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The Use of Economic Evaluation in Pediatric Research

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Glasgow et al reported a cost-utility analysis of prophylactic dextrose gel compared with standard care for neonatal hypoglycaemia in at-risk infants.[22] They found this simple intervention not only reduced long term morbidity and mortality but saved money too. Their analysis is based on a decision tree model, evaluated over a time horizon of 18 years.

A cost-utility analysis is a type of economic evaluation and provides information as to the value for money of different health care interventions. This in turn helps maximise the health benefit to a population subject to the available budget, whether that population be all citizens in a national health system or the members of a health insurance scheme.

What has economics got to do with medicine?

Economics starts with the observation that resources are finite: health systems in most countries are big, but nevertheless only have so many doctors, nurses, hospital buildings, scanners, and drugs at their disposal at any one time. This means that using those resources to treat one patient (or group of patients) leads to others foregoing treatment from which they could have benefited.

This operates at every level: an individual pediatrician who treats, say, two children with complex needs on a morning list has foregone the opportunity to treat, say, eight children with less complex needs. A hospital wishing to purchase a new scanner for one department may have to forego expanding staffing in a different department to pay for it. An insurer agreeing to reimburse a new, expensive cancer drug must make room for it by reducing coverage elsewhere (or shift the burden onto the insured who then have to decide whether to pay a higher premium and thus forego spending elsewhere, or shop around for a less comprehensive policy). This foregone benefit is what we call the "opportunity cost" and is fundamental to economics. 'Cost' is not simply a quantity of dollars. The dollars represent a quantity of resources reallocated from another use, and ultimately the foregone benefit from that other use: in medicine, cost is someone else's health gain foregone.

It is reasonable to suppose that a "decision maker" wants to maximise the benefit for the available resources, or conversely, to minimise the opportunity cost.[1] In each of the examples above, the

decision maker needs to weigh-up the benefits and (opportunity) costs of their decisions: does the benefit of the new scanner outweigh the foregone benefit the extra staff would have provided? More provocatively, does the health gain received by the two seriously ill children outweigh the foregone health gain from the other eight?

Arguably then, decision making involves identification of the winners, identification of the losers, measuring whether the gains to the winners exceed the losses to the losers (efficiency), and evaluating whether we (as individuals and/or 'society') are comfortable with the result (equity). Economics provides a toolkit to assist in this process, and health economic evaluation is one such tool.

What is economic evaluation?

Economic evaluation is defined as "the comparative analysis of alternative courses of action in terms of both their costs and consequences".[2] The first key point to note is that it is always a *comparative* (aka, *incremental*) analysis.[3] When a manufacturer claims their drug is 'cost-effective', the first response should be 'compared with what'? It should be compared with the next best alternative, and this may, of course, be 'do nothing' or 'treatment as usual'. The second key point is that it involves measurement and valuation of both costs AND effects (ie, outcomes).

The key statistic is the incremental cost effectiveness ratio, or ICER (Table I). Suppose we are evaluating a new drug compared with treatment as usual (TAU). The ICER is the difference in cost between the two divided by the difference in outcome. This states how much it costs for every extra unit of outcome we obtain by switching to the new treatment from TAU. The ICER is compared with some maximum "willingness to pay" threshold representing the opportunity cost of other displaced treatments. If the ICER is below this threshold, the intervention is deemed good value for money. If it is above this threshold it is poor value for money: more health could be gained by investing the resources elsewhere. It is often useful to depict the difference in cost and outcomes graphically on the cost-effectiveness plane, especially when it comes to displaying sensitivity analyses (Figure 1).

Economic evaluations come in four 'flavors' (Table II).[2] They all measure costs (the numerator in the ICER) in the same units, whether dollars, euros or pounds etc, but differ in the outcome measure (the denominator of the ICER). Perhaps the most useful is the CUA, measuring outcomes in overall life expectancy adjusted for the quality of that life, known as Quality Adjusted Life Years (QALYs), or their closely related cousin, DALYs (disability adjusted life years).[4] CUA is technically a subset of CEA, but the terms 'cost-effectiveness analysis' and 'cost-utility analysis' are often used interchangeably. For example, we tend to talk in terms of 'incremental cost-*effectiveness* ratios' whether the analysis is a CUA or CEA.

Measuring costs and outcomes

When measuring the cost of an intervention, it is not just the acquisition cost of the drug or device that must be measured, but the cost of the entire patient pathway. For example, a drug may be expensive to buy, but if it reduces the need for hospitalisations then the total cost of the 'treatment strategy' should take this into account. It is also important to define whose costs are included: are we only interested in the insurer's costs, the state's costs or out of pocket costs for patients too? And what about costs imposed on family members or carers, or lost economic output due to inability to work? The 'ideal' cost perspective is that of the whole of society. However, the broader the cost perspective, the more difficult it is to obtain robust estimates - and the more open those estimates are to manipulation. Therefore, some reimbursement agencies (eg, NICE in the UK) adopt a more limited 'public sector health and social services' perspective for their primary analyses.[5]

For outcomes, in CUA the key issue is how to put the 'Q' into a QALY. Being in a certain state of ill health is assigned a value relative to two anchor points: 1 for full health and 0 for dead. This is called the utility of that health state (the term 'preference weight' is also used). There are a number of methods to elicit these values from the general population, but all should involve weighing up trade-offs.[6, 7] The QALYs accrued are simply the amount time spent in a health state multiplied by its utility, so one QALY can be generated from one year in full health or two years at '50%' health etc.

The advantage of QALYs is that they capture not only treatment effects but the impact of adverse events, relapses etc in one overall measure.

Decision models vs clinical trials

There are two main approaches to economic evaluation. Resource use and cost measurement can be 'piggybacked' alongside a randomised controlled trial (RCT) measuring outcomes, allowing a 'within trial' ICER to be calculated. Whilst appropriate in many cases this is not always ideal,[8] not least because decision making should take into account 'all relevant evidence',[9] which usually means more than just a single RCT. The solution, then, is to construct a decision model, which can be defined as a synthesis of all relevant, quality-assessed evidence on the costs and consequences of the difference courses of action. A model can take many forms, but common ones are decision trees and Markov models.

A decision tree structures a decision problem into nodes of three types: decision, chance, and terminal (Figure 2). Costs and outcomes (eg QALYs) are assigned to each terminal node (although they can be assigned at chance nodes too). Analysis then proceeds from right to left, calculating the weighted mean cost and outcome at each node, ultimately calculating the cost and outcome of each strategy at the decision node (a process known as 'rolling back' the tree).

A Markov model divides a disease into several discrete health states (Figure 3). The model is evaluated over a number of 'transition periods' of a defined length (eg, year). Each period a simulated cohort of patients transition between the health states with given probabilities. Each health state has a cost and health outcome attached to it, and the costs and QALYs accrued from running the cohort through the model totalled. The model is run once for TAU and again for New drug, using relevant transition probabilities and costs each time.

Ultimately, the output of any model is the total cost under each treatment strategy, and the outcome (eg, QALYs) under each, evaluated over an 'appropriate' time horizon. These are the numbers needed to calculate the ICER.

Analysis of uncertainty

One-way sensitivity analysis explores the robustness of a model's conclusions by varying one input parameter at a time and observing how that changes the ICER. This has its limitations though, not least that it does not take into account how likely the upper and lower values are to occur in reality. A preferred approach therefore is a probabilistic sensitivity analysis, where every input parameter is assigned a probability distribution. The model then repeatedly samples (typically 10,000+ times) from the distributions and records the results in what is known as a Monte Carlo simulation. This generates multiple estimates of the incremental cost and incremental outcomes which can be plotted on the cost-effectiveness plane (as per Figure 1) or summarised in a cost-effectiveness acceptability curve (CEAC), showing the probability that a treatment is cost-effective at different willingness to pay thresholds.

Further reading

It is only possible to scratch the surface of the details of economic evaluation in this short introductory article. Issues I have not addressed include discounting future costs and benefits,[10] reporting net benefit instead of ICERs,[11] handling analyses with more than two comparators, quality assurance and reporting guidelines,[2, 12, 13] and controversies around the willingness to pay threshold.[14-16] The core textbooks on economic evaluation are Neumann et al (based on the second 'Washington panel' consensus meeting) and Drummond et al (the key textbook for health economic evaluation in the UK and elsewhere). [1] [2] Although 20 years old, the book by Jefferson et al is a very well written, short overview of the subject aimed at busy clinicians. [17] I would also recommend Briggs et al for more detailed learning on decision models, and Glick et al for economic evaluations alongside clinical trials. [18] [19]

Summary

Health economic evaluation is a tool to assist decision making in health care. The most important contribution economics brings to medicine and health is recognition that any decision involving resource allocation, whether time, doctors, nurses, equipment, or drugs bears an opportunity cost in terms of another patient's foregone health gain. Economic evaluation is an analytic tool to help weigh up the relative gains and losses to different groups to assist in decisions to allocate those resources to best effect.

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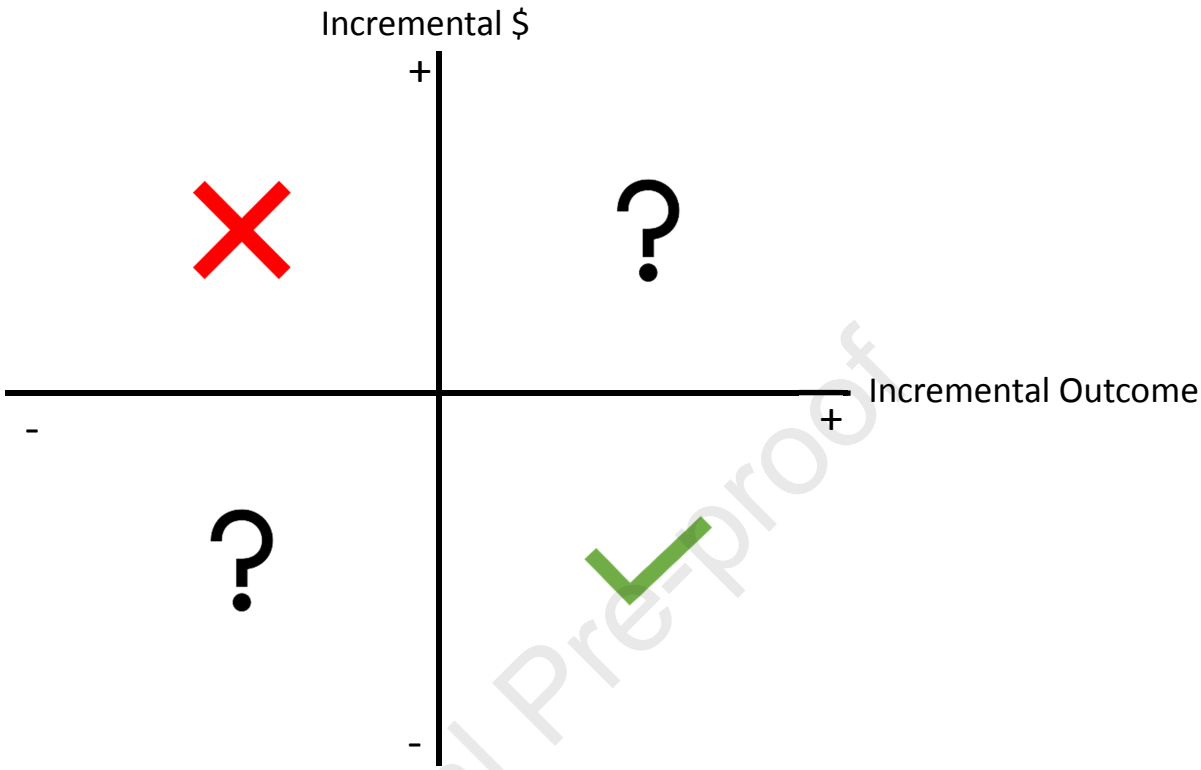
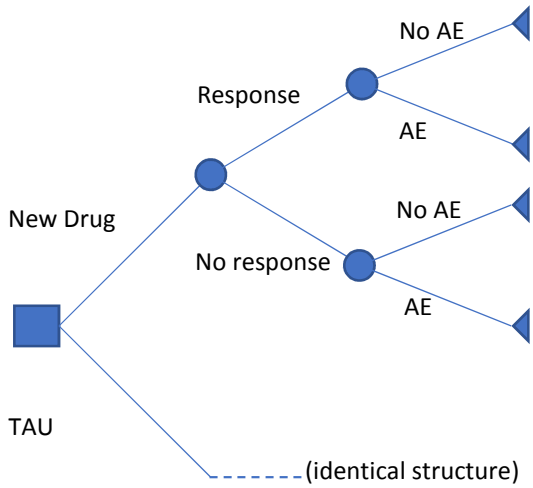
Figures

Figure 1: The cost-effectiveness plane



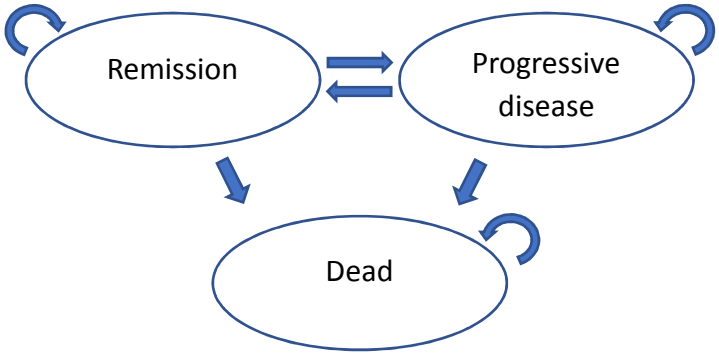
The cost-effectiveness plane centres Treatment as usual (TAU) at the origin, with incremental cost on the Y-axis and incremental effect or outcomes (eg Quality Adjusted Life Years, QALYs) on the X-axis. This defines four quadrants. If New lies in the South East quadrant, it is both less expensive and more effective than TAU, in which case we say New 'dominates' TAU, and we should accept New as cost-effective. The reverse is true in the North West quadrant. However, in the North East quadrant New is both more effective and more expensive so we need a decision rule: how much are we willing to pay for an extra unit of effect? This is where we need to compare the ICER with the threshold. (Again, we have the reverse situation in the South West where we need to consider how much we are willing to receive to forego an extra unit of effect. This may seem like an odd question to ask, but remember those freed up resources could be reinvested elsewhere to greater benefit.)

Figure 2: Decision tree example



Node types: square = decision, round = chance, triangle = terminal. Costs and outcomes (eg QALYs) are assigned at the terminal nodes (or sometimes, at the chance nodes), and the tree 'rolled back', working out the expected cost and outcomes at every node until the decision node is reached. AE = adverse event, TAU = treatment as usual.

Figure 3: Markov model example



A set of transition probabilities is defined, based on the natural history of the disease, and the model run for a number of cycles, calculating the proportion of a hypothetical cohort in each state each time period. Time spent in a state accrues cost and QALYs. The model is run once for TAU, and again for the New treatment, with treatment-specific probabilities and costs.

Tables

Table 1: Incremental Cost Effectiveness Ratio (ICER)

$$\frac{C_2 - C_1}{E_2 - E_1} \leq \lambda$$

The ICER is the difference in cost between two interventions (C_i), divided by the difference in outcomes (E_i). This must be below some maximum 'willingness to pay' threshold, λ.

Table 2: Four flavors of economic evaluation

Cost minimisation analysis (CMA)

CMA can only be used when there is evidence that outcomes between two treatments are identical. In which case, the economic evaluation reduces to a simple comparison of costs. CMAs are controversial though, as, except possibly in the case of generics vs branded medicines, it is almost impossible to say that two different treatments are of identical effect:[20, 21] a lack of statistically significant difference can only infer absence of evidence, not evidence of absence.

Cost-effectiveness analysis (CEA)

CEA measures outcomes in clinical units, such as mmHg change in blood pressure, number of fractures or life years accrued. The ICER then expresses the extra cost for an extra mmHg blood pressure reduction, fracture averted or life year gained. The problem with CEA is that comparisons are limited to within-disease area, yet decisions ultimately traverse these: how much is a recurrence of leukaemia avoided 'worth' compared with surgery to correct leg length discrepancy?

Cost-utility analysis (CUA)

CUA attempts to solve the limitations of CEA by converting clinical units into overall improvements in length of life, adjusted for the quality of that life, resulting in a generic, non-disease specific measure called the quality adjusted life year, or QALY. This in theory allows comparisons across all disease areas.

Cost-benefit analysis (CBA)

CBA is where costs and outcomes are measured in the same units, usually in currency (dollars etc). This allows a simple comparison of the value of the costs with the value of the outcomes, again overcoming the comparability problems of CEA. CBA is the standard decision analytic approach in 'core' economics.

Figure 1: The cost-effectiveness plane

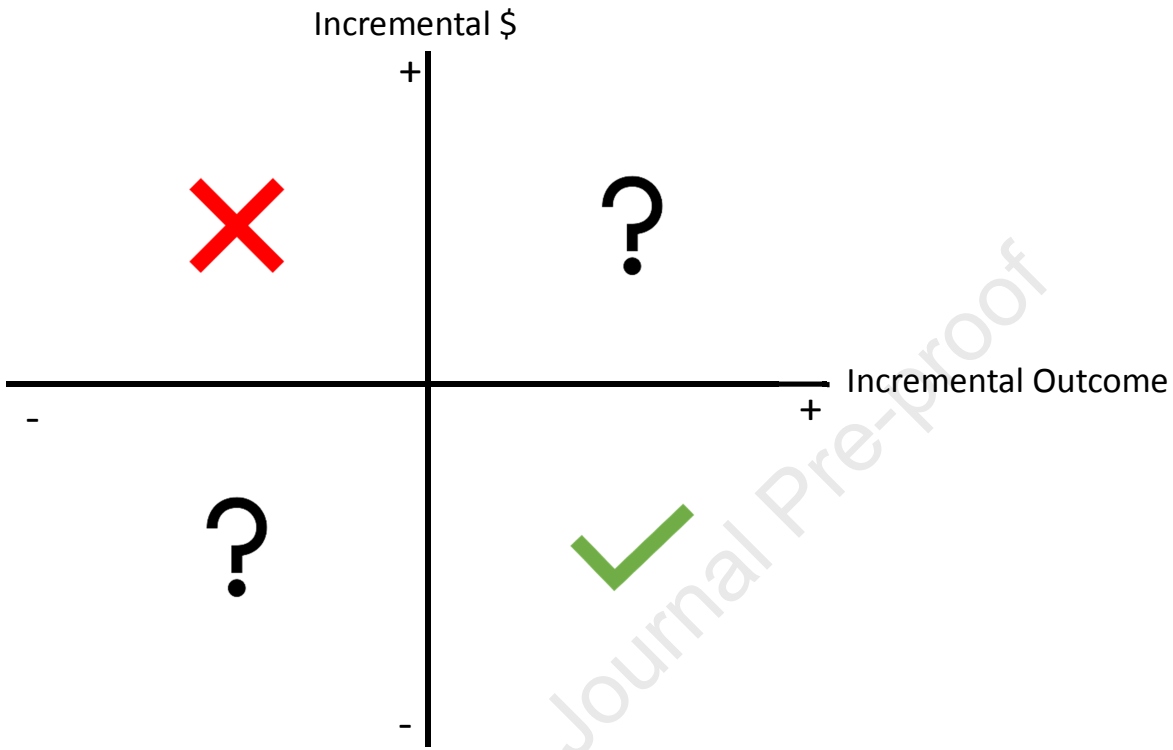


Figure 2: Decision tree example

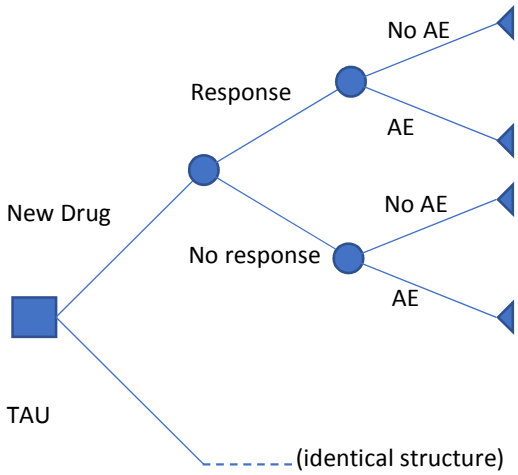


Figure 3: Markov model example