Cost-effectiveness assessment of cardiac interventions: determining a socially acceptable cost threshold

Healthcare is of such vital importance to every individual that it is considered by some to be a human right applicable to all human beings. Unfortunately, given this infinite demand, healthcare resources are limited even in rich countries and therefore need to be distributed efficiently to avoid waste. Thus, the relative value of a health intervention – cost compared with its effectiveness – needs to be taken into consideration when deciding which interventions to adopt. Cost-effectiveness analysis provides the crucial information that guides these decisions. As the field of medicine and indeed cardiology move forward with innovations that are effective but often expensive, it becomes imperative to employ these cost-effectiveness analytic tools, not with the intention of denying vital health services but to ascertain what society is willing to pay for.

KEYWORDS: clinical trials  cost–effectiveness  percutaneous coronary intervention  prevention  transcatheter valve therapy

In the current environment of astronomically rising healthcare costs, it has become imperative to seek the value of any new medical intervention especially where there is already standard treatment available. Cost–effectiveness analysis (CEA) offers tools that assist decision-makers in reviewing the relative value of health interventions. It involves evaluating competing therapies with the aim of informing medical and policy decisions. However, the limitations of CEA have led to some criticism. Critics of CEA state that it perpetuates the concept that there is a fixed value for all clinical interventions irrespective of medical disciplines and characteristics of patient populations [1]. A threshold sum of US$50,000 per quality-adjusted life-year has been widely cited in the USA as a threshold above which interventions may not be considered cost effective [2]. However, this has been arbitrarily based on CEA studies from renal dialysis [3], where willingness to pay (WTP) was agreed upon before the CEA studies were published. Critics of CEA further argue that potentially life-saving interventions may be perceived as being without economic merit if their costs are above US$50,000 or any other threshold, giving rise to concern that ‘death panels’ could make therapeutic decisions, with far-reaching consequences on choice of healthcare services made available to patients [1].

Conversely, CEA proponents emphasize that these methods should only act as a guide or, better still, used to provide insight into the value of a particular intervention, and not as a means to deny access to certain healthcare services with the goal of reducing healthcare expenditures [2]. In addition, proponents argue that if society is not aware of how much value a particular intervention offers, then it would lose information towards responsible appropriation and utilization of increasingly scarce healthcare resources [4]. Given the diversity of opinions, the aim of this review is to highlight how the CEA, a key method employed in health economic analytics, is used to assess the relative value of health interventions to the society with respect to the costs. Its unique ability to display cost–effectiveness ratios at different thresholds thereby making for a better informed decision will be discussed. Cost–effectiveness analyses of certain studies in interventional and preventive cardiology will be discussed for illustrative purposes.

The fundamental metric in cost–effectiveness research is the incremental cost–effectiveness ratio (ICER). When additional costs and incremental measures (and their individual distributions) of effectiveness of a new form of therapy as well as the previous standard are available, an ICER as well as its distribution can be measured [5]. The ICER is the ratio of the incremental cost of the new therapy compared with the standard divided by the incremental measure of benefit. It can be measured in cost per life-year or quality-adjusted life-year gained if the measure of benefit is expressed in life-years or quality-adjusted life-years respectively. The ICER should not be evaluated only as a...
In the cost–effectiveness plane, the difference in costs and the difference in health benefits can both be either positive or negative, there are four possible combinations, which are reflected in the four quadrants of the cost–effectiveness plane. When the ICER falls in quadrant 2 (southeast) where a certain intervention has more benefits and lower costs than its comparator otherwise called ‘dominated’, it represents the ideal situation. In the opposite quadrant 3 (southwest) where an intervention has fewer benefits as well as lower costs than its comparator, decision-making becomes more complex in quadrant 4 (northwest) where a certain intervention yields more benefits but also incurs higher costs. The economic merit of the intervention then depends, primarily on whether the ICER is lower than the threshold cost society or policy-makers are prepared to pay for an increase in health benefit. In health economics, quadrant 1 and quadrant 3 are sometimes treated similarly due to the complexity of decision-making involved in both scenarios. Unlike in dominant or dominated therapies where decision making is straightforward, the ICER in quadrant 1 applies to situations where there are potential opportunity costs for adopting a more expensive, albeit more effective intervention. Herein lies the dilemma.

The complementary approach to visualizing CEA results is a cost–effectiveness acceptability curve, which displays a range of willingness-to-pay thresholds on the x-axis and probability that the new therapy has an ICER below the threshold on the y-axis. This curve is a different way of displaying the same data illustrated by the different quadrants discussed above. In quadrant 1 of the CE plane, when the entire scattergram of the distribution is contained within the quadrant, as the threshold value of the ICER is varied from low to high, the probability of the ICER being below that threshold increases. A key advantage of this approach is that the probability that an intervention is cost effective when compared with an alternative will be displayed for a range of maximum cost the decision-maker will be willing to pay to gain a certain benefit, for example, 1 year of life. Therefore, this information de-emphasizes the potential limitation of the arbitrary threshold of US$50,000 in decision-making, thereby offering a greater understanding of value and costs of the intervention in question.

Cost–effectiveness analysis may be performed as simulations or alongside clinical trials using patient level data. A distinct
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The advantage of CEA alongside clinical trials is that it preserves randomization and the use of patient level data, permitting consideration of stochastic error with fewer assumptions than pure modeling exercises. The time horizon in a cost–effectiveness study alongside a clinical trial may consider in-trial data, but may also include modeling beyond the trial period. Using a lifetime time horizon permits fuller consideration of effectiveness and costs than in-trial data permit, albeit with additional assumptions, which may also be subject to sensitivity analysis.

If CEA was perfectly informed, then presumably a societal threshold can be used to pay for those things that are below the threshold. However, CEA always involves multiple assumptions concerning both costs and efficacy. In addition, there is the ‘rule of rescue’, which highlights the ethical inclination to use scarce resources to care for patients with acutely life threatening problems as opposed to programs for prevention. Both the uncertainty in the data and the rule of rescue limit the applicability of CEA to prevention, where there may be long term therapies with upfront costs, but with benefit years in the future. Nevertheless, CEA can be used to make the underlying assumptions concerning therapeutic effectiveness and costs more apparent and thus help inform policy decisions in the public sphere. Thus, CEA can inform without setting a threshold.

Furthermore, it should be noted that cost of health services can be different between countries and this difference may affect the results of the cost analyses. Different costs have been reported in USA and Europe for percutaneous coronary intervention (PCI) [10]. There are different determinants of costs in different geographical areas [11] or even clinical practice models which may include financial incentives, availability of resources versus demand, institutional policies, and variations in cost of devices amongst others. Therein lies the need for putting all these variables into account when cost-analysis of a certain intervention is being conducted. Moreover, it is imperative to note that cost analysis conclusions also vary according to the subsets of population. An intervention is likely to be more cost effective in a sicker group of patients than a healthier subgroup. Hence, it is important not to consider patients as a single homogenous population. Finally, aforementioned economic consequences of medical decisions, especially with regards to new technologies, have become forefront considerations in recent years. This applies to all aspects of medicine and is especially important in the field of interventional cardiovascular medicine where innovation and exponential growth within the last 10–15 years is arguably unparalleled by most other fields in medicine. PCI is the poster child of escalating healthcare costs as well as potential improvement in clinical outcomes with these phenomenal advances in cardiovascular medicine. Consequently, this highly technical subspecialty will serve as an

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**Figure 2. Cost–effectiveness of percutaneous coronary intervention plus optimal medical therapy versus optimal medical therapy along in the COURAGE trial.** (A) Scatterplot of the joint distribution of cost and effectiveness differences in the CE plane and (B) CE acceptability curve; QALY as unit of effect on x-axis; lifetime time horizon with QALYS as the effectiveness measure. CE: Cost–effectiveness; ICER: Incremental cost–effectiveness ratio; PCI: Percutaneous coronary intervention; QALY: Quality-adjusted life year. Adapted with permission from [9].
COURAGE: PCI versus optimal medical therapy

The COURAGE trial compared PCI in addition to intensive pharmacologic and lifestyle intervention with optimal medical therapy (OMT) alone as an initial strategy in reducing the risk of cardiovascular events in patients with stable ischemic heart disease [12]. After 4.6 years, there was no difference in the primary endpoint of death or myocardial infarction, although PCI improved quality of life.

In the CEA of this trial, the point estimate for the in-trial ICER for PCI was US$206,229 per quality-adjusted life year (QALY) gained [9]. The frequency with which medical therapy dominated PCI and the absence of domination by PCI indicated considerable probability that medical therapy alone provided better clinical outcome at lower cost (Figure 2A). A cost–effectiveness acceptability curve (Figure 2B) shows that the bootstrap-derived cost–effectiveness estimates were rarely <US$50,000 per QALY gained, and a minority were <US$100,000 per QALY gained. With an in-trial point estimate ICER for PCI approximately US$200,000 per QALY gained and the life time projected ICER for PCI of more than US$160,000 per QALY gained with considerable uncertainty in both cases (in-trial and lifetime projected estimates), including the possibility that OMT alone is actually a dominant strategy, it would seem unlikely society will be willing to pay that high price for PCI as an initial therapy in stable ischemic heart disease.

One of the important benefits in COURAGE was seen in the improvement of quality of life among patients with PCI. The ICER for PCI was calculated as the difference in costs divided by the difference in proportion of patients with clinically significant improvement in angina severity. There was significantly greater improvement in angina for PCI patients in severe and moderate angina, but not in patients with mild angina. For one additional patient to reach significant clinical improvement in health status, ICERs ranged from US$80,000 up to US$330,000 for the severe and moderate, and from US$520,000 to more than US$3 million for patients with mild angina. Thus, the incremental cost of PCI to provide meaningful clinical benefit above that achieved by OMT alone was lower for patients with severe angina than in those with mild or no angina.

In conclusion, the results from COURAGE demonstrate that compared with OMT alone, PCI as an initial strategy did not provide significant benefit in life years, even with much higher
cost. However PCI can improve quality of life and relieve angina severity, but with extremely high cost, which may be beyond a socially acceptable WTP level for many patients.

**PARTNER (A & B) trial: transcatheter aortic valve replacement**

The PARTNER trial was a randomized trial comparing transcatheter aortic valve replacement (TAVR) with standard-of-care therapies in high-risk patients with aortic stenosis. Patients were randomized within either the high surgical risk or inoperable cohorts. In the high-risk cohort, patients were first assigned to either transfemoral (TF-TAVR) or transapical (TA-TAVR) categories and were then randomized to either TAVR or surgical aortic valve replacement (AVR). Overall, 34% of the screened patients were randomized in the PARTNER trial.

1-year mortality outcomes from PARTNER demonstrated that TAVR was superior to standard therapy in patients who could not undergo surgery \[13\] and was noninferior to surgical AVR in high-risk patients who could undergo surgery \[14\]. The economic analyses of both studies, as discussed below, illustrate the wide range of distributions of ICER for the same therapy in different patient populations and consequently the influence of the study findings on the societal WTP threshold \[15,16\].

**PARTNER B: TAVR versus medical therapy**

**CE Plane: Quadrant 1**

The PARTNER trial B randomized 358 patients with severe aortic stenosis who were considered inoperable to standard medical \(n=179\) therapy and TAVR \(n=179\). After 1 year of follow-up, it was found that there was a significant reduction in all-cause mortality, repeat hospitalization and cardiac symptoms in the TAVR group, although a higher incidence of major strokes and other vascular events were also reported. To fully evaluate the value of this intervention and assess how much the society is willing to pay for an increment in effectiveness of this therapy in this elderly cohort, a health economic analysis of this procedure was subsequently performed \[15\].

Based on the first 12 months of follow-up and trial-based survival and cost projections, a lifetime ICER of US$50,212 per life-year gained was estimated. Bootstrap simulation demonstrated that the ICER was fairly stable, with 95% of replicates <US$60,000 per life-year gained and 100% <US$100,000 per life-year gained.

**Figure 4. Mean incremental 12-month costs and quality-adjusted life-years (transcatheter aortic valve replacement vs surgical aortic valve replacement).**

Mean incremental 12-month costs and QALYs (TAVR - AVR) are plotted on the cost–effectiveness plane for (A) the transfemoral and (B) transapical cohorts. The solid circles represent base-case estimates, the surrounding open circles represent individual results for 1000 replications of the study using bootstrap resampling, and the dashed lines represent a willingness to pay a threshold of US$50,000/QALY gained. For the transfemoral cohort, the base-case results are a gain of 0.068 QALYs and cost savings of US$1250 per patient. For the transapical cohort, the base-case results are a ‘loss’ of 0.070 QALYs and a net increase in costs of US$9906.


Adapted with permission from \[16\].

Mean utility scores in this population remained lower than ideal, even after successful TAVR. Consequently, the gain in quality-adjusted survival was smaller than the gain in
absolute survival, and the cost-utility analysis resulted in an ICER of US$61,889 per QALY gained. Sensitivity analyses did not meaningfully impact the results. In conclusion, for patients with severe aortic stenosis who are not candidates for surgery, TAVR increases life expectancy at an incremental cost per life-year gained reasonably close to the traditional WTP threshold in the USA of $50,000/QALY gained (Figure 3).

PARTNER A: TAVR versus surgical AVR
CE plane: quadrant 1 & 2 (TF-TAVR); quadrant 4 (TA-TAVR)
All 699 patients with severe aortic stenosis and cardiac symptoms who were eligible for conventional surgical aortic-valve repair but judged to be high operative risk were randomly assigned to undergo either TAVR or surgical AVR [14]. After 1-year of follow-up, the TAVR group was similar to the surgical AVR group with respect to rates of death from any cause. However, while TAVR did result in significant early health-related quality of life benefit, this was not only diminished after 6–12 months but was associated with only the TF-TAVR placement and not with TA-TAVR [17]. Consequently, TAVR resulted in slightly higher 12-month costs and a small gain in QALYs with a resulting ICER of US$76,877/QALY gained. This result was thought to be highly uncertain, because TAVR was found to be dominant in only 34.5% of bootstrap replicates and either dominated or economically unattractive (ICER US$100,000/QALY) in 48.5%. Furthermore, the CE results differed substantially according to access site. Among patients who underwent TF-TAVR, cost savings of US$1250 per patient and a modest gain in QALYs compared with surgical AVR were reported.

Bootstrap simulation demonstrated that TF-TAVR was economically dominant compared with surgical AVR in 55.7% of replicates and economically attractive at an ICER of US$50,000/QALY gained in 70.9% (Figure 4A). On the other hand, among patients who underwent TA-TAVR, higher 12-month costs and lower quality-adjusted life expectancy than surgical AVR were reported and the procedure was economically dominated by surgical AVR in 86.6% of bootstrap replicates (Figure 4B). At an ICER threshold of US$50,000/QALY, TA-TAVR was economically attractive relative to surgical AVR in just 7.1% of replicates.

Procedural costs for both TF-TAVR and TA-TAVR were greater than surgical AVR, primarily due to difference in costs of the valves of the two different procedures. However, length of stay was shorter in the TF-TAVR and the associated cost savings as well as higher quality of life in the TF-TAVR arm compensated for the more expensive percutaneous valves. These advantages were not apparent in the TA-TAVR group. In conclusion, in the PARTNER A trial, when TAVR was compared with surgical AVR, distinctively different results were obtained with CEA by access site. TF-TAVR as a dominant therapy and TA-TAVR as a dominated therapy.

PCI-CURE: clopidogrel versus placebo
CE Plane: quadrant 1 with a low ICER
The PCI-CURE study was a pre-specified analysis of efficacy of clopidogrel in patients undergoing PCI during the course of the CURE trial where >12,000 patients with acute coronary syndrome already on aspirin were randomized to pre-treatment with loading dose of clopidogrel or placebo [18,19]. The primary clinical outcome, the composite of cardiovascular death, MI, or urgent target-vessel revascularization within 30 days of PCI was significantly lower for clopidogrel (4.5 vs 6.4%; p = 0.03). From PCI to the end of follow-up, there was a 25% relative reduction in the composite outcome or MI or cardiovascular death in the clopidogrel group. The aim of the subsequent economic analysis of the PCI-CURE study was to evaluate the cost-effectiveness of the pretreatment with clopidogrel in this patient population who were already receiving aspirin therapy with those who had no pretreatment with clopidogrel [20].

![Figure 5. Scatterplot of the joint distribution of cost and effectiveness differences of clopidogrel versus placebo. Incremental effectiveness per life year gained. Adapted with permission from [20].](image-url)
The incremental cost per life year gained with clopidogrel for the overall population ranged from US$2856 to US$4775. Treatment with clopidogrel was a dominant strategy for the early PCI subgroup. In addition, there was a life expectancy benefit with cost savings as the estimated incremental cost per life year gained with clopidogrel was US$935. In the plots of the joint distribution of cost and effectiveness differences derived from bootstrap resampling, 94% of the overall population and 92.4% of the early PCI subgroup lie below a societal WTP of US$50,000 per year of life gained (Figure 5).

Cost–effectiveness acceptability curves are presented in Figure 6. In CURE, PCI was post-randomization, so that there may have been some treatment selection, which was adjusted for by propensity score methods. After adjusting for the propensity score, in the early PCI subgroup, there was a 90% probability of clopidogrel being cost effective at a threshold ratio of US$10,000 per life year gained. It can also be seen that the therapy with clopidogrel has a >80% probability of being cost effective at a threshold of US$10,000 per life year gained in the entire cohort as well. Overall, therapy with clopidogrel meets the societal WTP at a range of ceiling ratios.

The authors stated that this economic analysis did not incorporate health-related quality of life into the life expectancy gains due to lack of available data. However, when they assumed an average utility for all postacute coronary syndrome patients to be as low as 0.80, the estimated cost per quality-adjusted life year gained with clopidogrel based on Medicare costs was estimated to be US$5975. This ICER value is highly favorable when compared with the societal WTP threshold of US$50,000.

It should be noted that, as is the case with variation in costs of economic goods, changes in the cost of stents, medications and overall healthcare resource utilization over time will affect the economic analyses of any intervention. Hence, there is need to interpret these results in the light of recent or at least near-recent cost estimations and/or modest extrapolations from available data.

**FAME 2 trial: fractional flow reserve-guided PCI versus best medical therapy**

- **CE plane: quadrant 1**

The FAME 2 trial was a prospective, multicenter, randomized, controlled trial that enrolled patients with stable angina and CAD amenable to PCI with a second-generation drug-eluting stent [21]. Fractional flow reserve (FFR) was measured across all lesions that appeared angiographically significant prior to randomization. Patients with an FFR ≤0.80 across one or more lesions were randomly assigned to either PCI or to best medical therapy. A total of 888 patients were randomized. There was a significant reduction in subsequent coronary revascularization among patients who were randomized to PCI compared with best medical therapy although there was no difference in mortality.

The recently published economic analysis of this study was conducted to compare the economic and quality of life implications of the FFR-guided PCI strategy used in the FAME 2 trial [22]. Medical costs were calculated based on resource use and clinical events during the index procedure, hospitalization, and subsequent follow up. All follow-up events were assigned costs based on the Medicare reimbursement rate for the appropriate diagnosis-related group. Angina was assessed at baseline and again at one, 6 and 12 months. Quality of life was assessed using the Euro Quality of Life 5 D questionnaire with US weights at baseline and one month. Because the trial was stopped early due to the rate of urgent revascularization in the medical group, which was significantly higher when compared with the FFR-directed PCI group, only 11% of patients had 12-month quality-of-life data. The quality-of-life outcome was calculated by projecting 1-month Euro Quality of Life 5 D change scores.
The analysis showed that the mean 1-year cost of FFR-guided PCI was US$11,374 compared with US$8866 for medical therapy. The mean cumulative cost difference of US$5482 at baseline decreased to US$2508 at 12 months based on increasing costs for follow-up care in the medical therapy group. Quality of life at 1 month increased to 0.054 for the PCI group and 0.003 for the medical therapy group (p < 0.001). The combination of cost and quality of life changes yielded a QALY cost of US$53,000 for PCI based on in-trial results, and US$32,000 based on 3-year projections. The conclusion of this analysis was that FFR-guided PCI significantly improved quality of life when compared with medical therapy and therefore is cost effective, especially in the long term (Figure 7).

**Preventive therapies in cardiovascular disease: ICERs are low but difficult to estimate**

While cardiovascular disease is preventable to an extent, there has been controversy as to whether prevention offers good value. As is generally known, the clinical substrates for clinical cardiovascular disease (CVD) begin early in life and are influenced over time by potentially modifiable risk factors, behaviors and the environment. Studies have demonstrated the association of lower lifetime risk for CVD mortality and increased survival and quality of life [23]. Hence the emphasis on the need for prevention of CVD at all levels – primordial, primary and secondary. Given the significant benefits that can be derived from effective primary preventive strategies and
therefore meets the generally accepted societal WTP threshold [28].

**Tobacco control & prevention**

The most yield is seen with excise taxes on prices of cigarettes where it has been estimated that a 40% tax will reduce smoking prevalence to 15.2% by 2025 with QALYs of up to 13 million and total cost savings of US$682 billion [29]. A comprehensive coverage of tobacco cessation programs in Medicaid programs have been demonstrated to lead to reduced hospitalizations for myocardial infarction with net savings of US$10.5 million or a US$3.07 return on investment for every US$1 spent [30].

**Conclusion**

The economic merit of an intervention with respect to its effectiveness is variable and depends on whether the ICER is higher or lower than the threshold value the society or policy-makers are willing to pay at that particular point in time. However, since CEA has a certain degree of uncertainty in its computation and, therefore, is not perfectly informed, the adoption of a stoic stance to pay for only the interventions that are below a certain threshold may not be appropriate. Nonetheless, critically evaluating CEA results alongside those of clinical trials or their low costs relative to most treatment options, it becomes evident their cost–effectiveness value will almost always be below the societal WTP, at least when compared with the standard treatment options. Overall, high risk groups tend to benefit the most.

**Cholesterol screening & prevention**

Full adherence to ATP III primary prevention guidelines would prevent 20,000 myocardial infarctions and 10,000 CVD deaths at a total cost US$3.6 billion or US$42,000 per QALY if low-intensity statins cost US$2.11 per pill. At a US$50,000 WTP threshold, statins are cost effective up to US$2.21 per pill [24]. Given that at present, a 30-day supply of generic statin can cost as low as US$4, statin therapy is very cost effective even at much lower WTP thresholds [101].

**Physical activity interventions such as walking programs**

ICERs ranging from US$14,000 to US$69,000 per QALY gained relative to no intervention have been estimated [25–27].

**Hypertension treatment**

Medication therapy of hypertension for primary prevention of CVD has an ICER of approximately US$37,100 per life year saved and therefore meets the generally accepted societal WTP threshold [28].

### Executive summary

**Cost–effectiveness analysis**

- Cost–effectiveness analysis evaluates competing therapies with the aim of informing medical and policy decisions.
- Incremental cost–effectiveness ratio (ICER) is the fundamental metric in cost–effectiveness research and examining its distribution is more informative than the point estimate.
- Results of analyses are presented graphically in the cost effectiveness plane with four quadrants reflecting positive or negative ICERS.
- The evaluation of ICER is critical in situations where there are potential opportunity costs for adopting a more expensive albeit more effective intervention, but not as much in dominant or dominated therapies where decision-making is straightforward.
- Economic merit depends on whether the ICER is lower than the threshold cost society or policy-makers are prepared to pay (willingness to pay [WTP] threshold) for an increase in health benefit.

**ICER & percutaneous cardiac interventions**

- In the COURAGE trial, PCI as an initial treatment strategy for stable ischemic heart disease did not provide significant benefit in life years, even with much higher cost when compared with optimal medical therapy. However, PCI can improve quality of life and relieve angina severity, but with extremely high cost which may be beyond a socially acceptable WTP level for many patients.
- In the PARTNER B trial, in patients with severe aortic stenosis who were not candidates for surgery, transcatheter aortic valve replacement (TAVR) increased life expectancy at an incremental cost per life-year gained reasonably close to the WTP threshold when compared with standard therapy.
- In the PARTNER A trial, when TAVR was compared with surgical AVR, distinctively different results were obtained with cost–effectiveness analysis by access site with transfemoral-TAVR as a dominant therapy and transapical-TAVR as a dominated therapy.
- In the PCI-CURE trial, when compared with placebo, treatment with clopidogrel was a dominant strategy for the early PCI subgroup with life expectancy benefit with significant cost savings.
- In the FAME 2 trial, fractional flow reserve-directed PCI in patients with stable coronary artery disease was considered an economically attractive alternative to optimal medical therapy.

**ICER & cardiovascular disease preventive therapies**

- Significant benefits derived from effective primary preventive strategies, and their low costs relative to most treatment options led to a cost–effectiveness value which is almost always below the societal WTP threshold when compared with the standard treatment options.
- Overall, high-risk groups tend to benefit the most.
outcome studies may serve as a much-needed restraint on the present burgeoning healthcare expenditure in the USA. By accomplishing this lofty goal, CEA would have achieved a fundamental purpose – informing without setting a threshold.

**Future perspective**

The methods for conducting CEA both as simulations as alongside clinical trials are well developed. The limitations of these CEA are also well understood. We are likely to see CEA alongside clinical trials frequently in the future. However, the use of CEA in helping to guide medical decision-making and public policy remains uncertain and contentious. Indeed, clinicians should be patient advocates, and cannot realistically make societal decisions concerning cost while taking the best care of their patients. This does not mean that physicians should ignore cost. Where outcomes are equivalent, as far as we know, physicians should choose the less expensive alternative. In addition, physicians can be constrained to make cost effective choices by guidelines or public policy.

Building cost–effectiveness into professional society guidelines has proven to be difficult. In the USA, while clinical effectiveness is used explicitly in determining insurance coverage, cost–effectiveness is not. In the UK, NICE does use cost–effectiveness to help guide policy recommendations to the National Health Service for coverage determinations. How to more explicitly use CEA to guide public policy in the USA will likely an issue in the coming years.

**Financial & competing interests disclosure**

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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**References**

Papers of special note have been highlighted as:

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