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EXPERT REVIEWS

Assessing cost-effectiveness in healthcare: history of the $50,000 per QALY threshold

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Cost–effectiveness analyses, particularly in the USA, commonly use a figure of $50,000 per life-year or quality-adjusted life-year gained as a threshold for assessing the cost-effectiveness of an intervention. The history of this practice is ill defined, although it has been linked to the end-stage renal disease kidney dialysis cost-effectiveness literature from the 1980s. The use of $50,000 as a benchmark for assessing the cost-effectiveness of an intervention first emerged in 1992 and became widely used after 1996. The appeal of the $50,000 figure appears to lie in the convenience of a round number rather than in the value of renal dialysis. Rather than arbitrary thresholds, estimates of willingness to pay and the opportunity cost of healthcare resources are needed.

KEYWORDS: cost–effectiveness analysis • cost–utility analysis • health policy • league tables • quality-adjusted life -year • willingness to pay

Cost–effectiveness (CE) analyses (CEAs) are intended to inform decision-makers on how much improvement in health can be expected for a given expenditure of resources [1–3]. A CEA compares pairs of nondominated interventions in terms of CE ratios, which is the net cost to achieve a given unit of health, typically either life-years (LYs) gained or quality-adjusted LYs (QALYs) gained. Although LYs and QALYs are not equivalent, in most cases, rankings of CE ratios for medical interventions are similar for the two measures [4,5]. In this paper, 'cost per QALY' is shorthand for net cost per QALY gained relative to the comparison with either no intervention (average CE ratio) or the next most effective nondominated strategy (incremental CE ratio [ICER]).

Cost–effectiveness ratios must be interpreted to decide whether an intervention yields good value for money [6], cost-effective [7] or economically attractive [8]. Decision analysts have multiple options for interpreting a CE ratio. If there is a fixed budget constraint or if a newly funded intervention comes at the cost of a reduction in an existing program, the intervention is cost-effective if it yields more health gains than other interventions with the same cost [9]. This is the original definition of CE, with the opportunity cost of resources at the margin used to calculate a 'critical value' or λ [7,10]. However, calculation of opportunity cost is rarely done.

In the absence of direct evidence on opportunity cost of healthcare resources, a traditional approach to interpret CE ratios is to refer to a league table of published CE ratios for other health interventions [11–15]. Empirical challenges in using league tables include differences in methods used to calculate costs and QALYs, and the fact that ICERs for a given intervention vary depending on the comparison intervention. More critically, because existing interventions are associated with a wide range of CE ratios, such an approach does not provide definitive guidance as to what should be considered cost-effective.

Analysts often use an arbitrary rule of thumb (benchmark, yardstick, cut-off or threshold), such as US$50,000 per QALY, to assess CE. Many analysts use them merely as points of comparison, as indicators of services generally regarded as cost-effective. Others treat these as a decision rule, with any intervention with a CE ratio below the threshold value stated to be 'cost-effective' and deserving of funding. This latter approach assumes that decision-makers have a fixed value they are willing to pay for a

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unit of health outcome or that there is a well-established shadow price of health improvements that reflects the opportunity cost of investments. However, there are reasons to question these assumptions [2,13,15–18].

In particular, there is a lack of evidence of a constant willingness to pay (WTP) for a QALY by consumers that is independent of the amount, duration or type of health gain [19–25]. Also, decision-makers do not appear to maintain a fixed value across different types and contexts of decisions [26–28]. In particular, there is mounting evidence that the average individual WTP for QALYs resulting from improvements in health status from relatively minor conditions is lower than the WTP for QALYs gained from life-saving interventions [29–31].

Certain experts use a range of critical values [32–35]. In 1982, Kaplan and Bush proposed that interventions with CE ratios below $20,000 per QALY be regarded as cost-effective, and interventions with ratios above $100,000 per QALY be regarded as economically questionable [32]. In 1992, Laupacis and colleagues similarly proposed lower and upper CE ratios of CAN$20,000 and CAN$100,000 [33]. (Unless otherwise specified, dollar estimates refer to US dollars.) Although others have suggested that they adopted the Kaplan–Bush rules of thumb without taking into account inflation or the difference between the value of US and Canadian dollars [16,36], the $20,000 threshold was based on CE ratios for commonly funded procedures in Ontario at the time [Feeny D, Pers. Comm., 5 June, 2006].

The use of multiple critical values has been formalized in CE acceptability curves, which show the probability of an intervention being regarded as cost-effective for different critical values [37]. CE acceptability curves can also be used to reflect the degree of uncertainty in parameter estimates, although this has been questioned [38]. Since ratios lack desirable statistical properties, many analysts prefer calculating measures of net health benefit by converting QALY gains into monetary equivalents using a range of critical values [39,18].

In recent years, CE analyses in the USA have commonly employed a CE threshold of US$50,000 per QALY or LY [35,40]. In an international registry of more than 500 cost-utility studies published through 2003, half of all studies with explicit thresholds used a single value of $50,000 per QALY [41]. Indeed, CE studies often refer to use of this $50,000 benchmark as 'generally accepted', 'commonly cited' or 'established practice' in the USA. This is not the only value used, and the second most popular value is $100,000 per QALY [41]. Many observers argue that the $50,000 per QALY critical value is not based on economic theory, does not derive from a formal expert consensus and is of questionable empirical validity [16,42,43]. In the final section, we discuss the critiques and alternative bases for thresholds.

This paper seeks to identify how the $50,000 per QALY value originated and spread as a CE threshold in the USA. Although this topic has been addressed in previous reviews, Neumann has accurately characterized the history of the $50,000 threshold as 'murky' [3]. One reason is the evident appeal of round numbers, such as $50,000 [7,42,44]. The $50,000 per QALY value has been commonly, although imprecisely, referred to as a 'dialysis standard' [44–47], although others have taken exception to this assertion [48]. For this reason, we begin with a brief review of the CE literature on renal dialysis in end-stage renal disease (ESRD) before reviewing separately the evolution of $50,000 per LY and $50,000 per QALY CE thresholds.

The first published use of $50,000 per QALY as a CE threshold occurred in 1992. This value did not become widely adopted until several years later (Table 1). It is essential to set this evolution in the context of the rapid growth in the number of CEAs using QALYs or cost–utility analyses. The Tufts Cost–Effectiveness Analysis Registry, which includes more than 1000 published

Table 1. Steps in the development of the $50,000 per quality-adjusted life-year cost-effectiveness threshold.

Year	Action	Ref.
1992	First widespread use of CE thresholds, $20,000 and $100,000 per QALY, in Canada	[33]
1992	First publication to use a CE threshold of $50,000 per QALY	[87]
1995	Second publication to use CE threshold of $50,000 per QALY and first to promote it	[92]
1995	Widely cited article using CE threshold of $50,000 per LY published	[61]
1996	Panel on Cost-Effectiveness in Health and Medicine issues report that mentions $50,000 per QALY figure and discourages its use as a criterion for CE	[127,128]
1996	Use of $50,000 per QALY or LY as a common point of comparison begins to take off	[70,76,95]
1997–1998	Experts begin referring to anything costing less than $50,000 per QALY as 'economically attractive' [75] or 'reasonably efficient'	[99]

CE: Cost-effectiveness; LY: Life-year; QALY: Quality-adjusted life-year.

analyses from 1976 to 2006, has found that only a handful were published prior to 1990, and it was 1993 before the number published each year was consistently in double digits [201]. In the mid-1990s, a rapid expansion began (Figure 1). As the CE field grew from one with a small number of practitioners to one with large numbers of analysts who were often new to the field, demand emerged for short-cut solutions to interpret and summarize findings.

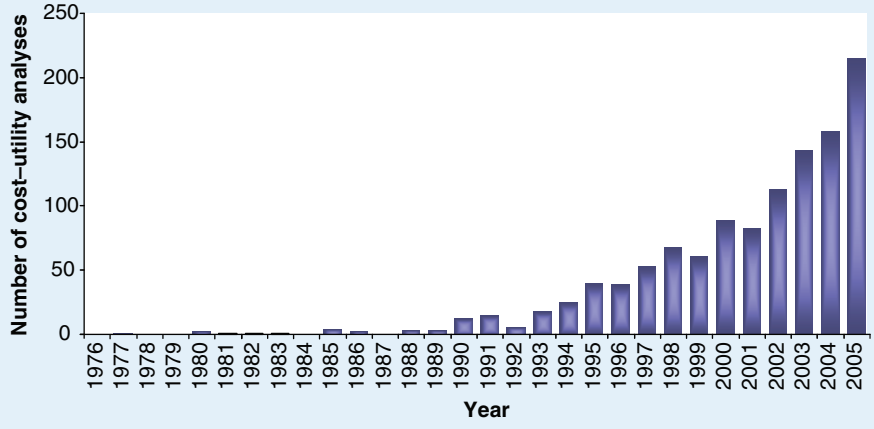

Figure 1. Trend in publication of cost–utility analyses.
Source: Center for the Evaluation of Value and Risk in Health. *The Cost-Effectiveness Analysis Registry* [Internet]. (Boston), ICRHPS, Tufts-New England Medical Center. Available from [201].

Renal dialysis CE literature

In the late 1970s, when a number of CEAs of dialysis for ESRD were conducted in the USA, CE ratios for center-based hemodialysis relative to no dialysis were mostly in the range of $25,000–30,000 per LY in current dollars [49]. Winkelmayer and colleagues took CE ratio estimates from 11 studies in Europe and North America published between 1968 and 1998, and standardized for differences in currencies and inflation [50]. This effort yielded CE ratios of $60,600–80,100 per LY in 2000 US dollars (Table 2) [50]. The investigators used the general Consumer Price Index to adjust estimates from different currency years for inflation.

To convert LYs to QALYs, one applies preference-based measures of the utility of health states for each year lived in a health state, such as ESRD [51]. Several studies have reported QALY weights for patients with ESRD receiving hospital-based dialysis ranging from 0.4 to 0.8 (typically approximately 0.6) [52–54]. The number of QALYs gained through dialysis is calculated as the product of number of years lived on dialysis and the average QALY weight for dialysis patients [50,54]. For example, a gain of 10 LYs with an average QALY weight of 0.6 implies a gain of 6.0 QALYs. For QALY weights for ESRD patients in a range from 0.4 to 0.8, a CE ratio of $50,000 per LY would yield an equivalent CE ratio of $62,500–125,000 per QALY (Table 2).

The first league table to include hemodialysis treatment was published in 1984 by Torrance and Zipursky [56] and was reprinted in 1986 [57]. Hospital-based dialysis was listed as having

Table 2. Published cost–effectiveness ratios for center hemodialysis relative to no renal replacement therapy, North America and Western Europe, 1968–1998.

Year of publication	Country	Currency (year)	CE ratios in 2000 US dollars	Ref.
1968	USA	US$ (1966)	61,600 per LY	[166]
1975	UK	GB£ (1972)	63,000 per LY	[167]
1978	USA	US$ (1976)	80,300 per LY	[160]
1980	USA	US$ (1978)	65,500 per LY	[169]
1981	UK	GB£ (1976)	52,000–82,100 per LY	[170]
1984	Canada	CAN$ (1980)	80,100 per LY	[58]
1986	Sweden	SEK (1985)	66,200 per LY	[171]
1987	USA	US$ (1981)	52,700–60,600 per LY	[49]
1995	Sweden	US$ (1993)	71,500 per LY	[172]
1996	Canada	CAN$ (1994)	73,600 per LY or 129,200 per QALY	[173]
1998	Netherlands	NLG (1996)	71,600 per LY or 102,300 per QALY	[174]

CE: Cost-effectiveness; LY: Life-year; QALY: Quality-adjusted life-year.
Adapted from [51].

a CE ratio of US$54,000 per QALY in 1983 US dollars, based on a CE ratio of CAN$48,700 per LY in 1980 Canadian dollars [58]. However, the authors did not convert LYs into QALYs [TORRANCE G, PERS. COMM., 4 OCTOBER, 2006]. If they had used a QALY weight of roughly 0.6 as reported by Sackett and Torrance [52], the CE ratio would have been at least US$70,000 per QALY in 1983 US dollars.

As shown in TABLE 2, if QALYs are used as the end point, the CE ratio for standard, hospital-based hemodialysis for ESRD patients by 2000 was generally at least US$100,000 per QALY [50]. Similarly, Hirth and colleagues estimated CE ratios of US$74,000–95,000 per QALY in 1997 dollars [44]. More recent estimates of the CE ratio for hospital-based hemodialysis for ESRD patients are generally in the range of US$125,000–150,000 per QALY [50,55,59].

Evolution of CE thresholds

Cost per life-year saved

During the early 1990s, US CEA studies typically either reported league tables or cited selected CE ratios as comparisons. The CE ratios chosen depended on the intervention being considered, with analysts typically selecting interventions with somewhat higher CE ratios as the basis for comparison. Thus, in an analysis of smoking interventions with estimated CE ratios below US$10,000 per LY, Tsevat reported that medical interventions generally cost at least US$10,000 per LY [60]. On the other hand, an analysis of an HIV preventive intervention (zidovudine), with an estimated CE ratio above US$60,000 per LY, chose a CE ratio of approximately US$85,000 per LY for treating high blood cholesterol as a comparison [61]. The league table presented by Schulman and colleagues included an estimated cost of US$46,500 per LY for hospital dialysis for men with ESRD in 1989 US dollars, but that comparison was not mentioned in the text [61].

Several authors use ranges of accepted CE ratios, following the lead of the Canadian group that proposed values between US$20,000 and $100,000 [33]. Indeed, Canadian CEAs have generally used $20,000 and $100,000 thresholds, regardless of whether LYs or QALYs were used as the denominator [62]. Certain authors have proposed an upper value for a CE threshold from $70,000 to $100,000 per LY. Thus, Smith and Hillner included a league table of common medical interventions costing in the range of $20,000–70,000 per LY and concluded that anything higher was outside the accepted range [63]. The same authors elsewhere suggested an accepted range of $42,000–80,300 per LY in 1992 dollars [64], citing the earlier Garner–Dardis CEA of renal dialysis for men with ESRD [49]. One group suggested a lower limit for an acceptable CE ratio of $35,000 per LY based on an estimated CE ratio for dialysis for ESRD, and stated that any CE ratio above $100,000 per LY would be 'generally considered too high' [65]. Another group stated, "Programs that cost less than about $40,000 per LY saved, which corresponds roughly to renal dialysis, have been recommended by some authors. Conversely, at costs above about $75,000 per LY saved, we find it difficult to generate enthusiasm for an intervention…" [14].

Other authors at the time suggested a CE threshold of approximately $40,000 per LY. For example, Goldman and colleagues cited an estimated CE ratio of $35,000–40,000 per LY for renal dialysis as the basis to determine which cardiovascular therapies were 'relatively cost-effective' [66]. McCarthy and colleagues stated, without citing specific studies, that there appeared to be, "A WTP at least $40,000 per LY gained" for interventions targeted to adults [67]. Owens and colleagues proposed that the range of CE ratios reported for hypertension screening of $12,200–42,600 per LY be used as a comparison for assessing CE [68]. Retrospectively, Morrison and Glassberg stated that the generally acceptable CE ratio in the early 1990s was approximately $30,000 per LY, although that appears low [69].

During the mid 1990s, decision analysts in the USA began to use a figure of $50,000 per LY as a CE benchmark or comparison value. This quickly developed into a folk tradition, leaving experts unclear as to how the practice emerged and spread. References that were cited in confirmation of this value often did not provide confirmation. For example, Tosteson and colleagues stated that most common medical interventions had CE ratios less than $50,000 per LY [70] and cited three publications, none of which used or supported such a cut-off [7,11,66].

The hypothesis that the $50,000 per LY threshold adopted in the mid-1990s was based on CE ratios for hemodialysis for patients with ESRD overlooks widespread confusion and misunderstanding at the time of dialysis costs. Many analysts in the mid-1990s underestimated the CE ratio for dialysis for ESRD, stating it to be in the range of $35,000–40,000 per LY [14,65,66,71]. Other estimates were higher. Schulman *et al.* had estimated the CE ratio to be $46,000 per LY in 1989 US dollars [61]. Another group of investigators estimated net expenditures on hemodialysis to be $46,000 per LY in 1994 US dollars [72], and yet another group calculated CE ratios in the range of $42,000–80,300 per LY in 1992 US dollars [64]. In 1995, Hillner and colleagues stated, "A common benchmark for such assessments is the cost for dialysis for ESRD at $40,000–50,000 per LY" [73]. However, the source given actually reported a range of $42,000–80,300 per LY and suggested that $100,000 per LY was nearer the accepted range [64].

One of the first CEAs to use $50,000 per LY as a benchmark was published in the *New England Journal of Medicine* in 1995 [65]. Mark and colleagues used two arbitrarily selected threshold values, $50,000 and $100,000, in sensitivity and subgroup analyses. They did not attribute either figure to CE ratios for dialysis, which they believed to be substantially less costly. They did not use either figure as a critical value to assess the CE of the interventions being analyzed. Nonetheless, this study has been cited more than 300 times and appears to have been influential in popularizing the $50,000 per LY threshold.

Subsequently, Mark proposed that interventions with CE ratios below $50,000 per LY be considered economically attractive and that CE ratios above $100,000 per LY be considered too high [74,75]. In 1996, Hayman and colleagues had written, "Based on 'league tables' comparing the results of CE analyses of various interventions accepted by society as 'reasonable', consensus appears to be forming that those interventions costing less than an additional $50,000–100,000 per year of life saved are 'cost-effective'" [76].

In a review article, Winkelmayer and colleagues [50] attributed the $50,000 per LY benchmark to a 1984 Canadian study by Churchill and colleagues [58], which had reported a CE ratio for hospital dialysis of CAN$48,700 per LY. They stated that US researchers had unwittingly used a "Nebulous benchmark of $50,000 per LY, not knowing that it was … initially expressed in Canadian rather than US dollars." However, there is no evidence that any CEA that used a $50,000 per LY benchmark cited that study as the source. Rather, as discussed above, CEAs cited studies that had reported CE ratios in US dollars.

Cost per QALY

As was the case with other CEAs, early cost–utility analyses (CUAs) compared CE ratios with estimates for other types of interventions. For example, Detsky and Naglie cited a comparison of two hypothetical strategies to prevent heart disease: cholesterol screening at $50,000 per QALY and aspirin prophylaxis at $10,000 per QALY [11]. After 1992, Canadian decision analysts mostly used the CAN$20,000 and CAN$100,000 per QALY thresholds [33,77], although at least one study used a figure of CAN$60,000 per QALY [78]. In the USA, analysts cited CE ratios for commonly accepted interventions from $40,000 to $80,000 per QALY. For example, one study reported mammography screening, treatment of moderate hypertension, zidovudine for HIV and treatment for Hodgkin's disease as having CE ratios of less than $70,000 per QALY [63]. As with the cost per LY literature, the strategies chosen for comparison were typically those with CE ratios somewhat higher than the intervention being analyzed. Thus, one group cited CE ratios of $78,000 or more per QALY for critical coronary care for relatively low-risk patients [79], another cited artery bypass surgery for three-vessel disease in patients with severe angina and depressed ventricular function of $48,600 per QALY [80], and yet another study used hypertension treatment, reported to cost less than $40,000 per QALY, as a comparator [81].

To the extent that US CUA studies published during 1996 or earlier used a fixed threshold, the most common value was $40,000 per QALY. In 1992, Goldman and colleagues commented that most accepted interventions cost less than $40,000 per QALY [82]. Other US studies began to use the $40,000 value as the upper limit of the cost-effective range [14,83,84]. Of CUAs published before 1996 that used a threshold, almost none used a value of $50,000 per QALY. For example, of 40 cancer-related CUAs published during 1997, just two used a $50,000 per QALY threshold [85].

In an influential book chapter on the interpretation of CE ratios, Weinstein mentioned league tables as one potential approach to setting a CE criterion or critical value based on CE ratios for 'well-accepted programs' [7] and cited Torrance as an example of a league table [57]. Although the Torrance estimates of $46,000 per QALY for home dialysis and $54,000 per QALY for hospital dialysis were mentioned, they were not singled out or endorsed as critical values. In fact, Weinstein argued against the use of a fixed CE benchmark [7], although he has been cited by some analysts as the basis for a $50,000 per QALY CE threshold [86].

The first apparent use of a $50,000 per QALY threshold was a 1992 article by Freedberg and colleagues on HIV interventions [87]. This study considered that interventions with CE ratios below this threshold were 'potentially reasonable', although they acknowledged that this threshold was 'arbitrary.' The authors noted that "Many currently accepted practices in medicine" had higher CE ratios and cited three studies [88–90], all of which reported CE ratios well in excess of $50,000 per LY.

One indirect and perhaps inadvertent contribution to the development of the practice of using a $50,000 per QALY benchmark is a 1993 conference abstract that used a figure of $45,000 per QALY as a comparison [91]. Two articles published in 1995 and 1996 cited this abstract [92,93], as well as two other studies [83,94], as reportedly giving similar estimates of WTP for a QALY. However, Patrick and Erickson did not propose a threshold for CE ratios [94]. Owens and colleagues cited the $45,000 figure as an example of a CE ratio for purposes of comparison, but did not advocate its use as a decision rule or measure of WTP [91]. Furthermore, Owens and colleagues did not use the $45,000 per QALY figure in their subsequent research [68].

An influential article that did use a $50,000 per QALY threshold for assessing CE was a 1996 CEA by Kuntz and colleagues of cardiovascular interventions [95]. This study has been widely cited as justification for treating $50,000 per QALY as a threshold for cost-effective healthcare [72,96–98]. However, the study did not state that it was using this threshold as a decision rule and also mentioned CE ratios for other cardiovascular interventions costing up to $110,000 per LY. Regardless of the authors' intentions, this study appears to have contributed to the popularity of $50,000 per QALY as a critical value.

A 1998 article by Owens [99] has also been widely cited as an authority for the $50,000 per QALY threshold [100–102], although Owens did not endorse it as a decision rule. Owens, in commenting on Azimi and Welch [103], stated that most US decision-makers would regard anything less than $50,000–60,000 per QALY as 'reasonably efficient' and that an intervention costing between $60,000 and $175,000 per QALY would be regarded as 'sufficiently efficient' by certain decision-makers, but not others [99]. Owens implicitly equated QALYs with LYs, because most of the 65 CEAs reviewed by Azimi and Welch used LYs rather than QALYs. Furthermore,

Owens implicitly assumed that the views of decision analysts as summarized by Azimi and Welch were the same as those of decision-makers.

The majority of investigators who used a $50,000 per QALY threshold beginning around 1996 were unclear as to the origin of the practice. Many used this value without citing a source for the practice [104–107]. Still others cited sources that did not provide either theoretical or empirical support for thresholds of $50,000 per QALY or LY [109–111].

Discussion

It has become popular in recent years to refer to the $50,000 per QALY threshold as a dialysis standard [44] and to attribute that value to the early 1980s [36,43,45] or even the early 1970s [112,113]. In fact, it was in the 1990s that the $50,000 per QALY threshold first came into use, and the studies that first used it did not mention dialysis as a basis. Hirth and colleagues cited two references from 1995 [65] and 1997 [71] in support of their assertion of a $50,000 per QALY dialysis standard [44]. Both of the latter studies used a threshold of $50,000 per LY, not per QALY, and neither study based that estimate on the cost of dialysis for ESRD patients.

Rather than being tied to a specific intervention, the widespread use of a CE threshold such as $50,000 per QALY is probably due primarily to its attraction as a convenient round number [7,42]. As Garber and Phelps stated, "The $50,000 criterion is arbitrary and owes more to being a round number than to a well-formulated justification for a specific dollar value" [42]. This could account for the failure of subsequent studies to adjust the value for inflation or changing levels of income or healthcare budgets, a common criticism of the $50,000 per QALY value [36,43–45,114] that applies to any fixed monetary threshold [1].

At the time that the $50,000 per QALY threshold came into use in the 1990s, CE ratios for hospital hemodialysis for male ESRD patients at the time were considerably higher [48], between $60,000 and $100,000 per QALY [44,50]. It was superficially consistent with estimates reported by Torrance of CE ratios of $46,000–54,000 per QALY for dialysis in 1984 US dollars, although in fact those estimates were in terms of LYs and not QALYs [57]. Similarly, if no adjustment is made for health utilities for ESRD patients, there is evidence of an approximate $50,000 per LY CE ratio for ESRD dialysis in the early 1990s [61,72]. In any case, according to recent estimates, center-based kidney dialysis is now associated with a CE ratio of $100,000–150,000 per QALY [50,59,115]

The fact that reimbursement for dialysis treatment for ESRD is a federally funded mandate in the USA as a result of the 1972 End-Stage Renal Disease Amendment to the Medicare program is widely recognized to not be a valid basis for setting a standard of value [7,44,48]. The Medicare policy decision was controversial and proved to be much more costly than projected [7,16,48,116]. Also, it did not set a precedent for Medicare coverage for other services [16]. A small number of treatments covered by Medicare cost more than $50,000–100,000 per QALY [117], but the Medicare program is barred from explicitly considering CE ratios for coverage decisions [2,47].

The often interchangeable use of LYs and QALYs in the literature on CE ratios, including specifically with regard to ESRD dialysis, raises an important methodological question concerning the use of QALYs for informing resource allocation decisions. Use of QALYs requires that one adjust LYs downwards (and CE ratios upwards) for therapies that extend the lives of people with serious health conditions and low utility weights [51]. Nord and others have suggested that is ethically preferable to not adjust LYs in that type of situation and have proposed alternative 'ethical' or 'social value' QALY measures that assign a utility weight of 1 for extension of life, regardless of health state [118–121]. It has been argued that the fact that UK decision-makers appear to use the same nominal CE thresholds, whether expressed per LY or per QALY, lends support to this perspective [122].

The other major problem with QALYs identified by Nord is that standard instruments and methods for eliciting utility weights appear to substantially overstate the willingness of people to trade-off life extension for reduction in chronic symptoms [118,123]. The implication that people have a substantially lower WTP for QALY gains resulting from reductions in chronic morbidity than for the same number of QALY gains resulting from reduction in mortality risk has received consistent empirical support. For example, a survey in Norway found an average WTP per QALY that was five- to seven-times greater for two life-saving interventions than for a strategy that would have increased the availability of hip surgeries [124]. Studies that have focused on WTP to reduce morbidity have found relatively low valuations of QALY gains, such as a study in Denmark that found an average WTP of approximately $10,000 per QALY for alleviation of EuroQol 5 dimension health states of 0.68 or greater [29]. Similarly, measures of individual WTP for treatments for specific chronic conditions have been estimated to be less than $6,000 per QALY for osteoarthritis [30] and $21,000–32,200 per QALY for neurosurgical conditions [31].

The precise estimates of WTP per QALY depend on methods used to calculate both WTP and QALY weights. For example, a study that evaluated WTP for a cure of asthma yields estimates of $21,000–25,000 using a bidding game WTP method and either time trade-off or standard gamble, but only $7,000 per QALY when a rating scale was used [125]. It should be noted that WTP estimates for QALY gains often show results inconsistent with assumptions regarding how people think [20–29].

It is not clear that correcting QALY estimates, either using the person trade-off method proposed by Nord [119] or estimates of WTP, would yield consistent estimates that would permit the use of valid threshold for CE ratios. In particular, the first approach would not address the issue of apparent differences in WTP for health improvements based on perceptions of voluntariness of risk, duration and other such context-specific

factors. Second, empirical as well as theoretical research has shown that the idea of a consistent WTP per QALY estimate is unrealistic [22,126]. A recent meta-analysis of studies reporting WTP and QALY estimates for acute conditions found a wide range of estimates, apparently ranging from $200 per QALY for a 1-day episode with a 0.7 utility weight to $50,000 per QALY for prevention of 10-day episodes with a 0.4 utility weight [28]. In other words, there is a very weak association between individual WTP and QALY gains. Similarly, empirical WTP for QALY studies for chronic conditions have found very low correlations between WTP and QALY estimates [27].

The emergence in around 1996, of a common practice of using $50,000 per QALY as a criterion for CE was not supported by a consensus that this was a valid estimate at the time of societal WTP for health improvements. The 1996 report of the Panel on Cost-Effectiveness in Health and Medicine (PCEHM), which brought together distinguished North American experts, did not endorse that practice [127]. In particular, Siegel, Weinstein and Torrance, on behalf of the Panel, refused to endorse any CE criterion for general use [128]. The only mention of a $50,000 per QALY threshold came in a footnote [128]. Similarly, Graham and colleagues stated, "'No consensus currently exists about what levels of expenditures are cost-effective…" [129]. Likewise, experts in the UK and Canada at approximately the same time did not endorse the use of a single CE threshold [130].

One of the ironies of the US CE literature is that numerous studies have claimed to follow PCEHM recommendations while ignoring the recommendation that investigators not use CE thresholds, such as $50,000 per QALY, as criteria for defining CE [128]. The PCEHM did not discourage the reporting of thresholds as long as they were used as simple comparisons and not to define CE [128]. A number of studies have used CE thresholds appropriately in this way, using a range of thresholds, including $20,000, $50,000 and $100,000 per QALY, as indicators of potential economic acceptability [131–133].

Analysts and decision-makers in other countries have used a range of CE thresholds in other currencies, beginning with the ground-breaking work of Canadian researchers [33]. In Australia, researchers calculated that the Pharmaceutical Benefits Advisory Committee in deciding on reimbursements for drug submissions during the period 1991–1996 appeared to use lower and upper thresholds of AUS $42,000 and AUS $76,000 per LY [134]. Eichler and colleagues stated that these values were equivalent to 1.3- and 2.3-times per capita gross domestic product (GDP) for Australia [45].

In the global arena, the WHO classifies interventions that cost less than three times the GDP per capita per disability-adjusted LY (DALY) as cost-effective and those costing less than the GDP per capita as very cost-effective [135,136,45]. In the USA, nominal GDP per capita in 2006 was $44,200 which would imply a CE threshold of $133,000 if this approach were used, although DALYs and QALYs are not theoretically equivalent [51,137,138]. The WHO criteria lack a clear theoretical rationale, unlike Garber and Phelps, who developed a life-cycle simulation model and proposed a benchmark of twice the per capita private income per QALY, which was equal to $36,000 in 1989 US dollars for the USA and $72,000 in 2006 US dollars [42].

Since 1999, the National Institute of Health and Clinical Excellence (NICE) has promoted the use of CE thresholds in coverage decisions in the UK [122]. Initially, NICE staff maintained that NICE used no CE threshold, but researchers demonstrated that therapies with ICERs below £20,000 per QALY were almost invariably approved and those above £30,000 per QALY were less likely to be approved in unrestricted form [139]. Subsequently, in 2004, NICE endorsed these two values as lower and upper thresholds [122], although there is evidence that NICE in practice employs an even broader range of thresholds [140]. National Health Service (NHS) health technology assessments typically treat £30,000 per QALY as the default CE threshold [141], which is also the figure widely acknowledged by individuals involved with NICE [142]. This figure approximated, at exchange rates prevailing in 2000, the $50,000 per QALY threshold already in common use in the USA. It would be interesting to know whether this reflected common WTP per QALY preferences between the two countries or intellectual influence from the $50,000 per QALY threshold that had recently come into vogue in the USA.

Other analyses suggested that the CE threshold used by NICE in practice is sometimes well above £30,000 per QALY [143]. The Department of Health, in one situation, set a threshold of £36,000 per QALY as the maximum it would be willing to pay for a drug, with rebates guaranteed for patients for whom the drug was less effective [122]. NICE now acknowledges that although some CE thresholds are necessary to define CE in NICE appraisals, they insist that they do not set the threshold but rather 'search' for it in reviewing funding decisions [144].

The idea that a CE threshold could be identified by reviewing funding decisions returns us to the challenges of league tables [7,116]. League tables typically do not reveal any clear breakpoint in CE ratios and it is left to analysts to select the value they find most acceptable [15]. For example, one group calculated CE ratios for over 40 interventions in 1995 US dollars with QALYs calculated using standardized weights [145]. They reported CE ratios ranging from less than zero to more than $1 million per LY or QALY, although most were in the range of $10,000–100,000 per QALY. More recently, a categorical league table of clinical preventive services recommended by the US Preventive Services Task Force for general use was recently compiled using standardized methods [146]. That table classified services into quintiles with breakpoints in 2000 US dollars at $0, $14,000, $35,000 and $165,000 per QALY [147]. Of all recommended services, two-fifths were estimated to cost in excess of $35,000 per QALY in 2000 US dollars, and one-fifth to cost more than $165,000 per QALY.

An even wider range of CE ratios has been reported for US public health policies or programs [148]. Certain strategies, such as mandating folic acid fortification to prevent birth defects, have been reported to be cost saving [149]. By contrast, nucleic acid testing of donated blood products to screen for HIV and hepatitis C virus has been estimated to cost more than $1.5 million per QALY [150].

Expert commentary

The use of fixed CE thresholds is widespread, but remains controversial. One argument is that thresholds have been set too high, thereby driving up aggregate healthcare expenditure through the coverage of expensive new technologies that meet thresholds [16–18]. In particular, Gafni and Birch argue that the widespread use of CE thresholds, such as $50,000 per QALY in the USA or the equivalent £30,000 pounds per QALY in the UK, have facilitated the rise of healthcare costs by encouraging the coverage of costly new therapies, especially pharmaceuticals [17,18]. It has been reported that CEAs funded by commercial sources are much more likely to report maximum CE ratios below $50,000 per QALY, which could mean that analysts and firms are using $50,000 per QALY as a 'target' CE ratio [151].

A response by CE threshold advocates is that additional expenditures on new interventions should be accompanied by 'disinvestment' of interventions that have not been shown to be cost-effective; however, this is rarely done [144]. More to the point, the Centre for Health Economics at the University of York has produced evidence that suggests that current CE thresholds might exceed the actual opportunity cost of healthcare resources in the NHS. Specifically, the marginal cost of a LY saved averaged £7400–19,000 for four chronic conditions and £26,500 for diabetes care, which are all below the £30,000 threshold that is apparently used by NICE [152]. An implication is that reallocation of resources from new technologies to expanding utilization of technologies of proven effectiveness in those disease categories could both reduce total healthcare expenditure and improve health.

Others argue that CE thresholds have been set too low, thereby discouraging the adoption of new technologies for which society is willing to pay [36,43,44]. One presentation attributed the continued use of the $50,000 per QALY threshold to 'inertia, indifference or irrationality' [114]. One justification recently offered for a higher threshold is a new estimate of the average CE ratio associated with the expansion of healthcare in the USA between 1950 and 2003 of $183,000 per LY [43]. That argument presumes that the entire increase in expenditure was needed to raise life expectancy, which was certainly not the case. Specific estimates of the incremental CE of increased US expenditure on cardiovascular disease management and prevention during 1987–2000 are in the range of $15,000–55,000 per LY [113].

The most common argument for a higher CE threshold among US economists is that the value-of-ife estimates used in regulatory policy decisions are consistently higher than $50,000 [36,44]. Indeed, at the same time that the $50,000 per LY/QALY value first emerged, economists working on benefit–cost analyses had settled on a figure of $100,000 per LY [153–155]. This served as the basis for Cutler and others to calculate the monetary value of health improvements in the USA using $100,000 per QALY [156]. This is in spite of well-known theoretical differences between WTP and QALY estimates that make the two types of metric difficult to compare [19,20].

Estimates of the value of a statistical life (VSL) used in US regulatory policy analyses vary within a range of $1–10 million [157], although there is new evidence of convergence at $6–7 million. The highest VSL estimates come from occupational risk studies, with estimates in the range of $5.4 million in 2000 US dollars [158] or $5.5–7.6 million [159]. Other types of preference studies based on consumer behavior often yield lower estimates, but there are methodological problems [112]. Stated preference studies using contingent valuation methods yield mean and median VSL estimates of $2.7 and $1.7 million in 2006 US dollars, respectively [160]. Until recently, $3 million was the VSL figure used by one agency to value transportation risks, whereas a VSL estimate of $7 million was used by another agency to value reduction of environmental contaminants [157]. These differences are consistent with an earlier suggestion, based on evidence from older studies of consumer WTP to reduce different types of mortality risks, that policy-makers should be willing to spend twice as much to prevent deaths due to cancer as to prevent deaths from motor vehicle collisions [155]. However, there is a preference for uniform valuation of life, and the US Department of Transportation on 5 February 2008 issued guidance endorsing a VSL of $5.8 million adjusted to 2007 prices [161].

As already mentioned, a number of economists in the 1990s divided VSL estimates by the number of discounted LYs to calculate the value of a statistical LY (VSLY) [153–155]. The implicit assumption is that WTP for a reduction of mortality is directly proportional to the number of discounted LYs remaining. However, there are theoretical reasons and empirical evidence that this assumption is not necessarily correct, and many experts are uncomfortable with assuming an age-invariant VSLY [162,202]. Nonetheless, if one is willing to overlook these issues, the average VSLY calculated with a 3% discount rate that corresponds to a VSL of $6.3 million is $275,000 [162].

Certain US governmental agencies use VSLY estimates to value nonfatal health end points. In particular, the US FDA uses estimates of $100,000–500,000 per LY to monetize QALYs from nonfatal end points [161], which happens to be consistent with the range estimated by Hirth and colleagues [44]. However, the practice of using VSLY estimates to monetize QALYs is controversial [202] and was discouraged by a panel of experts recently convened by the US Institute of Medicine [24]. An obvious limitation to the use of VSLY estimates for this purpose is the lack of evidence that individual WTP for gains in QALY from preventing morbidity bears a

close relation to the WTP for saving lives. One expert on WTP and QALYs characterized trying to use information on individual WTP preferences to value QALY gains as a wild goose chase [163].

An alternative to eliciting WTP for QALYs as a means to indirectly value health strategies based on their estimated QALY gains is to directly elicit WTP for different types of health policies and programs. A number of hypothetical exercises of this type have been published, mostly involving a very limited set of choices. Some lessons from this research are clear. One is that there is a substantially greater WTP for health gains from preventing deaths than from reducing morbidity [124]. Another study reported that, comparing strategies with the same expected health outcomes, people said that they would be willing to pay three-times as much on average for a hypothetical treatment strategy than for a prevention strategy [26]. Recently, the EuroWill project sought to elicit public WTP over three different types of health programs from samples in six European countries, with only limited success [164]. One interesting finding from the French study was that perceptions of value depended on nonhealth attributes of programs as well as the expected health gains [165].

Five-year view

I predict that round numbers, such as $50,000, 50,000 or £30,000 will continue to maintain their appeal as CE thresholds. However, I expect that over the next 5 years higher values will increasingly be used, particularly in the USA. It will become increasingly common for experts to either use a threshold of $100,000 per LY or QALY. Whether $100,000 is too high or too low a threshold for CE will be the subject of ongoing debate. The WHO criteria of one- and three-times the GDP per capita would suggest a slightly broader range, within the next year or so, from $50,000–150,000 for the USA or 33,000–100,000 for the Euro zone.

Divergent opinions could lead to a wider range of values for CE thresholds. We could do worse than to return to the lower and upper thresholds of $20,000–100,000 per QALY that were first proposed by Bush and Kaplan in 1982 [32], followed by Laupacis *et al.* in 1992 [33]. Adjusting for inflation on the basis of the general Consumer Price Index, the Bush–Kaplan lower and upper thresholds would now be somewhat above $40,000 and 200,000, respectively. Medical interventions costing up to $200,000 per QALY are often adopted in the USA. However, it would be very expensive if all interventions with a CE ratio at this level were regarded as providing good value for money. A challenge is to understand what influence perceptions of value for those interventions that have CE ratios between $40,000 and $200,000 per LY or QALY. It is likely that spillover from the regulatory benefit–cost analysis arena will exert pressure to raise the implied value of life in healthcare sector decisions, which could pose even greater problems for healthcare payers. The VSL estimates from the occupational risk literature now used in US regulatory analyses are consistent with values of $250,000–300,000 per LY.

I anticipate increased support for the idea that thresholds could vary depending on type of disorder, outcome and risk being addressed. This could include different thresholds for QALY gains from reductions in mortality and QALY gains from reductions in morbidity. I expect more research will be undertaken to quantify estimates of public WTP for health gains and health programs of various types, and to better understand the trade-offs that health policy-makers and payers are prepared to make in funding decisions. Accurate

Key issues

- The $50,000 per quality-adjusted life-year (QALY) threshold is an arbitrary decision rule that lacks theoretical or empirical justification and is in any case outdated.
- The $50,000 per QALY threshold might have had something to do with estimates for hemodialysis for end-stage renal disease patients in the early 1990s, in terms of cost per life-year (LY) saved rather than cost per QALY, but this appears to have been a retrospective rationalization rather than an actual justification.
- The 1992 Canadian recommendation of a range of cost-effectiveness thresholds from $20,000 to $100,000 per QALY had justification in terms of the range of interventions that were considered worth funding at the time.
- The WHO cut-offs of one- and three-times the per-capita gross domestic product have the advantages of international comparability and automatic indexing for inflation but lack a clear theoretical rationale.
- League tables of incremental cost–effectiveness ratios do not provide clear guidance because of diverse ratios and because differences in how costs and outcomes are calculated and the comparison strategies make incremental cost–effectiveness ratios treacherous to compare across studies.
- Estimates of the value of a statistical life used in regulatory benefit–cost analyses have been used to support cost–effectiveness thresholds of $100,000–500,000 per LY or QALY, with more recent estimates of $250,000–300,000 per LY, but it is unclear whether such benefit estimates can be transferred from the prevention of risk of fatal occupational injury to healthcare settings.
- It is unclear whether people's willingness to pay for health is closely related to QALYs or that QALY maximization describes preferences.
- Estimates of willingness to pay suggest that higher thresholds may be justified for life-saving interventions than for interventions that reduce relatively mild symptoms.

estimates of the opportunity cost of healthcare resources, which is the only universally agreed upon basis for CE thresholds, are essential.

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Disclaimer

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