heath care (such as HMOs in USA), and agencies such as NICE in the UK and PBAC in Australia who help guide health service reimbursement decisions. If a new method is perceived to be needed, because it is accepted by decision-makers as improving the quality and validity of the results of CEAs, then it is more likely to reach the stage of widespread empirical

application. Initially, a research need for a new method has to be generated and accepted by the academic and scientific health economics community.

On the supply side, the empirical application of CEA methods is dependent upon the existence of a pool of trained individuals with the health economics skills to understand and apply the techniques and to explain to decision makers the relevance and importance of the cost-effectiveness outcomes generated (see the long box at the bottom of Figure 2). In the UK, there has been a growth in health economics research capability over the last 10 years, with more trained researchers employed within academic health economics units, within the pharmaceutical industry and within specialist health economics consultancies. The issue of the range of skills required to keep pace with new methodological developments in CEA is discussed later.

A CEA method will only reach the stage of widespread empirical application and be used by decision makers if it improves the quality and rigour of CEAs, and value for priority setting and clinical decision making. Because the use of new or underused methods usually mean extra complexity in the conduct of the CEA the outcome is dependent upon the skills of researchers in different settings to apply and demonstrate the value of SOA methods in improving the reliability of the final result from CEAs.

5. State of the Art Methods

In this paper, we have defined a list of state of the art methods in CEA which represent a response to a methodological research need in the areas of:

i. Cost measurement
ii. Outcome measurement
iii. Uncertainty
iv. Time preference
v. Analysis of cost-effectiveness

The list of state of the art methods and techniques have been drawn primarily from two leading economic evaluation texts published in the last 5 years: Drummond et al. (1997) and Gold et al. (1996). The list is presented in table 2. It is not intended to be comprehensive, but instead to represent some of the methods that might be included in state of the art pharmacoeconomic evaluations.

The SOA list is applied to pharmacoeconomics studies with a prospective design, with varients applicable to modelling studies (Table 2). two types of pharmacoeconomic evaluation. A prospective study includes primary resource use and clinical/health outcomes data from RCTs or observational datasets (although modelling approaches may be included within these - for example, to model longer term outcomes), whereas an economic modelling study is one that primarily uses secondary data sources (e.g published data, retrospective observational datasets), hypothetical patient cohorts, and/or decision analytical approaches (e.g. probabilities of clinical events estimated).

Prospective studies, if well designed, represent the ‘gold standard’ approach for CEAs and should produce results with greatest reliability and rigour. Modelling studies are

most useful for providing indications of the potential cost-effectiveness of a drug, to test initial hypotheses regarding key cost and outcome drivers, and as an iterative tool to aid design and data collection for more definitive prospective CEAs (Sculpher et. al. 1997, Duffy et al 1997). The results from economic models using secondary data could be undertaken as a good substitute for prospective studies if existing data of sufficient quality exists, and especially if time and resources are limited to conduct prospective studies.

Table 2: Selected State of the Art CEA Methods

CEA Area	SOA Methods (for both prospective studies and economic models)	Variant of Method Applicable to Economic Models
A: Cost and cost consequence measurement	(i) Societal perspective adopted (min. direct health care costs and indirect productivity costs) (ii) Long term medical (and other) costs and cost consequences measured prospectively or modelled (iii) Indirect costs of mortality/morbidity measured using frictional method	
B: Outcome measurement	(i) Pragmatic comparative trials (single or meta analysis) used as primary data source to measure effects. (ii) Meta analysis of clinical/outcomes data performed (iii) Long term clinical or health outcomes measured prospectively or modelled (e.g. markov, epidemiological models, extrapolation) (iv) QALYs measured using standard gamble or TTO methods for utilities (direct measurement or using recognised generic tool such as EQ 5D or HUI)	Long term clinical or health outcomes modelled using Markov or similar method
C: Uncertainty	(i) Confidence intervals around ICERs (e.g. parametric estimates - Taylor's or Fiellers methods, non-parametric bootstrapping, or Bayesian estimates).	Probabilistic sensitivity analysis performed (e.g. Monte Carlo simulations or other simulation method)
D: Time Preference	(i) Future effects (health outcomes) discounted at 3, 5 or 6%	
E: C-E Analysis	(i) ICERS calculated (ii) Statistical analysis of differences in costs and/or outcomes between interventions (iii) Generalisability of results demonstrated through modelling or multi-national data collection.	Statistical analysis of differences in outcomes between interventions

BOX A - Cost measurement: The perspective or viewpoint of the analysis influences the resource costs for inclusion (Davidoff and Powe 1996). Possible perspectives include the individual, the health service, society and the decision-maker. Additional ones include the clinician, professional organisation, patient group and purchaser (Drummond et al., 1996). Some economists argue on theoretical grounds that a societal perspective should be adopted in all cases (Johannesson, 1995). The Canadian guidelines corroborate this (CCOHTA, 1994) and Gold et al. (1996) also recommend that their reference case should be from a societal perspective and any deviations from this perspective should be explained and justified. Any studies with narrow perspectives may result in suboptimal allocation of resources and a corresponding loss in societal welfare.

If a societal perspective is adopted, time costs incurred by individuals in receiving treatment reflecting the loss to society should be included i.e. the indirect costs or productivity losses. Traditionally, indirect costs have been estimated using the human capital-cost approach and defined as the lost gross income during the time absent from work. In measuring productivity losses, Koopmanschap et al. (1995) have proposed the use of the friction cost approach. The fundamental idea is that individuals on short term sick leave can make up for the loss of production when they return to work, or that this can be taken care of by internal labour reserves, or that nonurgent jobs can be cancelled and that individuals on long term sick leave can be replaced by someone currently employed (after a 'friction period').

The time horizon of the economic evaluation is largely determined by the perspective of the study and the period of time for which the decision-maker has an interest. Although the analysis can be performed for a number of time horizons, a long-run perspective has been recommended (Gold et al., 1996). The main reason for this is that the longer the time period, the greater the number of costs that may change or that are variable, ultimately affecting the direction and magnitude of cost differences.

BOX B - Outcome measurement: Pragmatic trials allow the opportunity to evaluate the effectiveness or cost-effectiveness of an intervention under real world conditions that would prevail once the intervention is in routine use. The main design features of such studies include: patients are enrolled typical of the normal caseload; the therapy of interest is compared with current care; the settings and physicians are representative; physicians and patients are not blind to the therapy; patients are followed under routine conditions and a wide range of endpoints are measured (e.g. efficacy, feasibility, tolerance, quality of life, resource use, etc.). Ideally, but not necessarily, patients will be randomly allocated to the different treatment options.

Meta-analyses of clinical/outcomes data are reliable sources of clinical/outcomes data for economic evaluations although the values (point estimates and confidence intervals) need to be incorporated into CEA using appropriate techniques. Such reviews are likely to have been performed systematically covering aspects such as a rigorous literature search, determination of inclusion/exclusion criteria, quality assessment, tests of statistical homogeneity, statistical pooling techniques, and sensitivity analyses.

Extrapolation models can be used to extrapolate data beyond the period observed in the clinical trial. This is usually needed to estimate the survival benefits of therapies in order to produce a measure of the life years gained, a measure more useful and

appropriate in pharmacoeconomic evaluations than short-term measures such as percentage mortality at 30 days. Epidemiologic models are appropriate for linking intermediate biologic endpoints with such final health outcomes, whereas Markov models can be used where diseases and treatments are characterised by recurrence or chronicity. The Markov model proceeds by dividing the disease in question into distinct states and transition probabilities are assigned for movement between these states over a discrete time period known as a 'Markov Cycle'. By attaching estimates of resource use and health outcome consequence to the states and transitions in the model, and then running the model over many cycles, it is possible to estimate the long term costs and outcomes associated with a disease and a particular healthcare intervention.

Conducting a CUA instead of, or more usefully alongside, a CEA could enable comparison of the relative cost-effectiveness of different types of pharmaceutials and other interventions, and so aid priority setting in the use of health service resources. However, the value of QALYs produced in such studies is dependent on a reliable, valid and comparable method for generating health utility outcomes. The state of the art currently for doing this is a recognised generic tool such as the EQ-5D or Health Utilities Index (HUI), or direct measurement of preferences for health using standard gamble or time trade off methods (ref???). Less reliable methods often used in empirical pharmacoeconomic studies are the generation of utility values based on clinician or expert opinion, or published utility values for the condition being evaluated.

BOX C: Uncertainty: More recently, in prospective evaluations, methods have been developed for allowing statistical tests of economic hypotheses to be performed and uncertainty in stochastic data to be quantified using confidence intervals. The calculation of confidence intervals around cost-effectiveness ratios is important because the economic importance of a change in cost can only be considered in combination with the clinical importance of changes in effect. This has given rise to different approaches for confidence interval estimation for the ICER such as the confidence box, Taylor Series Expansion, confidence ellipses and Fieller's method.

However there are major problems with confidence intervals in that negative ICERs might be generated and the close association with hypothesis testing, but the relevant hypothesis in economic evaluation is likely to be only one-sided. To avoid these problems, cost-acceptability curves have been proposed. These curves quantify the probability that the intervention in question is cost-effective. The issue of negative ICERs does not arise, the test is one-sided and the probabilities for all potential values of the ceiling ratio are quantified. In economic models in which outcomes probabilities have been estimated, probabilistic sensitivity analysis using monte carlo simulation, or computer generated simulation models, offer a more rigorous approach to dealing with uncertainty than conventional one or two way sensitivity analysis and threshold analysis alone.

BOX D - Time Preference: Discounting of costs and effects is performed to allow comparison between costs and benefits that occur at different times (Drummond et al., 1987; Luce and Elixhauser, 1980). Although there is general agreement on the need to discount costs based on individuals' having a time preference individuals for consumption in the current time period, there is less agreement that the same principle applies to the

discounting of health benefits (Parsonage and Neuberger, 1992). However, the weight of evidence seems to be pointing to inclusion in economic evaluations of a positive discount rate for health outcomes such as life years gained and QALYs (with a zero rate btested in a sensitivity analysis), and so this has been included in the SOA list in table 2. Pharmacoeconomic guidelines generally recommend that both costs and outcomes should be discounted at a rate of 3 or 5%, although 6% is frequently used in pharmacoeconomic evaluations.

BOX E – Analysis of Cost-effectiveness data: Calculation of incremental cost-effectiveness ratios (ICER) is especially crucial when an intervention is more costly and more effective than the comparator. A negative ICER indicates that an intervention is less costly and more effective than a comparator, and so represents a dominant therapy of those considered. The state of the art approach is to calculate ICERs as average cost-effectiveness ratios could result in sub-optimal resource allocation decisions (Golds et al 1996) , although arguments have been put forward that average cost-effectiveness ratios are more clinically relevant.

Statistical tests of significant differences in costs and/or outcomes between the therapies being analysed can be undertaken in prospective studies. It is not possible to test statistically for differences in costs in economic models, although if the clinical or health outcomes data used in the model is drawn from trials or observational datasets then statistical inference tests can be used for these.

The generalisability of results is an issue important to both economic and clinical data (Leidl, 1994) and can be affected by factors such as differences in comparators, medical practice, relative costs of resources, and epidemiology. Generalisability can be considered in the context of multinational clinical trials or the modelling/adaptation of economic data from setting to setting.

6. Review of Empirical Application

6.1 Methods/Literature Search

A literature review covering a sample of pharmacoeconomic studies was conducted to provide an indication of the extent to which the methods listed in Table 2 had diffused into empirical application (see end box in Figure 2).

Our initial strategy was to identify all CEA and CUAs published in the journal PharmacoEconomics between January 1997 to November 1999 (as a major journal for international pharmacoeconomic studies). Cost analyses, in which costs of the pharmaceutical intervention were compared with economic savings, but not linked directly to clinical or health outcomes, were excluded. We have avoided clinical journals at this stage, although it is recognised that studies using state of the art methods may have been published in such journals. A total of 28 studies have been included - basic details of these are presented in table 3. As a next step a more comprehensive literature search will be conducted of other health economic and clinical journals. However, our initial search should be sufficient to provide indications

of whether SOA methods are being used, and the level of sophistication of current CEAs of pharmaceuticals.

Table 3: Empirical CEA/CUAs from the journal PharmacoEconomics 1997-1999

Prospective Studies

STUDY	COUNTRY	THERAPEUTIC AREA	DATA SOURCE FOR COSTS AND OUTCOMES	TYPE OF EVALUATION & CER	DRUGS EVALUATED
1. Gudex et al 1997	UK	Dystonia	Observational	CUA - cost per QALY	Botulinum Toxin v no drug
2. Pelc et al 1997	France	Acute Myocardial Infarction	Observational	CEA - cost per life year	Alteplase v Streptokinase
3. Erhardt et al 1997	Sweden	Heart Failure	Observational	CEA - cost per life year saved	Ramipril (Ace inhibitor) with conventional treatment v conventional treatment alone (diuretics/digitalis)
4. Fagnani et al 1998	France	Osteoarthritis	Pragmatic Randomised Trial	CEA - cost per point scored on Lesquene's functional index	diacerein (anti-osteoarthritic drug) v standard therapy alone (e.g. NSAIDs, analgesics)
5. Hamilton et al 1999	USA	Schizophrenia	RCT	CEA - costs v clinical improvements	Olanzopine v haloperidol (antipsychotics)
6. Walters et al 1999	USA	Intra-abdominal infections	RCT for clinical outcomes and resource use from hospital database	CEA - cost per patient treated successfully	Ciprofloxacin + metronidazole v imipenem-cilastatin
7. Volmer et al 1999	Germany	Moderate Asthma	pragmatic RCT	CEA - costs per successfully treated patient, costs per symptom free day	Fluticasone proprionate v flunisolide (inhaled corticosteroids)

Economic Models

STUDY	COUNTRY	THERAPEUTIC AREA	DATA SOURCE FOR COSTS AND OUTCOMES	TYPE OF EVALUATION & CER	DRUGS EVALUATED
8. Genc et al 1997	Sweden	Gonorrhoea	decision model using literature based estimates for outcomes and costs	CEA - cost per cured patient	Intramuscular ceftrixone v cefixime v ofloxacin v ciprofloxacin
9. Evans et al 1997	Canada	Migraine	decision model using literature, expert opinion, author estimates for outcomes and costs	CEA (cost per attack aborted) and CUA (cost per QALY)	Oral sumatriptan v oral caffeine/ergotamine
10. de Tiedra et al 1997	Spain	Inflammatory dermatosis (e.g. dermatitis, eczema)	decision model using RCT meta analysis for outcomes, resource use estimated	CEA - cost per successfully treated patient	topical prednicarbate v fluocortin
11. Hummel et al 1997	UK	Myocardial Infarction	decision model: expert opinion, literature, documented data, author estimates	CEA (cost per life year gained) and CUA (cost per QALY)	Prophylactic treatment with captopril (ACE inhibitor) v no prophylactic treatment
12. Einarson et al 1997	Canada	Major depressive disorder	decision model: literature, expert opinion	CEA - cost per success, and per symptom free day	SNRI's (e.g. venlafaxine) v SSRIs (fluoxetine) v TCAs (amitriptyline)
13. Milne et al 1997	New Zealand	Cardiovascular disease	Secondary pooled data from comparative trials for outcomes, costs estimated	CEA - cost per life year gained	celiprolol v atenolol (antihypertensives/lipid lowering)
14. Badia et al 1997	Spain	Duodenal Ulcer	hypothetical patient cohort: RCT data for outcomes, resource use data from published sources	CEA - cost per symptom free day	omeprazole (antisecretory therapy) v omeprazole/clarithromycin/amoxicillin (eradication therapy)
15. Gruger et al 1997	UK	Herpes Zoster	A multinational RCT for outcomes and some resource use, secondary sources for other resources	CEA - costs v clinical improvements	famciclovir v aciclovir (oral antiviral treatments for shingles)
16. Arnal et al 1997	Spain	Hepatitis A	decision model using literature values for outcomes and resource use	CEA - cost per case prevented	hep A vaccine v nonspecific immune globulin
17. Cockrum et al 1997	USA	Begnign Prostatic Hyperplasia	decision model using literature and expert opinion for outcomes and resource use	CEA - costs v clinical improvements	androgenic hormone inhibition (finasteride) v alpha blockade (doxazosin, prazosin, terazosin)
18. Chancellor et al 1997	UK	HIV Infection	hypothetical patient cohort using published data for outcomes and community care resource use, and prospective data for hospital care resource use	CEA - cost per life year gained	3TC/ZDV combination therapy v ZDV monotherapy
19. Lafuma et al 1997	France	Paget's disease of bone	secondary data from a clinical RCT for outcomes, costs from documented sources.	CEA - costs v clinical improvements	Low dose tiludronic acid v etidronic acid
20. Rosner et al 1998	Canada	Osteoarthritis	Secondary data sources (trials, published data) for clinical events/outcomes and delphi panel for resource use	CEA - cost per vertebral fracture averted	9 multitherapy strategies including bisphosphonates, OHT, calcium therapy and no therapy
21. Levin et al 1998	Sweden	Deep Vein Thrombosis	decision model with outcomes data from published RCT, costs from publishd sources	CEA - cost per life year saved	Standard prophylaxis with subcutaneous unfractionated heparin v desirudin (recombinant hirudin)

STUDY	COUNTRY	THERAPEUTIC AREA	DATA SOURCE FOR COSTS AND OUTCOMES	TYPE OF EVALUATION & CER	DRUGS EVALUATED
22. Detournay et al 1998	France	Deep Vein Thrombosis	decision model with outcomes from 2 published RCTs, resource use estimated and verified by expert opinion	CEA - cost per life year saved & per venous thromboembolitic event avoided	long term prophylaxis with enoxaparin (low molecular weight heparin) v short term perioperative prophylaxis
23. Gupta 1998	Canada	Toenail Onychomycosis	decision model with outcomes from meta analysis of controlled trials, resource use from expert opinion	CEA - cost per symptom free day	griseofulvin v itraconazole v terbinafine v fluconazole (commonly prescribed oral antifungals)
24. Schadlich et al 1998	Germany	Alcohol dependence	decision model using data from a pragmatic comparative trial, epidemiological data and expert opinion for outcomes, and published sources for costs.	CEA - cost per additional abstinent alcoholic patient	adjuvant acamprosate therapy v standard care
25. Messori et al 1999	Italy	Amyotrophic lateral sclerosis	secondary data using meta analysis of RCTs for outcomes, published sources for costs	CEA - cost per life year gained	riluzole v usual care
26. Rachlis et al 1999	Canada	Cytomegalovirus Retinitis	decision model using RCT data for outcomes, expert opinion for resource use/costs	CEA - cost per disease progression free day	IV maintenance ganciclovir v oral ganciclovir
27. Balen et al 1999	Canada	Acute Coronary Syndromes	decision model using published clinical trial data for outcomes, and published costs data	CEA - costs v clinical outcomes	enoxaparin therapy v unfractionated heparin therapy
28. Chambers et al 1999	UK	Recurrent ischaemic stroke	decision model using clinical trial and published data for outcomes, and published sources for costs	CEA/CUA - costs per disabled life years averted, per disability free life year gained, per stroke averted, per stroke free life year gained, per QALY	Coformulation v aspirin (or v no therapy)

6.2 Results of Review

We initially reviewed the 29 selected studies to assess whether they met basic standards for a CEA or CUA of a pharmaceutical. This is important to provide a baseline for the quality and comparability of the studies, and so for identifying the extent to which recent studies have gone beyond the basics and used any of the SOA items listed in table 2. The "basic standards" criteria we used are presented in table 4.

Table 4: Basic Standards Criteria for Reviewed Studies

CEA Area	Minimum Standards
Perspective:	The perspective adopted is stated/clear
Comparator	The intervention is a pharmacuetical and is set against a clearly stated comparator (or no pharmaceutical option)
Costs	Main direct health care costs and cost consequences of intervention measured
Outcomes	A primary effectiveness/health outcome measure stated
Uncertainty	Sensitivity Analysis of key variables conducted using a recognised method (e.g. one way sensitivity analysis, threshold analysis).
Discounting	Discounting of costs conducted if appropriate using recognised discount rate (3%, 5%, 6%).
Analysis of cost-effectiveness	Costs set against clinical/health outcomes for each intervention to enable conclusion to be reached as to relative cost-effectiveness of interventions analysed.

All the studies in table 4 reached the minimum standards criteria. Table 5 outlines the use of the SOA methods in these. Although the SOA methods are largely objective in

nature, their use in the studies were assessed independently by the authors (KT and FP) and a consensus reached where there was disagreement.

Table 5: State of the Art Methods Used in Sample of Pharmacoeconomic Evaluations

Prospective Studies

Study	**State of the Art Methods Used (see table 2 for classification)**											
	A			**B**				**C**	**D**	**E**		
	i	**ii**	**iii**	**i**	**ii**	**iii**	**iv**	**i**	**i**	**i**	**ii**	**iii**
1. Gudex et al							X			X		
2. Pelc et al										X	X	
3. Erhardt et al		X				X			X	X		
4. Fagnani et al				X						X	X	
5. Hamilton et al											X	
6. Walters et al											X	
7. Volmer et al				X						X	X	

Economic Models

Study	**State of the Art Methods Used (see table 2 for classification)**											
	A			**B**				**C**	**D**	**E**		
	I	**ii**	**iii**	**i**	**ii**	**iii**	**iv**	**i**	**I**	**i**	**ii**	**iii**
8. Genc et al	X	X							X	X		
9. Evans et al	X					X	X	X		X		
10. Tiedra et al	X	X			X						X	
11. Hummel et al				X					X	X		X
12. Einarson et al					X			X		X	X	
13. Milne et al		X				X			X	X		
14. Badier et al		X				X			X			
15. Gruger et al.		X				X			X	X		
16. Arnal et al		X				X		X	X			
17. Cockrum et al.		X						X				
18. Chanceller et al		X			X	X			X	X		
19. Lafuma et al						X						
20. Rosner et al	X								X	X		
21. Levin et al		X				X			X	X		
22. Detournay et al						X		X		X		
23. Gupta					X						X	
24. Schadlich et al				X				X			X	
25. Messori et al					X	X		X	X		X	
26. Rachlis et al	X									X	X	
27. Balen et al										X		
28. Chambers et al		X				X				X	X	

The majority of the applied pharmacoeconomic studies reviewed were economic models (71.4%). Models are generally quicker and represent a lower cost than prospective studies, and so are used when speed or resources limit the feasibility of a prospective study. They may be the study design of choice if the research objective is to identify the key costs and outcome variables toencourage or aid the design of a thorough prospective pharmacoeconomic evaluation. It is likely that even if the primary mode of enquiry is not an integrative decision model, a prospective based study to fully address issues such as the long run cost-effectiveness of a drug intervention may still require some from of modelling to adjust or extrapolate data for use in the pharmacoeconomic study.

Although the societal perspective is recommended, only 18% of studies adopted such a perspective. The majority took the perspective of the health service. In the studies that estimated indirect costs, none used friction cost methods to estimate productivity losses.

Only one prospective study considered medical and other costs and cost consequences over the long term in contrast to almost half of decision models (47.6%), illustrating the flexibility of modelling techniques.

Four studies were based on effectiveness data from pragmatic comparative trials. Despite recommendations that pragmatic (or naturalistic) trials represent the optimal approach for CEAs as they provide "real world" data on resource use and the effectiveness of drug therapies, rather than efficacy, in actual clinical settings, their use has not filtered through to empirical application. This is likely to be due to cost and design issues – phase IV studies may offer the best potential for future pharmacoeconomic studies to employ this approach.

Only 5 economic models were based on meta-analyses demonstrating the general lack of rigour in the review of clinical/outcomes data on which the economic evaluations are based. In 53% of models, clinical or health outcomes were modelled. QALYs were measured in 4 CUA studies, but only two used generic utility instruments (HUI and QWB – table 5) and none employed direct measurement of utilities using standard gamble or time trade-off techniques.

The majority of studies accepted the concept of time preference as applied to future health outcomes and discounted in the range 3-6%. Despite the increasing literature and the intensive research activity on the use of statistical methods for dealing with uncertainty, this does not seem to have been diffused into empirical application as yet – none of the prospective studies in the review produced confidence intervals around the cost-effectiveness ratios. However, as these are stochastic approaches their application is limited by the small proportion of prospective data studies published in PharmacoEconomics in the last 3 years.

The majority of the studies reported incremental cost-effectiveness ratios, but not all the studies agreed that ICERs should be reported, stating that average cost-effectiveness ratios were more clinically relevant (e.g. study no. 18 in table 3)**.** Five studies (no's 5, 15, 17 19 and 27 in table 3) linked clinical outcomes to costs without the production of a cost effectiveness ratio. One study (Evans et al., 1997) mentioned

distributional issues citing that the calculations do not take into account whether benefits are received by one group while costs are borne by the other nor is any consideration given to the fact that society may want to value certain lives over others for certain purposes. They recommend that such social decisions need to be made outside the quantitative framework of economic evaluation.

Although the generalisability of results to other settings is an important element of cost-effectiveness analyses, only one study addressed this issue. Hummel et al (study no. 4) developed a model to test the cost-effectiveness of catopril recognising the differences in North American and European practice in relation to the investigation and treatment of myocardial ischaemia.

8. Discussion

Since 1984, there have been significant methodological advances in the field of economic evaluation. Despite these advances, the history of the development of pharmacoeconomics and the development, diffusion and empirical application of CEA methods has not been reviewed extensively. This paper has demonstrated that while there has been intense activity in methodological research, very few pharmacoeconomic evaluations which have published in the journal 'Pharmacoeconomics' have consistently applied what might be considered "state of the art" methods and analytical approaches.

A possible reason is the lack of training of economists in state of the art techniques, although this is being addressed through the recent establishment of three courses (compared below). It would be interesting in several years time to see whether these 'advanced' methods have filtered through into applied pharmacoeconomic studies as more economists participate in this training.

Conversely the lack of awareness and training among decision-makers in the methods of economic evaluation may also hinder the progression of state of the art techniques into the pharmacoeconomic literature.

Table 6: Content of Advanced Courses in Economic Evaluation

TOPIC	HARVARD[1]	OXFORD[2]	YORK[3]
Design issues	Yes	Yes	Yes
Multicentre and multinational trials	Yes		Yes
Outcome/naturalistic trials	Yes		Yes
Within and outside data collection	Yes		Yes
Sample size calculation for economic analysis			Yes
Confidence intervals around cost-effectiveness ratios		Yes	Yes
Bootstrapping		Yes	Yes
Presenting cost-effectiveness data	Yes	Yes	Yes
Handling missing data		Yes	
Censored cost data		Yes	
Multi-attribute utility scales	Yes		Yes
Contingent valuation techniques	Yes		Yes
Conjoint analysis			Yes
Survival analysis techniques		Yes	
Decision analytic modelling	Yes	Yes	Yes
Markov modelling	Yes	Yes	
Value of information analysis			Yes
Bayesian approaches			Yes

[1] Harvard School of Public Health
[2] Health Economics Research Centre, Institute of Health Sciences, University of Oxford
[3] York Expert Workshops, Centre for Health Economics, University of York

Within the drug industry pharmacoeconomics is at the interface between research and development and marketing. This begs the question what are the needs of the different audiences. Do different audiences all require pharmacoeconomic evaluations using the latest state of the art methods or simply better reported and transparent studies? It is crucial to further explore the link between state of the art methods and decision-making within the healthcare field. Without such a link, much new activity in CEA method development could remain primarily an academic exercise.

The SOA list we have developed in table 2 is not comprehensive or definitive. It is meant to be general (rather than the use of specific technical methods such as bootstrapping) to express the range of methods and approaches that would raise the rigour of a pharmacoeconomic evaluation above that which might be expected as standard. They represent methods that have had sufficient time to have diffused into empirical application. The list could and should be reviewed, for instance for inclusion of new methods (e.g. censored cost data, Bayesian approaches to modelling cost data – see paper by Nicola Cooper at this HESG)) that have not had sufficient lag time to be found in published pharmacoeconomic studies, in a journal such as PharmacoEconomics.

One issue that remains a recurring theme is the issue of bias in industry-sponsored studies. The logic behind this controversy is that sponsors can gain commercial

advantage by showing that their drugs are more cost-effective than their competitors and because of the current lack of adequate regulation of the design, conduct and reporting of pharmacoeconomic analyses. Suggestions for reducing bias have included recommending codes of ethical conduct between researchers and their sponsors, recommending adherence to published methodological guidelines and recommending audits of pharmacoeconomic research similar to those undertaken by the accountancy profession. Therefore state of the art research should be directed at identifying, measuring and adjusting for bias in economic evaluations.

Although the field of pharmacoeconomic evaluation using CEAs has come a long way in the last 30 years, it is still emerging and developing in terms of empirical application and many of the methods used are in an experimental stage. It seems that many published CEAs of pharmaceuticals rely on well established methods (such as may be found in texts such as Drummond et al, 1997). It is thus important to continue methodological development in the field and to allow different approaches to be used simultaneously. We have outlined what we consider to be some of the key elements of a state of the art pharmacoeconomic evaluation, and examined the extent (or lack of it) to which these methods have diffused into empirical application. An important issue for further research is whether the limited use of SOA approaches in our review is due to our review not being representative of pharmacoeconomic studies, or (as depicted in the conceptual model of figure 2) a lack of sufficient supply of health economics skills to undertake state of the art studies, or a lack of demand by decision makers for more sophisticated studies.

Quality is important to raise the credibility of pharmacoeconomic studies, especially those sponsored by the drug industry. We now plead for some help in improving the quality and rigour of this paper.

This paper is a first step towards identifying to what extent state of the art pharmacoeconomic studies are being conducted in empirical research. Advice is much welcomed on the approach adopted, the preliminary list of "SOA" methods and how to extend the literature review and other steps that could be taken to further address the research questions posed.

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