Monthly Focus: Pharmacoeconomics

Evaluation and review of pharmacoeconomic models

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Difficult decisions as to whether to provide or withhold drug therapy to patients are needed to be made on a daily basis. These decisions should be based on carefully designed and constructed pharmacoeconomic models, with explicit and justifiable parameter values, validated by publication in peer-reviewed literature. This review describes and evaluates the common types of pharmacoeconomic models, modelling approaches and methods. It also discusses model quality, validity and usefulness.

Keywords: cost-benefit analysis, cost-effectiveness analysis, decision modelling, economic evaluations, pharmacoeconomic guidelines


1. Introduction

1.1 Background
Drugs are increasingly important to clinical decision making as newer therapies gain acceptance. With healthcare and pharmaceutical costs continuing to escalate, pharmacoeconomic analyses and models are becoming implicit or explicit requirements for drug use decision making [1]. Many countries have implemented formal pharmacoeconomic evaluation processes [2,3,101]. The Academy of Managed Care Pharmacy (AMCP) in the US has promulgated dossier requirements for drug formulary reimbursement in managed care organisations covering > 130 million Americans [4,5]. At the same time, the number of scientific papers and conferences using pharmacoeconomic models has exploded, with new scientific organisations and peer-reviewed journals devoting substantial focus on this field [6,7,102].

1.2 What are pharmacoeconomic models?
Pharmacoeconomic models are mathematical equation systems that apply economic analysis to value and rank alternative drug interventions [1,8]. Although the application of cost-effectiveness ‘cost per life year saved’ models to medical decisions goes back nearly 40 years [9], the term ‘pharmacoeconomics’ was coined by Lyle Bootman, Ray Townsend and William McGhan in their introductory textbook applying these health economic evaluation techniques to drug therapy [10].

All modelling entails abstraction from reality to capture essential details that are relevant to decisions, while ignoring details that add complexity without improving model reliability, validity or predictive accuracy. The archetype of good modelling practice was Copernicus’ sixteenth century astronomical model of the solar system, replacing the Ptolemaic earth-centred model, and its complicated planetary precessions and loop-the-loops with a sun-centred model, with planets orbiting in simple ellipses. Although politically incorrect at the time, the Copernican model was more accurate and provided crucial new insights into astronomy that eventually led to Newton’s laws of physical motion and to modern physics.

In fact, all real-world decisions, from what route to take to work to what asthma medicine to use, are based on either formal or informal decision models [11]. Even after a definitive outcomes trial on alternative drug treatments is completed, the decision-maker (physician, patient, formulary committee) must still extrapolate from the
characteristics of the clinical trial study participants, study time frame and study circumstances to the relevant target population. Such extrapolations inevitably involve numerous simplifications and assumptions. Modelling allows the decision-maker to specify assumptions and parameter values in a formal and transparent manner, and to assess how sensitive results are to these assumptions and values [12]. Even though others may not agree with all model inputs, through model inspection, anyone can see which aspects of the inputs and findings are acceptable from their own perspective, and which need adjustment or refinement. Open and transparent models allow decision-makers to establish the value of obtaining better information to reduce areas of disagreement and uncertainty [13].

Pharmacoeconomic modelling involves both art and science. The modeler must choose the best information to use, given limited research resources. They must combine disparate data sources into a plausible representation of treatment alternatives, taking care to accurately extrapolate from known data to future time periods, patient categories, costs and/or treatment outcomes. Simplicity is preferable when possible. For example, in the early days of modelling the costs of the US HIV/AIDS epidemic, simple projections of HIV prevalence based on reported AIDS cases and known HIV incubation distributions, ultimately proved to be more accurate and reliable than official Centers for Disease Control and Prevention (CDC) HIV forecasts based on more complex biologically-grounded models of population mixing, disease transmission dynamics and prevalence of risky behaviours [14,15]. As the US HIV epidemic has stabilised and new therapies have altered HIV disease progression rates, more complex dynamic models are becoming more useful than simple models that were successful earlier [16].

Before any model parameters are chosen, there are many initial steps that affect model results substantially but are essentially subjective decisions (Box 1). Optimally, the modeler will choose the best approach based on the needs of the model user - the decision-maker. The modeler should first establish the decision-maker’s perspective, as alternative perspectives (e.g., patient, provider, government, society) will imply large potential differences in the cost, health status and outcome valuations for ‘treatment alternatives’. They must establish the relevant treatment comparisons (e.g., is the analysis comparing all antihypertensives, or only β-blockers? Are they comparing a new drug against placebo or against the best available therapy?). They need to set a relevant analytical ‘time horizon’ (e.g., 30 days post-hospital discharge, 1 year and lifetime). They should choose an appropriate modelling ‘methodology’ (e.g., decision tree model, Markov model and Monte Carlo simulation model). Finally, they must decide what types of ‘data’ will best inform the model parameters. Will they use data from the literature, collect the data retrospectively or prospectively, or use a panel of experts to establish certain model parameter values?

Other approaches to pharmacoeconomic research besides modelling exist, including pharmacoeconomic demonstrations and outcomes trials, evaluation of retrospective databases, and syntheses of available pharmacoeconomic literature, but ultimately, the decision-maker will rely on assumptions to extrapolate beyond existing data or studies to specific patients. Such extrapolations generate an informal pharmacoeconomic model; even the simple projection that outcomes observed in study populations will persist over time in non-study patients is a ‘model’ and should be subjected to modelling techniques.

1.3 Pharmacoeconomic modelling types

Although pharmacoeconomic models come in many variants and hybrids, there are four primary modelling genres: medical decision trees, Markov models, discrete event simulation/backwards induction models and Monte Carlo simulation models (Table 1). None are unique to pharmacoeconomics but all of them have specific advantages in pharmacoeconomic applications.

The most versatile modelling type is the medical decision tree model [17]. In this approach, all relevant outcomes, costs and health states are modelled graphically as sequential probabilistic branches from an initial state of health or medical intervention decision. By assigning costs, utilities, health state valuations or other outcome measures to each node and branch of costs or other outcomes along all potential paths, and then knowing the probability of each pathway, estimate the total expected cost, benefit, quality of life (QoL) or other expected outcomes for patients receiving each alternative. The example in Figure 1 presents a simple decision tree model for comparing the cost-effectiveness of an implanted cardioverter defibrillator relative to conventional medical therapy for sudden death prevention in congestive heart failure patients [18].

Decision tree models are extremely flexible and can be used to model nearly any pharmacoeconomic decision process. The primary drawback is that the information requirements grow...
Table 1. Pharmacoeconomic model types.

<table>
<thead>
<tr>
<th>Model type</th>
<th>Description</th>
<th>Pros and cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decision tree models</td>
<td>Depicts patient health state changes with sequential probability branches from initial state or intervention</td>
<td>Pros: intuitive, very versatile and flexible, easy to depict clinical pathways graphically. Cons: data requirements easily expand beyond available information, does not allow direct accounting of time spent in various states of health</td>
</tr>
<tr>
<td>Markov models</td>
<td>Depicts patient health state progression over multiple time cycles with fixed health state transition probabilities</td>
<td>Pros: all costs and outcomes easily calculated for every time interval, parameter uncertainty and sensitivity analysis easy to incorporate, parsimonious information requirements. Cons: assumes that transition history does not matter, state transition probabilities are fixed over time</td>
</tr>
<tr>
<td>Discrete event simulation models</td>
<td>Depicts patient health state progression over multiple time cycles with variable health state transition probabilities</td>
<td>Pros: costs and outcomes calculated at each time interval, more realistic than fixed transition probability models. Cons: can be difficult to compute results and sensitivity analyses, has greater data requirements</td>
</tr>
<tr>
<td>Monte Carlo simulation models</td>
<td>Depicts patient health state progression through computer simulation of multiple individuals with random pathways based on model probabilities</td>
<td>Pros: extremely flexible and realistic. Cons: most computationally difficult, requires the most data</td>
</tr>
</tbody>
</table>

Figure 1. Decision tree for implanted cardioverter defibrillator compared to conventional therapy for sudden death prevention in congestive heart failure. Reprinted with permission from the Journal of Cardiovascular Drugs and Therapy [18].

HF: Heart failure; ICD: Implanted cardioverter defibrillator; SD: Sudden death.
exponentially with the number and depth of decision tree branches. For this reason, decision tree models are best suited to shorter-term (e.g., acute care episodes) analyses, or to analyses that cannot be reduced to a smaller set of transition states in each model time period. Because adding a time dimension is ad hoc and cumbersome, decision tree models are not ideal in situations where time spent in alternative health states needs to be carefully tracked in order to measure costs, QoL or other outcomes.

Markov models explicitly capture event timing through periodic fixed length time cycles, with patients in a set of discrete health states during each cycle. After each cycle, patients transition probabilistically to other health states or remain in their current state. Markov models are frequently used in situations where a set of recurrent health states are observed (e.g., migraine headache, irritable bowel syndrome) or where patients progress over time through a sequence of definitive chronic disease stages (e.g., disease severity levels for diabetes, Alzheimer’s disease or congestive heart failure), and each stage does not depend on prior progression history [19].

Figure 2 depicts a simple Markov model of health states and possible state transitions for patients with ulcerative colitis. Because health state transition probabilities only depend on a patient’s health state in the current cycle, the Markov model is fully characterised by its cycle length and its health state transition probabilities. This makes it straightforward to compute and characterise the expected costs, QoL or other outcomes after any arbitrary number of time periods. From the example in Figure 2, patients can freely transit from each disease severity level to any other severity level, although many Markov models allow only progressive transitions to higher levels of disease severity, or transitions to end states such as death.

Discrete event simulation and backwards induction models are designed primarily to model lifetime or other chronic diseases in situations where Markov health state transition cycles are not practical, or where transition probabilities are not independent of time or past medical history [20-22]. Backwards induction models are similar in scope to discrete event simulation models but simpler and less general, as they impose a recursive structure on adjacent time intervals. In many circumstances, there is information on disease incidence, survival, QoL and costs for a range of age–gender cohorts (e.g., 5-year intervals) that change with age and prior medical history, thus rendering Markov models impractical. In such circumstances, one can split the patient’s (expected) life into a finite number of discrete time periods and calculate the costs or other outcomes for all health states in each given time interval. As there are numerous permutations of events and health states that are possible, the backwards induction model is analysed by starting in the final time interval (e.g., highest potential age category before death) and estimating the expected costs or other outcomes in that period, accumulating those outcomes backwards one period and adding those (appropriately discounted) final period outcomes, multiplied...
by the probability of surviving to the final period, to the expected outcomes in the penultimate time period. By repeating this ‘backwards induction’ method sequentially on each prior period, one eventually calculates all expected outcomes for all time intervals from the final period (e.g., end of life) to the first period (initial disease onset). This backwards induction approach either requires assignment of all appropriately discounted disease costs and other outcomes to the time period where they initially occur, so that only disease-free individuals transition forward to each subsequent time period, or requires iterative recalculation to ensure that the proportion of individuals in each disease state transitioning to the next period are consistent with future period calculations.

A final modelling approach, known as Monte Carlo simulation, can be applied to any of the modelling methods already described, or to arbitrary model structures or modelling hybrids [23,24]. With Monte Carlo simulation, instead of directly calculating expected outcomes based on model transition probabilities, one uses computer algorithms to simulate large numbers of individual patients progressing through the decision model. At each probabilistic transition point for each patient, a random value is drawn by computer, based on pre-assigned model probability distributions, to determine progression direction. The simulation is reiterated numerous times, intermediate and final patient transition frequencies are accumulated, and empirical averages and confidence intervals are calculated for all relevant outcomes. As with bootstrap estimation methods and other computer-intensive algorithms, Monte Carlo simulation models are becoming increasingly feasible, complex and realistic as computational power advances [25,26]. The advantage of Monte Carlo simulation models is that one can easily build more sophisticated stochastic processes than with models that rely only on probability expectations. One has to be careful to accurately reflect Monte Carlo simulation model precision and how it is affected by underlying parameter uncertainty and iteration frequency.

2. Pharmacoeconomic modelling issues

2.1 Which economic evaluation methods are best?

Although four methodologies are typically identified for pharmacoeconomic evaluation; cost-benefit analysis, cost-effectiveness analysis, cost-utility analysis and cost-minimisation analysis (Box 2), only the first two methods are substantive and distinct. Cost-minimisation analysis considers only intervention costs. It does not permit quantification of the outcomes associated with different interventions, and thus, has very limited application. Cost-utility analysis can be considered a special case of cost-effectiveness analysis, in which the outcome to be balanced against cost is a utility index value for each alternative intervention health states.

Any economic evaluation method will have embedded assumptions and implications for how the values of different individuals and population subgroups are weighted in the analysis [27-29]. Cost-effectiveness analysis predominates in pharmacoeconomic modelling, and is the evaluation approach recommended by the US Public Health Service Task Force Panel on Cost Effectiveness in Health and Medicine [27]. Their ‘reference case’ evaluation is a cost per quality adjusted life-year (QALY) outcomes analysis conducted from a societal perspective. This methodology is advocated because it does not require the analyst to assign monetary values to changes in risk of patient survival, pain, suffering or QoL. Moreover, as all QALYs are valued equally, irrespective of patient demographic characteristics or patient privilege, status or fortune, the cost per QALY has a built-in egalitarian bias, particularly relative to cost-benefit analysis, which gives greater weight to outcomes occurring among those patients with greater economic resources [30]. Nevertheless, concerns exist with the cost per QALY evaluation method. It is only consistent with optimal healthcare resource allocation under very restrictive assumptions regarding patient utility and social welfare [31-35]. It is somewhat arbitrary as to which cost or outcomes to include in the cost per QALY analysis, and how to include them. There has been a debate about whether future non-medical costs or medical costs that are unrelated to the evaluation alternatives should be included in the cost-effectiveness analysis [33]. There are concerns that QALYs do not adequately capture employee productivity losses in some circumstances, or how productivity losses should be measured in cost-effectiveness analysis [36,37]. Moreover, some intervention effects could be just as easily allocated to either the numerator (costs) or the denominator (QALY’s) with very different effects on the cost-effectiveness ratio. For example, consider a diabetes intervention (e.g., oral insulin) that eliminated the daily need of the patient to measure blood sugar and use self-injected insulin. The amount of time that the patient gained in reduced daily time for self-care could be subtracted from the indirect costs of disease treatment (numerator), or it could be added to the

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**Box 2. Economic evaluation types differ by method for quantifying outcomes.**

<table>
<thead>
<tr>
<th>Method Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost-minimisation analysis</strong></td>
<td>Which alternative has the lowest cost? (Health state outcomes are not quantified)</td>
</tr>
<tr>
<td><strong>Cost-effectiveness analysis</strong></td>
<td>Which alternative has the lowest cost in achieving the stated outcomes objective? (Health state outcomes are quantified in some fashion)</td>
</tr>
<tr>
<td><strong>Cost-utility analysis</strong></td>
<td>Which alternative has the lowest cost in achieving the stated outcomes objective? (Health state outcomes are quantified in a utility index)</td>
</tr>
<tr>
<td><strong>Cost-benefit analysis</strong></td>
<td>Which alternative achieves the greatest net benefits minus costs? (Health state outcomes are quantified in monetary terms)</td>
</tr>
</tbody>
</table>
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improved patient QoL (denominator). The resulting cost-effectiveness ratios could conceivably be very different and lead to different policy decisions, based on arbitrary accounting differences for treatment effects.

Cost–benefit analysis, or more precisely, net-benefit analysis (benefits – costs), has long been preferred by economists, as it is easier to ground cost–benefit analysis in traditional utility theory and social welfare analysis, and it does not require ratios of outcome measures as with the cost-effectiveness method. Ratio measures are problematic for several reasons. Intervention A may have a very favourable cost-effectiveness ratio but be applicable to a rare disease and not produce many societal benefits whereas intervention B, for a common disease but with a less favourable cost-effectiveness ratio, may produce more total net benefits to society, and thus, should receive higher priority. Finally, given scarce resources, any healthcare decision-maker facing the task of ranking and allocating alternative healthcare interventions will ultimately have to establish an implicit monetary cost per QALY threshold value to decide which interventions are acceptable at the margin [38]. As a cost–benefit analysis does this explicitly, it fosters greater decision-making transparency and wider applicability.

A key shortcoming in cost–benefit analyses has been establishing monetary values for intervention health impacts. The cost-effectiveness method is inherently more egalitarian, as a cost–benefit analysis accepts existing wealth and income distributions in deciding how much people are willing to pay for alternative medical interventions. This is not an unambiguous advantage for the cost-effectiveness analysis method. Firstly, QALYs or other outcome measures that are based on the underlying life expectancy of the individual are not perfectly egalitarian. They have a definite bias favouring those patient categories with longer normal life expectancies, including Asians, Caucasians, younger patients, females and those without chronic disease; as QALYs gained through reducing disability in these populations will be relatively larger.

Secondly, in market economies, those with greater financial means are always able to command more resources, including healthcare. If the rich perceive that they are not getting medical services that they are willing to pay for, they will go elsewhere; either to black markets or to international healthcare providers. It can be argued that health insurance and government healthcare programmes already reflect the level of income and wealth redistribution for the provision of healthcare that each society is politically willing to assume, and that benefit estimates based on existing subsided healthcare prices reflect societal willingness to pay at the margin. In any case, whether using cost-effectiveness or cost–benefit analysis, it is important to point out any distributional inequalities resulting from different weighting of outcomes in patient subgroups, whether due to socioeconomic, demographic, medical history or to other factors.

In non-medical cost–benefit analyses, economists typically use revealed preference (RP) methods to determine benefit values – how much people are willing to pay for goods and services, usually through estimating demand functions with market data. Such an approach is impractical for most health improvements, as relevant markets either do not exist, or are heavily curtailed, regulated or distorted (e.g., the market for donor organs). Recent research in establishing benefit valuations has focused on the use of stated preference (SP) methodologies rather than RP methods.

SP methods involve asking subjects to rank or value alternative hypothetical health states in a series of choice experiments. When evaluated appropriately, such SP rankings are then convertible into preference and willingness-to-pay benefit measures. Current SP methods, particularly conjoint analysis, can be used to establish valid and reliable monetary valuations for healthcare interventions that can be incorporated into cost–benefit analyses [39,40]. Conjoint analysis is rigorously grounded in both economic utility theory and econometric estimation models with testable parameter restrictions, providing a direct assessment of consumer willingness-to-pay for treatment options in a framework that is resistant to subject ‘response gaming’. It can be combined with data from RP studies to provide results that are more precise than either method separately. It has been used and validated in numerous private-sector and public-sector studies in many different fields of preference elicitation, and is growing rapidly in the healthcare evaluation literature [41].

The reliability and validity of SP value elicitation methods have been criticised as not being behaviourally accurate [42,43]. It is claimed that the artificial aspects of a hypothetical choice situation lead subjects to respond differently than in real life. Nevertheless, these methodological concerns apply as strongly to the health outcomes valuation methods used for measuring QALYs or alternative outcome measures used in cost-effectiveness analyses. It is very difficult to measure subject health state preferences without having them consider hypothetical trade-offs in artificial experimental settings.

2.2 How should model time horizons and discounting be handled?
Pharmacoeconomic models should base the analytical time horizon on the period in which the intervention has significant costs, health status or other outcome impacts. This is particularly difficult in lifetime chronic disease models, where available clinical trial data or treatment cost data seldom capture decades of therapeutic intervention [31]. Even if such lifetime data were available, cost, utilisation or clinical outcomes data that were decades old would often have limited relevance to decisions being made for patients anticipating treatment today, and over several decades into the future.

There have been controversies about time discounting in pharmacoeconomic models; how to convert future streams of costs, benefits or QALYs into comparable present value equivalents [27,44,45]. Many of these controversies stem from failure to recognise differences in the decision-maker perspective. Each perspective could plausibly imply different opportunity costs of time and possible differences in time trade-offs for...
Box 3. Pharmacoeconomic model data sources.

**Literature review**
- Use systematic inclusion and exclusion criteria to decide which data available in the peer-reviewed or other literature is relevant to the analysis

**Prospective data collection**
- Use a prospectively designed and implemented study to obtain parameters of interest

**Retrospective data collection**
- Use data from a pre-existing study or database (e.g., insurance records, medical history records) to obtain parameters of interest

**Expert opinion**
- Obtain parameters of interest by polling experts in the relevant field

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Inclusion and exclusion criteria, it is less likely that the resulting parameter estimates will exhibit bias. A meta-analysis is the data synthesis part of a systematic review. It will increase parameter precision when individual studies do not have enough power to detect a significant effect, as it includes more patients than any single constituent study. It produces more reliable results over a wider range of settings and contexts. Pharmacoeconomic models have generally not incorporated systematic review and meta-analysis methods as completely as possible, often using a non-systematic (ad hoc) approach to establishing base case parameter values from the available literature.

Prospective analyses, particularly when based on randomised, controlled trials, are the most rigorous and internally valid approaches to establishing pharmacoeconomic parameter values [51]. Random assignment of study subjects to intervention alternatives ensures that costs, QoL and other outcome measure differences reflect true intervention differences, rather than artifacts of patient and/or provider selection bias. Because the analyst designs the prospective data collection instruments and sample in advance, whatever variables are needed can be captured with adequate precision. The drawbacks for prospective data collection studies are study costs, study time requirements and potential concerns about the external validity and generalisability of results [52].

It should be pointed out that merely piggybacking a pharmacoeconomic study on top of a typical clinical drug trial is often ineffective for capturing pharmacoeconomic parameters. Most Phase II and III clinical trials are not well-suited or designed to capture valid and reliable pharmacoeconomic data. They are usually placebo-controlled, rather than employing active comparisons, they have built in patient selection, treatment protocols and medical utilisation patterns that are atypical in a real-world setting, and they are subject to Hawthorne effects - patients and providers do not behave the same as they would if they were not being studied.

Retrospective analyses have a different set of strengths and weaknesses than prospective studies [53-55]. They are limited to
existing available data sets, such as insurance or government programme claims history or utilisation records. It is usually difficult to get retrospective cost or utilisation data that are linked to medical charts or other medical history information, so many aspects of patient health status and outcomes must be assessed indirectly. They have serious potential problems with patient and/or provider nonrandom selection of treatments, and require more sophisticated econometric analysis techniques than prospective studies [56]. Despite these drawbacks, retrospective data reflect real-world medical care utilisation and outcomes unburdened with study protocols. They are less expensive and easier to obtain than prospective studies, and are the only feasible available alternative for capturing pharmacoeconomic data in many circumstances.

In nearly all pharmacoeconomic models there are at least some parameters or modelling decisions that are not formally supported by literature or existing data. For these situations, the analyst is called on to use their best judgement, and to state the rationale clearly for the chosen parameter values and ranges. Even here, there is an opportunity to improve parameter precision by using ‘expert opinion’ to establish ranges for crucial unknown parameters. For example, in order to extend the cardiovascular disease risk reduction parameter beyond the time frame of existing statin clinical trials, one might assemble an expert panel of cardiologists, and choose the median value and parameter ranges based on their feedback. Even though no one knows what will happen to patients long beyond clinical trial timeframes, it would be difficult to contest the views of the best experts in that field. A variety of methods for systematically incorporating expert opinion into valid consensus estimates have been developed. The best-known of these is the Delphi method, which involved obtaining anonymous estimates from the various experts, providing feedback to them on group estimates and asking them to consider refining their estimates. This is iterated until the range of responses fails to converge further [57,103].

2.4 Incorporating uncertainty in pharmacoeconomic models

There are several sources of uncertainty in pharmacoeconomic models [27]. In fact, one of the most important contributions that models provide is to quantify which sources of uncertainty and parameter variation are crucial to model results, and which sources do not impact model findings. This allows policy makers to gauge the strength of confidence warranted for their decisions, and helps allocate research resources towards a better understanding of key model parameters.

Healthcare leads to uncertain patient outcomes, and nearly all pharmacoeconomic models use probability-weighted expected values to capture the inherent randomness in costs, health states and other model outcomes. There are also uncertainties because many parameters are not known precisely, or have different values for different decision-makers. For example, the true efficacy of a drug may only be estimated up to a certain level of precision, based on available clinical trial data. This type of uncertainty is defined as stochastic parameter uncertainty.

Some model parameters may be fully known or otherwise non-stochastic, but may still have variable effects on model results. For example, the rate of time discount might be set at 3% in the model, whereas a decision-maker in a different setting might rather use a 5% discount rate, or someone in another country may want to use different known hospital prices. Finally, the choice of the modelling framework and model structure itself will lead to uncertainty in model results.

Pharmacoeconomic models should be reported in terms of a ‘base case’ that reflects the best judgement of the analyst for all parameter values, with upper and lower bounds reflecting both stochastic and non-stochastic parameter uncertainty. The base case values are often chosen to reflect some midpoint, median or central tendency of available data or literature review results. However, the main criterion for the base case values should be the decision-maker’s informed beliefs concerning parameter value plausibility, regardless of parameter data ranges.

Non-stochastic model parameters should be varied across their plausible ranges, with the results reported in either one-way or multi-way sensitivity analyses, depending on whether one or more parameters are varied at the same time. Sensitivity analyses should usually report best case and worse case scenarios for key model parameters. Threshold sensitivity analyses are used to show how much one or more parameters would have to change before the model results would imply a different policy conclusion.

In situations where model parameter means and standard errors (or other measures of precision) are available from the literature, clinical trials or other sources, there are several approaches to assessment of parameter uncertainty. A major issue in handling stochastic uncertainty relates to the philosophical distinction between Bayesian and classical frequentist analysis of random data [58]. In the traditional frequentist analysis, parameters are fixed and data are random, whereas in the Bayesian approach the converse is true. Frequentists use data to accept or reject hypotheses about parameter values or establish parameter confidence intervals. Bayesians use available data to estimate a ‘posterior’ parameter distribution, applying Bayes theorem to update and improve the precision of their prior beliefs about parameter values.

Bayesians have strong prior beliefs that their approach is superior, particularly in the context of healthcare decision making [59]. Nevertheless, most healthcare and pharmacoeconomic analysts remain unconvinced. Bayesian analysis has yet to establish a ‘killer application’ where the results are so superior to frequentist analysis that it becomes indispensable. Although Bayesian analysis is quite attractive on theoretical grounds, it adds a complicated set of new mathematical tools and jargon, making pharmacoeconomic models even less accessible to the unsophisticated user. Bayesian analysis often creates posterior statistical distributions that are too complex to even write down in closed form, and whereas these distributions can still be
Table 2. Alternative data sources for the declining exponential approximation of life expectancy method mortality calculations.

<table>
<thead>
<tr>
<th>Data source example</th>
<th>Study population example</th>
<th>Estimated excess mortality rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality rate</td>
<td>56-year-old men</td>
<td>Compound mortality rate – population mortality rate</td>
</tr>
<tr>
<td>Life-expectancy</td>
<td>56-year-old men and women</td>
<td>1/(patient-specific life-expectancy) – 1/(population life-expectancy)</td>
</tr>
<tr>
<td>5-Year survival</td>
<td>55-year-old men</td>
<td>-(1/5) (natural log of 5-year survival)</td>
</tr>
<tr>
<td>Median survival</td>
<td>56-year-old men</td>
<td>= -0.693/(survival time)</td>
</tr>
<tr>
<td>Survival curve</td>
<td>56-year-old men</td>
<td>Slope of negative log-survival curve</td>
</tr>
</tbody>
</table>

Adapted from [66].

Table 2 demonstrates the simplicity and flexibility of the DEALE methodology, showing how multiple alternative information sources can be used to estimate disease-specific hazard rates.

2.5 Pharmacoeconomic model quality, validity and usage guidelines

There are several international guidelines, recommendations and checklists for pharmacoeconomic model development and presentation [67-74]. Some of these are established by scientific organisations and peer-reviewed journals, some are established by healthcare reimbursement authorities and some are promulgated by the pharmaceutical industry. There is a fairly broad consensus on issues that are crucial to ensuring pharmacoeconomic modelling quality. Chiou et al. [75] developed and validated a conjoint analysis-based measure of pharmacoeconomic study quality scoring that is relatively easy to apply to pharmacoeconomic models reported in the literature [76]. The components and scoring weights of this quality index are shown in Box 4.

Pharmacoeconomic models are most useful and convincing when they are fully transparent to the user. Some peer-reviewed journals require that all models and data be made publicly available for others to test and evaluate. This is not always practical, as many pharmacoeconomic models contain proprietary or confidential information that cannot be fully released. Additionally, models are often written in complex software code. It would be excessively burdensome to require that every model be made fully user-friendly. A compromise recommended by the International Society for Pharmacoeconomics and Outcomes Research Pharmacoeconomic Modelling Task Force is ‘... while the source code should generally remain the property of the modeller, reasonable requests for copies of models with adequate...’
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Box 4. Criteria and weights selected for quality of health economics scale grading system*.

- Was the study objective presented in a clear, specific and measurable manner? (7)
- Were the perspective of the analysis (societal, third-party payer) and reasons for its selection stated? (4)
- Were variable estimates used in the analysis from the best available source (i.e., randomised control trial (best), expert opinion (worst))? (8)
- If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study? (1)
- Was uncertainty handled by: statistical analysis to address random events; sensitivity analysis to cover a range of assumptions? (9)
- Was incremental analysis performed between alternatives for resources and costs? (6)
- Was the methodology for data abstraction (including value health states and other benefits) stated? (5)
- Did the analytical horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3 - 5%), and justification given for the discount rate? (7)
- Was the measurement of costs appropriate, and the methodology for the estimation of quantities and unit costs clearly described? (8)
- Were the primary outcome measure(s) for the economic evaluation clearly stated and were the major short-term, long-term and negative outcomes included? (6)
- Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used? (7)
- Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear transparent manner? (8)
- Were the choice of economic model, main assumptions and limitations of the study stated and justified? (7)
- Did the author(s) explicitly discuss direction and magnitude of potential biases? (6)
- Were the conclusions/recommendations of the study justified and based on the study results? (8)
- Was there a statement disclosing the source of funding for the study? (3)

*Criteria weights (out of a total of 100) listed in parenthesis after each criterion.

Adapted from [75]

user interface should be made available for peer review purposes, under conditions of strict security and protection of property rights [74]. This is the approach taken by Value in Health and many other peer-reviewed journals in the field.

Model validation is a difficult and imperfect process. Internal validation is a necessary step but not sufficient. Certainly, all efforts should be undertaken to test and debug model equations, and to calibrate model predictions against available information from other models or external data. For example if a breast cancer screening model projects a 30% reduction in breast cancer deaths in the US population based on known screening patterns over the past decade, this should be matched against what becomes known about the observed change in actual breast cancer mortality. Often the best way to catch logical flaws or other modelling problems is using one-way sensitivity analysis to set parameters at extreme values (even implausible values) and observe the resulting pattern of model results. ‘Shake it ‘til it breaks’ is a good way to gain insights into model robustness. Porting the model to a new population subgroup or country, and checking the resulting predictions is another way to ensure internal consistency.

Pharmacoeconomic models will always be limited by their underlying scientific knowledge base. For example, recent negative clinical findings for oestrogen replacement therapy from the Women’s Health Initiative trial have completely altered cost-effectiveness calculations for this intervention in ways that were not previously foreseen by clinicians or pharmacoeconomic modelers [77]. On the other hand, pharmacoeconomic models of statin therapy have stood the test of time reasonably well, primarily because early projections of statin therapeutic benefits based on Framingham risk reduction equations were somewhat conservative compared to the results of recent statin outcomes trials [20,78]. In situations where clinical trial data do not address longer term outcomes, or different patient subgroups pharmacoeconomic models can provide misleadingly precise estimates by assuming that observed relative risk reductions carry over directly beyond the bounds of the observed clinical trial results. While often plausible, this assumption is sometimes invalid.

One area where some pharmacoeconomic models have not done well is in projecting the benefits of cholinesterase inhibitor therapy for mild-to-moderate Alzheimer’s disease patients beyond the short-term data available from existing medication clinical trials [79-82]. Extrapolated risk reductions do not have the hypothesised impact on institutionalisation and survival that these models predicted, and yet, these extrapolated benefits drove very favourable cost-effectiveness results. More recent findings do not confirm that short-term improvements in cognitive function are associated with longer term reductions in institutionalisation or progression of disability [83-85]. It is important to make fully clear what the impact of beyond-trial extrapolations is on model results [86,87]. In these cholinesterase inhibitor cost-effectiveness models, the unsubstantiated extrapolations accounted for the full estimated therapeutic benefits and created inappropriate policy implications.
A final issue in evaluating pharmacoeconomic model quality is the determination of what biases may have been implicitly or explicitly imposed on model development and result presentation. While all research is subject to possible bias, an obvious source of potential bias is the model research sponsor. One safeguard against this is to ensure that funding sources or other potential conflicts of interest are fully disclosed in model presentations and in submissions to journals. Another is the requirement established by the World Association of Medical Editors that participating journals require authors to affirm that sponsors had no control or censorship of submitted material [104]. Ultimately, pharmacoeconomic models should be judged on their intrinsic merits rather than ad hominem criteria such as sponsorship or authorship. Unfortunately, the editorial policy of the New England Journal of Medicine disagrees with this, and excludes all cost-effectiveness articles that are ‘...by authors with any financial connections to companies whose products are featured prominently in the article (or their competitors)’ [88]. The policy of the New England Journal of Medicine is a minority view among scientific journals. As the Editors of the Journal of Mental Health Policy and Economics state [89] ‘Exclusion of submitted [cost-effectiveness] manuscripts by authors who have a personal conflict of interests is not consistent with the aims of our journal because the evaluation of the perspective that is under economic analysis and its implications for decision making are a fundamental part of the review process of this journal. The reviewers are able to judge the methods of the study and to check the reliability of a result on the implications of the results for decision making.’

Caveat emptor certainly applies to pharmacoeconomic models as it does to anything else. It is precisely the publication of pharmacoeconomic models based on existing guidelines in peer-reviewed scientific journals that ensures their credibility, validity and accuracy. It is much more likely that flaws in a pharmacoeconomic model submitted to a prominent scientific journal would be quickly discovered and discredited, usually prior to publication than in a model that was privately and confidentially shown to a managed care organisation formulary committee but never submitted for publication.

3. Expert opinion and discussion

Pharmacoeconomic models are not mathematical abstractions to demonstrate the analyst's intellectual prowess in stacking angels on the head of a pin. Every day, real-world decisions must be made with fixed budgets to either provide drug therapy to patients or withhold that therapy. Drug spending for one patient reduces resources available for the next patient. These decisions cannot wait for perfect information, or even for the next study. It is better that these decisions be informed by carefully constructed pharmacoeconomic models, with explicit parameter values open for inspection and validated through publication in the peer-reviewed literature, rather than by nameless or hidden bureaucrats reflecting their own prejudices.

Tremendous progress in methodological rigor and exciting new research directions have emerged for the development of pharmacoeconomic models over the past decade. This parallels the rapid growth of pharmacoeconomic models in the delivery of effective healthcare, and corresponding concerns about drug costs. It is likely that large-scale integrated healthcare delivery and medical history data systems will allow pharmacoeconomic microsimulation models of individual patient behaviour and outcomes that are vastly more sophisticated than today's models. The Medicare Modernisation Act will undoubtedly spur further substantial development in pharmacoeconomic modelling as the US federal government takes on the financial risk for managing drug therapy effectively and efficiently for millions of current and future retirees. In most other countries, concerns for the drug cost and utilisation requirements of rapidly ageing populations are already acute. Pharmacoeconomic modelling has a bright future, if for no other reason than the alternatives for social resource allocation are unsustainable in open societies. Even a flawed pharmacoeconomic model is better than an arbitrary and obscure medical decision process, if it leads to critical examination, open discussion and further research.

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A comprehensive evaluation of the literature up to 1996.


A useful introductory textbook.


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A useful contrast of Markov models and discrete event simulation models.


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An example of bootstrap confidence interval calculations.


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