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Title: Cost-effectiveness thresholds: the past, the present and the future

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Abstract

Cost-effectiveness (CE) thresholds are being discussed more frequently and there have been many new developments in this area. However, there is a lack of understanding about what thresholds mean and their implications. This paper provides an overview of the CE threshold literature. First, the meaning of a CE threshold and the key assumptions involved (perfect divisibility, marginal increments in budget, etc.) are highlighted using a hypothetical example. The use of historic/heuristic estimates of the threshold is noted along with their limitations. Then, the recent endeavours to estimate the empirical value of the thresholds, both from supply-side and demand-side, are presented. The impact on CE thresholds of future directions for the field such as thresholds across sectors and the incorporation of multiple criteria beyond QALYs as a measure of 'value' are highlighted. Finally, a number of common issues and misconceptions associated with CE thresholds are addressed.

Key Points for Decision Makers

- This paper describes the meaning of a cost-effectiveness threshold along with the assumptions involved using a simple hypothetical example, and highlights some of the common issues and misconceptions associated with thresholds.
- Cost-effectiveness thresholds that are being used across the world might be considered overestimates and have no empirical basis as they are based on historical estimates, heuristics or judgements.
- Empirical estimates of the supply-side threshold could be considered more appropriate for judging the cost-effectiveness of new technologies if the aim is to maximise population health.

1. Introduction

Cost-effectiveness analysis (CEA) is used to estimate the value for money (VfM) of new interventions in many countries across the world. In practice, the results of CEA are commonly expressed as the ratio of incremental costs to effectiveness outcomes or incremental cost-effectiveness ratios (ICERs). Effectiveness is generally measured using a generic measure of health, typically quality-adjusted life years (QALYs) or disability-adjusted life years (DALYs). ICERs (i.e. cost per QALY gained or cost per DALY avoided incremental to the next best alternative) are then compared to a CE threshold to identify whether the new intervention is good value for money. Interventions with an ICER below a threshold (i.e. if they add each QALY or avert each DALY at a lower cost than the threshold) are considered cost-effective while those with an ICER above the threshold are not.[1]

Despite the widespread recognition and use of CE thresholds by researchers conducting economic evaluations [1,2] as well as the adoption of their use into policy in some countries (e.g., the UK, Australia and Canada) [3–6], there is a lack of understanding among many about the meaning of thresholds, the assumptions involved, and their implications. Whether a given intervention is cost-effective or not depends upon how much health it would generate and whether that amount is greater than the health that could have been generated if the money required to fund it had been spent on something else, which is a measure of opportunity cost. As such, using a CE threshold to reflect this perspective has come to be known as a 'supply side' approach [7–10]. When non-health impacts on private consumption are also considered important, some assessment of the equivalent consumption value of health is required, i.e., 'demand side' empirical research [10]. Such approaches aim to represent societal willingness to pay (WTP) for additional health gains i.e. what individuals are willing to forego in non-healthcare/private consumption for gains in healthcare. When considering budget constraints on a healthcare system, supply-side thresholds can be considered more relevant since displacements to current health-generating interventions must happen to fund new interventions [11].

The aim of this paper is threefold: first, to provide an illustration of the CE threshold using a hypothetical example to highlight the key assumptions involved; second, to describe the various thresholds that are in use as policy tools in countries or have been estimated by researchers (sometimes, though not always overlapping – see the example of the UK); and third: to present the new developments and ongoing areas of research around thresholds. The remainder of the paper is structured as follows. Section 2 presents a simple hypothetical example to illustrate how the CE threshold can be determined using 'league table' approach and optimisation techniques and the assumptions involved. Section 3 describes the use of historic/heuristic estimates of the threshold, along with their limitations. Then, in section 4, the recent endeavours to estimate the empirical value of thresholds (e.g. work on opportunity costs in UK, Australia, Spain as well as work in estimating thresholds for LMICs) will be presented. Section 5 presents the future directions for the field (thresholds across sectors such as social care, incorporating multiple criteria beyond QALYs) and their impact on cost-effectiveness thresholds. Finally, Section 6 addresses some of the common issues and misconceptions associated with CE thresholds.

[1] CE thresholds reflecting opportunity costs can also be used to calculate the net benefit of an intervention (i.e., if net health benefit, benefit in terms of health over and above health opportunity costs).

2. A (hypothetical) example

In this section, a simple hypothetical example is used to illustrate how the CE threshold can be determined using a 'league table' approach and optimisation techniques [12]. We further outline the assumptions involved in each. Let us assume there is a fixed healthcare budget of £50 million available and the aim is to choose interventions to place in the health care package to maximise the total QALYs gained. In this example, for the sake of simplicity, the health care package is empty to start with and there are seven mutually exclusive, independent interventions to choose from, each with a different set of costs and QALYs gained, as shown in Table 1. Note that these are incremental costs and QALYs associated with each intervention compared to the 'do nothing' option. At a first glance, it is obvious that the budget of £50 million is not enough to fund all interventions.

Table 1: Costs and QALYs associated with the available interventions

Intervention	Cost (£m)	QALYs
A	32	7,000
B	22	4,000
C	20	3,500
D	10	2,000
E	12	1,900
F	4	600
G	3	400

League table approach

Under certain assumptions, which are outlined below, this 'league table' approach [13] can be used to identify the optimal allocation by including interventions according to highest VfM until the available budget is exhausted. Given our aim is to maximise health, the measure of 'value' in our example is QALYs. As we started with an empty package and are considering only independent options, we calculate VfM by dividing the costs by the QALYs of each intervention, as presented in the fourth column of Table 2 (i.e. they represent the ICERs for each intervention compared with the 'do nothing' option). The next steps involve sorting the interventions based on their VfM and adding the interventions to the package sequentially until the budget runs out, as illustrated in the fifth and sixth columns of Table 2, respectively. This process is described in detail in the next paragraph.

As shown in Table 2, intervention A has ranking 1 (i.e. provides the best value for money) so it is added to the health care package first. Intervention A generates 7,000 QALYs at the rate of £4,571/QALY, with a total cost of £32m, so there is £18m still left from the overall budget of £50m. The next best intervention is D, which costs £10m and provides 2,000 QALYs at the rate of £5,000/QALY. After incorporating intervention D into the health care package, there is £8m still left

which can be spent on the next best intervention B. However, £8m is not enough to fund intervention B in full (with a cost of £22m). Therefore, we can only fund a portion (8m/£22m = 0.36) within the budget. This would result in a gain of 1,454.5 QALYs (i.e. 0.36*4,000 QALYs) from intervention B at the rate of £5,500/QALY. In total, we achieve 10,454.5 QALYs (7,000 QALYs from A, 2,000 QALYs from D and 1,454.5 QALYs from B) for the £50m budget. (see the excel file in the supplementary material for a visual illustration of this approach as a 'bookshelf') [7,14].

In this example, the cost per QALY of the last intervention included (£5,500 per QALY for intervention B) represents the supply-side threshold where that last intervention is considered 'marginal' (i.e., would be displaced first). The necessary assumptions required for this to be true are outlined in the section below in the 'underlying assumptions' section.

Table 2: Costs and QALYs associated with the available interventions

Intervention	Cost (£m)	QALYs	Value for money (cost per QALY)	Ranking	Including in the health care package with 50m budget
A	32	7,000	£4,571	1	Yes (100%)
B	22	4,000	£5,500	3	Yes (partly funded, 36%)
C	20	3,500	£5,714	4	No
D	10	2,000	£5,000	2	Yes (100%)
E	12	1,900	£6,316	5	No
F	4	600	£6,667	6	No
G	3	400	£7,500	7	No
Maximum QALYs gained with 50m budget: 7,000 + 2,000 + 0.36 x 4,000 = 10,454.5 QALYs					

Budget constrained optimisation

Mathematical programming techniques can also be used to identify the optimal allocation that maximises the total QALYs gained within the budget constraint [15,16] (see supplementary material for the solution of the budget constrained optimisation problem). It can be seen that the optimal solution achieved is the same as that found using the league table approach. However, these two approaches find the same result only under a strict set of assumptions (perfect divisibility, linearity, and independence), which are described later in the 'underlying assumptions' section.

If the budget is bigger, say £51m, we could gain a further 181.8 QALYs by spending the additional £1m on intervention B. In fact, at the current allocation of the £50m budget (A, B, and D), 0.0001818 additional QALYs can be gained for every £1 increase in the budget. In optimisation terminology, this is termed the shadow price i.e. how much the objective (QALYs) would increase for one-unit increase in the constraint (budget). The shadow price can also be presented as decrements i.e. how much the objective (QALYs) would decrease for one-unit decrease in the constraint (budget). In our example, 0.0001818 is the shadow price of the £50m budget optimally allocated. It should be noted that this shadow price is the inverse of the cost per QALY of the last intervention included (£5,500

per QALY for intervention B). Note that this shadow price is only applicable for a range of budget between £42m (i.e. total costs of fully funded A and D) and £64m (i.e. total costs of fully funded A, D, and B).

The inverse of the shadow price at the optimal allocation in the budget, referred to as the 'critical ratio' in one of the first mentions of the threshold in published literature [17], represents the 'supply side' definition of the CE threshold, i.e., a threshold representing the notion of 'opportunity cost'. Whether a given intervention is cost-effective or not thus depends upon how much health it would generate and whether that amount is greater than the health that could have been generated if the money required to fund it had been spent on something else, which is a measure of opportunity cost.

With this allocation of the £50m budget, for a new intervention X to be included in the health care package (X does not have to be from the existing list in Table 1), we would need to disinvest first (assuming the overall budget is fixed at £50m). This disinvestment is only worthwhile if the replacement of existing interventions in the current health care package by X brings positive net QALYs gained. Let's introduce a new intervention X that costs £5.2m and provides 1,000 QALYs at the rate of £5,200 per QALY. Given the existing allocation (A, B and D), the decision is whether we should fund X.

Table 2: Introducing intervention X to the currently optimal allocation

	Intervention	**Cost (£m)**	**QALYs**	**Value for money (cost per QALY)**	**Ranking**
Existing intervention	A	32	7,000	£4,571	1
Existing intervention	B	22	4,000	£5,500	4
Existing intervention	D	10	2,000	£5,000	2
New intervention	X	5.2	1,000	£5,200	3

As illustrated earlier, the threshold is the inverse of the shadow price of the budget with its current optimal allocation, which is £5,500 per QALY (i.e. the cost per QALY of the last intervention included, intervention B). Since £5,200/QALY (value for money of X) is lower than £5,500/QALY (current inverse of the shadow price), it is cost-effective to replace B by X. That is, more QALYs can be gained by spending money on X than those lost by displacing part of B. In this case, X will be funded from the replacement of part of B, the proportion of B left after funding X is estimated as follows: (£8m-£5.2m)/£22m = 12.7%. Replacing B with X would generate 1,509.1 QALYs for the £8m (i.e. 1000 QALYs from X + 0.127*4,000 QALYs from part of B). In total, we achieve 10,509.1 QALYs (7,000 QALYs from A, 2,000 QALYs from D, 1000 QALYs from X and 509.1 QALYs from B) for the £50m budget, which is an increase of 54.6 QALYs (10,509.1 - *10,454.5 = 54.6 QALYs)* compared to the previous allocation.

Underlying assumptions

Through this example, we illustrate below a few key assumptions relating to CE thresholds that are worth further consideration – perfect divisibility, linearity, independence, marginal increments in budget, disinvestment plan, perfect information and other issues [14,18].

Perfect divisibility, linearity and independence

One assumption that applies to both the league table approach and budget constrained optimisation example is the notion of perfect divisibility (i.e. a proportion of the intervention can be funded if there are not enough funds to cover the costs of the whole intervention). In the above example for the optimal allocation (before X was introduced), the £8m left was not enough to cover the whole intervention B (£22m) and it was assumed that intervention B can be funded in part (0.36 = £8m/£22m) within the remaining budget, resulting in a gain of 1,454.5 QALYs from B (assuming linearity i.e. increase in costs results in a proportional linear increase in QALYs - also known as 'constant returns to scale'). It should be noted that the assumption of perfect divisibility may not always hold true in real life – for example, if there is a need for expensive specialist equipment, it must be purchased in full as fraction of equipment cannot be bought. Also, whilst the perfect divisibility may be achieved by limiting the patient population receiving the technology (e.g. by subgroup), the linearity assumption may not be valid (e.g. as the costs and QALYs for the subgroup maybe different from the overall population).

It should be noted that the league table approach cannot be used if the perfect divisibility assumption does not hold. In case of the optimisation, the problem needs to be solved again using integer constraints. In the above example, the resulting optimal solution with integer programming (before X was introduced) is to fund interventions A, D, F and G in full to achieve 10,000 QALYs for a budget of £49m (see Integer Optimisation sheet in the supplementary Excel file). This is because even though there are interventions with better VfM than F and G, they are not affordable within the leftover available budget after funding A and D (i.e. interventions B, C and E cost more than £8m).

Similar issues arise when considering interventions that are interdependent – VfM techniques are not applicable and optimisation techniques should be used to account for the interactions [19]. These issues arise because the league table approach assumes perfect divisibility, linearity and independence and are based on the use of cost-per-QALY ratios without considering budget impact. Whilst the optimisation problem can be structured using integer programming to overcome these issues, the shadow prices are no longer applicable for methods (and thus, the thresholds are not easily interpretable).

Marginal budget impact

The threshold, the inverse of shadow price or the cost per QALY of the last intervention included, is only applicable for interventions with a small impact on budget, typically termed 'marginal' impacts on budget. In the example above, the new intervention X had a budget impact of £5.2m, which meant only intervention B needed to be displaced, hence the threshold of £5,500/QALY. If the budget impact of X was high (which in our example is any amount above £8m, the money spent on intervention B), it would be necessary to consider whether it is cost-effective to also replace the next existing intervention in the package (intervention D) with X since there is still room to fund more X.

Now, the £5,500 per QALY from the inverse of the shadow price is no longer applicable.[2] We need to compare the value for money of X (£5,200 per QALY) with that of D (£5,000 per QALY). Since £5,200 per QALY > £5,000 per QALY, X should not replace D. Thus, as seen in the above example, whilst the threshold can be considered appropriate at marginal impacts on budget, the value of the threshold needs to be more conservative for interventions with higher budget impacts to accommodate the displacement of more cost-effective interventions. As such, many countries have started to impose a 'budget impact limit' alongside CE considerations (see section 6.4).

Disinvestment plan

In our example, we assume that the disinvestment to fund a new intervention should come from the least cost-effective intervention(s). The new intervention was only compared with the least cost-effective existing intervention within the optimal allocation, to keep with our original aim of maximising QALYs. Replacing interventions other than the least cost-effective intervention (i.e. with lowest VfM) in our healthcare package will result in greater QALYs lost than when displacing least cost-effective intervention. However, it is not always possible to ensure that the least cost-effective intervention(s) are disinvested first or that the healthcare package is 'optimal' [20]. Health care packages in real life settings tend to include a mix of interventions that are cost-effective as well as cost-ineffective and there might not be information on what interventions are being displaced. Thus, the empirical estimates of the 'supply-side threshold' use marginal productivity of the system, which describes the relationship between changes in health care expenditure and health outcomes (i.e. change in the QALYs of the health care system with change in the budget - see section 4.1).

Perfect information (and other assumptions)

In our example, we assume that we start with an empty health care package and that the information (i.e. the overall budget, the interventions available and the data on costs and QALYs for all interventions) is already known. Our example is a very simple approximation, whereas the reality of health care resource allocation is much more complex. For instance, the budget may vary with time (and in fact there could be different budgets to consider); there may be complementarities between interventions (e.g. early diagnostic interventions would improve the benefits of treatment interventions, violating the independence assumption); and the health care package may already include many pre-existing interventions (where the implications of disinvestment may need to be considered first). Also, full knowledge of costs and benefits for all interventions required to estimate the threshold value is usually incomplete (i.e. the data required, either to develop the comprehensive league table or to formulate the optimisation problem, to determine the threshold value is not available).

3. Past: Use of heuristics/historical estimates of thresholds

Given the challenges highlighted in specifying a threshold consistent with QALY maximisation from an optimisation perspective in the earlier section, many countries use a threshold value based on other methods and representing different concepts. For example, in line with previous WHO-CHOICE

[2] As described earlier, the shadow price of 0.0001818 relates to intervention B and as such is only applicable for a range of budgets between £42m (i.e. total costs of fully funded A and D) and £64m (i.e. total costs of fully funded A, D, and B).

guidance [8,21], some LMICs have employed a heuristic of one to three times GDP per capita [22,23] while the UK, Ireland and US use explicit thresholds broadly based on historical estimates/judgment [24,25]. Many countries (including Canada, Brazil, Australia, and Sweden) do not specify an explicit threshold at all [4,26]. This section briefly summarises how the thresholds based on heuristics or historical estimates, whether explicit or implied, are used across the world.

3.1. Explicit thresholds

UK (NICE)

NICE in the UK is a high-profile example of the use of explicit cost-effectiveness thresholds, and its guidance recommends in favour of funding interventions with an ICER below a threshold of £20,000/QALY or £30,000/QALY, and recommends against funding interventions with an ICER above these thresholds [27–29]. However, a higher threshold (i.e., £50,000/QALY) is used for life-extending treatments for small patient populations at the end of life –treatments that: offer an extension to life greater than three months compared to current treatment in the National Health Service (NHS); are for patients with a short life expectancy i.e. normally less than 24 months; and are for small patient populations normally not exceeding a cumulative total of 7,000 patients for all licensed indications in England [30]. Despite this guidance interventions with ICERs above £30,000 or £50,000 are often accepted even when lacking the requisite special evidence needed [31].

Ireland

The cost-effectiveness of all new medicines in Ireland is considered by the National Centre for Pharmacoeconomics (NCPE), in collaboration with the Health Service Executive (HSE), the public body with responsibility for delivering state-funded healthcare in Ireland. The Irish pharmaceutical healthcare association (IPHA) and HSE have an agreement which explicitly states that the QALY threshold to be used in the HTA process is €45,000 [32]. This value of the threshold is also confirmed on the NCPE website [33]. It is worth noting that, unlike NICE, NCPE's recommendations are not mandatory and can be overruled by the minister/HSE [25].

US

Whilst $50,000 per QALY has been mentioned anecdotally in the past in the US [34], the recent value frameworks mention explicit thresholds. Given the diversity of payers and health care organisations, it should be noted that there are differences in the thresholds used. A high-profile example of explicit reference to thresholds is the use of $100,000 to $150,000/QALY for value-based price benchmark by the Institute for Clinical and Economic Review (ICER) [35], a trusted non-profit organization that evaluates evidence on new technologies in the US. Premera Blue Cross, a large not-for-profit health plan in the Pacific Northwest, uses a value-based formulary tiers based on ICER thresholds – drugs are allocated to one of the four co-payment tiers (tier 1 <$10,000/QALY, tier 2 is $10,000-<$50,000/QALY, tier 3 is $50,000-<$150,000/QALY and tier 4 is > $150,000/QALY) [36].

3.2. Heuristics for the threshold value: WHO-CHOICE (one to three times a country's GDP)

One to three times a country's annual GDP per capita has been a widely used threshold for cost-effectiveness studies within global health, mainly among studies focused on LMICs [1,37]. A recent study found that the proportion of LMICs citing this threshold has substantially increased over time, with 10% of studies citing this threshold in the early 2000s to 76% between 2013 and 2015 [37].

While the origins for its intended use for CEA are less clear, the WHO first used these values in its 2001 Commission on Macroeconomics and Health (CMH) report [38]. While this report intuitively equates a year of life to per capita income, considering productivity and leisure time, it used per capita income to value the economic loss resulting from the burden of major diseases impacting countries. Despite its variant aim, the WHO-CHOICE thereafter adopted this range for promoting CEA [21,38]. There have recently been several opinions on this threshold value that have motivated calls for consensus and new primary research [8,9,37,39–43]. For instance, some analysts have argued that CE thresholds reflecting opportunity costs are much lower than the one to three times GDP per capita rule of thumb, while other analysts encourage applying a range of income elasticity estimates to account for the relationship between the value per statistical life (VSL) and income [39]. The WHO has since backed away from this threshold range and recognizes its limitations for CEA [8].

3.3. Implied/unspecified thresholds

A recent systematic overview of CE thresholds suggested that many countries do not specify a threshold [26]. Whilst researchers analysed previous decisions to identify the threshold value in these countries, they were unable to pin down a single number. Nevertheless, the manner in which these countries use different CE thresholds is briefly described below.

PBAC

The Pharmaceutical Benefits Advisory Committee (PBAC) in Australia does not formally specify a CE threshold. However, the cost per QALY of the technology is reported as belonging to one of the four bands AUD $15,000 - $45,000; $45,000 - $75,000; $75,000 - $105,000; $105,000 - $200,000. A recent study by Paris et al [44] at Organisation for Economic Co-operation and Development (OECD) suggested that technologies with ICERs greater than $75,000/QALY were rarely recommended and those greater than $45,000/QALY were recommended only in exceptional circumstances, where there was high clinical need and no alternative treatment. These findings are similar to those observed by Henry et al in their retrospective analysis of PBAC decisions [45].

CADTH

While the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines for the economic evaluation of health technologies recommend the use of a ‘supply-side’ estimate of the cost-effectiveness threshold, that value is not given in the guidance [4]. Whilst the reporting sometimes refers to the $50,000/QALY threshold (for example – the probability of being CE was x% at a threshold of $50,000/QALY), a review of all the publically available CADTH appraisals performed by Griffiths et al [46] suggested that this threshold is not consistently applied, with several technologies recommended with ICERs above $50,000 per QALY, while many were rejected with ICERs below this threshold.

NZ

Pharmaceutical Management Agency (PHARMAC) in New Zealand state that they do not have a cost-effectiveness threshold [47]. Whilst researchers have tried to imply the threshold from previous decisions [48,49], PHARMAC states that they fund medicines within a fixed budget, and as cost-effectiveness is only one of its nine decision criteria used to inform decisions, thresholds cannot be

inferred or calculated [50]. They also note that cost-effectiveness estimates for PHARMAC's investments has ranged between NZ$−40,000 (net cost savings to the health sector for health gains) to over NZ$+200,000 per QALY (€−20,000 to +100,000) [51].

Other countries

There are other countries, including Scotland [52], Korea [53], Brazil [54] which use cost-effectiveness analyses but do not explicitly specify a threshold.

4. Present: Empirical estimates of CE threshold

Recently, some countries have begun to conduct empirical research to identify CE thresholds for their setting. These studies have broadly been classified as either supply or demand side estimates [10]. Supply side estimates aim to reflect the opportunity cost of spending on health by linking the health care expenditure to health outcomes, while the demand side estimates aim to reflect societal willingness to pay for improvements in health.

4.1. Supply side thresholds

It should be noted that the example in section 2 illustrates an ideal situation in which the budget allocation is optimal; it is easy to identify the least cost-effective intervention(s) and the system (decision makers) only displace these least cost-effective interventions. This is a 'first best' situation. However, in practice, this is not always the case. In complex systems, the existing health care package may not be optimal, it may not be possible to specify exactly what activities are displaced, and decisions about disinvesment may be left to other decision makers in the system, for example at a local level. Thus, in empirically estimating the threshold, the aim is to estimate the shadow price of the budget in terms of the interventions that are likely to be displaced [42]. This is what Culyer (2015) describes as an approach to estimating the 'second best' threshold [7]. These empirical estimates of the supply side threshold tend to reflect the marginal productivity of the health care system, derived from the relationship between changes in health care expenditure and health outcomes, where expenditures at the margin may be committed to a mix of cost-effective and cost ineffective interventions (i.e. interventions with a range of cost per QALYs) [7]. In a world where the assumptions of the optimisation model are met, this conceptualization of the threshold should result in the same value as that which is derived by solving the constrained optimisation problem. However, where the necessary assumptions as set out in the preceding section are not met, the values may differ. The 'second best' approach provides an estimate that best informs the expected health opportunity costs of a new intervention and therefore, if robustly estimated, can be better relied upon to inform whether a new intervention is expected to result in a net health gain or net health loss.

There are challenges involved in estimating the relationship between changes in health care expenditure and health outcomes i.e. the marginal productivity of the health care system. Given the outcome of interest is QALYs, a combination of quality of life (QoL) and life years (LYs), there is a need to link the healthcare expenditure to mortality (to estimate the effect on LYs) and morbidity (to estimate the effect on QoL). The data on health care expenditure and its effect on mortality/morbidity may not always be readily available and as such, assumptions are often required. Furthermore, there are also econometric challenges which include, but are not limited to,

issues around controlling for the many non-health care factors that affect health [55], which if not properly accounted for may lead to biased and inconsistent estimates. To date, such within-country estimation has been undertaken in relatively few countries, which are described below alongside one example where cross-country data has been used to estimate these values for a number of countries.

UK

Claxton et al [42] empirically estimated the cost-effectiveness threshold for the NHS in the UK to be £12,936 per QALY. They used the English NHS programme budgeting data to estimate the relationship between changes in overall NHS expenditure and changes in mortality/LYs gained and subsequently extended this to QALYs. Their 'structural' uncertainty suggested that the estimate is likely to be an overestimate and reported that probability that the threshold is less than £20,000 per QALY is 0.89 and the probability that it is less than £30,000 per QALY is 0.97. The assumptions made in the estimation of the UK threshold have been discussed in a number of publications [28,56,57].

Australia

Edney et al [58] estimated the cost-effectiveness threshold, called the reference ICER, for Australia. They used an instrumental variable two-stage least squares regression to estimate the effect of changes in health expenditure on QALYs due to reduced mortality. Further empirical analysis was then used to inform the effect of health expenditure in terms of QALYs due to reduced morbidity. These are then combined to produce a central estimate of the reference ICER, which represents the average opportunity costs of decisions to fund new technologies, to be AUD28,033/QALY.

Spain

Vallejo-Torres et al [59] estimated the cost-effectiveness threshold for the Spanish NHS. They used 5 years of data across the 17 regional health services in Spain to regress Quality-Adjusted Life Expectancy (QALE) against health spending, controlling for region and year fixed effects and a comprehensive set of time- and region-variant indicators, applying a one-year lag to expenditure. They report that health expenditure has a positive and significant effect on QALE, with an average spending elasticity of 0.07 which translates into a cost per QALY of between 21,000€ and 24,000€.

LMIC CE thresholds

Ochalek et al [41] estimate cost-effectiveness thresholds for 123 LMICs using estimates of the effect of a change in government spending on health on health outcomes from cross-country data. Their study expands upon existing studies within the literature estimating the effect of a change in spending on mortality outcomes to estimate the effect of a change in spending on a range of mortality and morbidity outcomes. Using data on each country's demography (i.e., the gender and age structure of the population), epidemiology (i.e., underlying mortality and morbidity burden) and health expenditure, they are able to generate a range of cost per DALY averted estimates for 123 countries that captures some of the structural uncertainty associated with these estimates. Their results aim to reflect the rate at which the health care system in a given country is able to produce health, and, as such, can be used to inform health opportunity costs. For example, they have been used to help guide decisions around the design of the Essential Health Package in Malawi [60,61].

4.2. Demand side thresholds

The empirical methods of estimating demand side thresholds, namely willingness to pay and value of a statistical life studies, are reviewed and discussed in detail in Vallejo-Torres et al (2016) [10]. Below we offer a brief description of the application of these methods in policy in two countries: Thailand and Malaysia.

Thailand (HITAP)

Health Intervention and Technology Assessment Program (HITAP) in Thailand elicited the WTP for a QALY in the Thai health care setting [62]. The results of this study were adopted by decision-making bodies as the appropriate threshold for health investment in the Thai setting, the ceiling threshold is reported to be 160,000 Baht per QALY which is around 1.2 times of Gross National Income (GNI) per capita [63]. However, they also note that this single threshold is not used for resource allocation of all types of interventions – for example, sometimes medicines that treat rare diseases are included in the National List of Essential Medicines (NLEM) even though their ICER is much higher than the threshold.

Malaysia

Lim et al conducted a cross-sectional, contingent valuation study in four states of Malaysia to estimate the CE threshold for health care interventions as WTP for a QALY [64]. One thousand thirteen respondents were interviewed in person for their socioeconomic background, quality of life, and WTP for a hypothetical scenario. The authors reported that the CE thresholds ranged from MYR12,810 to MYR28,470 (US $4,000–US $8,900) and education level, estimated monthly household income, and the description of health state scenarios had the biggest effect on the WTP estimates. They concluded that there is no single WTP value for a QALY and that the CE threshold estimated for Malaysia was found to be lower than the threshold value recommended by the WHO (i.e., 1 and 3x GDP per capita, which was approximately $10,000 and $30,000 respectively in 2017) [65].

5. Future: Beyond QALYs? Other sectors?

Most of the work on CE thresholds has been based on using QALYs (or DALYs) as the measure of effectiveness. However, recently, there have been some developments that suggest an inclination to go beyond these measures of health benefit. These include the recent work on value frameworks [66], which mentions a number of additional criteria in addition to QALYs or DALYs and the recommendation statement from the Second Panel on Cost-Effectiveness in Health and Medicine [67,68], which supports the use of a societal perspective. The impact of these recommendations is discussed in brief below.

5.1. Thresholds for benefits beyond QALYs

Alongside the recent work on value frameworks [66], which mentions many additional criteria beyond QALYs, it is widely acknowledged that many HTA organisations consider multiple factors alongside cost-effectiveness [69]. More recently, there have been calls for including these multiple

criteria explicitly in the assessment of value [70], using techniques such as multi criteria decision analysis (MCDA) [71]. The current cost-effectiveness thresholds are based on QALYs (or DALYs) being the measure of effectiveness. If the value is redefined to include multiple criteria beyond QALYs (or DALYs), the measure of effectiveness is not QALYs (or DALYs) anymore but rather a new composite measure of effectiveness. As such, the threshold will need to be re-estimated for this new measure of 'effectiveness' to reflect the opportunity costs [6]. As observed in Section 4 (the empirical estimates of the supply side thresholds), this poses a significant informational challenge in identifying the marginal impacts on the different criteria that make up the overall effectiveness.

5.2. Thresholds in other sectors

The Second Panel on Cost-Effectiveness in Health and Medicine [67,68] supports a societal perspective and recommends the use of an 'impact inventory'; a structured table listing the health and non-health effects of an intervention that should be considered in a societal reference-case analysis. To evaluate interventions crossing multiple sectors, sector-specific thresholds are needed that represent the sector-specific outcome that would be forgone as the result of the additional costs of a new intervention. To date, no sector outside of health care has established a threshold. Whilst some sectors have established measures, such as Adult Social Care Outcomes Toolkit (ASCOT) used to estimate social care-related quality of life (SCRQoL), many sectors do not have standard definitions for their outcomes. The challenges involved in performing CEA when the intervention concerns multiple sectors are highlighted by Remme et al. (2017) [72].

6. Key issues/misconceptions with thresholds

6.1. Which thresholds should be used?

Unless there is clear reason to choose a different threshold value (e.g. political sensitivity), empirical estimates provide a more appropriate value of the threshold than historical/heuristic thresholds, which are based on judgement. The key question is whether supply side thresholds (which aim to represent the opportunity cost of investment to the system given budget constraints) or demand side thresholds (WTP estimates which aim to reflect the value that society places on a QALY) should be used [10]. A recent systematic review of WTP per QALY studies suggested that WTP per QALY varied substantially by condition, especially those for extending life or saving life and improving quality of life [73]. Supply side thresholds enable the quantification of the net health gains (or losses) that would result from the inclusion of a new intervention (whether doing so represents an increase in the budget or it displaces a currently funded intervention(s)) in the health care system. Decisions made on the basis of supply side CE thresholds ensure that aggregate health is improved by the inclusion of new interventions.

On the other hand, thresholds based on WTP for a QALY are generally higher than thresholds resulting from estimating the opportunity cost to the health care system [10]. As such, using WTP estimates may lead to decisions that reduce rather than improve health outcomes overall. This may also be the case with the use of WHO CHOICE guidelines for thresholds (i.e. one to three times the GDP), where the threshold is not related to the efficiency of the health care system. However, as WTP estimates reflect societal willingness to pay for improvements in health, the fact that they tend to be higher than estimates linked to the efficiency of the health care system provides suggestive

evidence for an increase in public budgets for health care. Some analysts have argued that in a privately funded health care system, in the absence of explicit health care budget constraint, WTP can be an estimate of the opportunity cost of private consumption [2].

6.2. Should the threshold be made explicit?

There are two questions here: a) whether there can be a single threshold and b) whether the threshold values should be made public. No HTA organization currently recommends the use of a single threshold, and many do not explicitly specify a threshold at all (as seen in section 3). Those that specify a threshold, tend to specify a range rather than a single value reflecting the belief that a single threshold should not be applied to the diverse range of technologies and conditions. In terms of the second question, the so-called 'silence of the lambda' [74] or reluctance to set out an explicit threshold may result from a number of concerns including fear of gaming by pharmaceutical companies to target ICERs just below the threshold, reduced flexibility to balance competing criteria when making funding decisions, and the issues associated with advocating a threshold value that may have little or no empirical basis (such as the potential for political and ethical concerns about the accuracy and validity of funding decisions) [75].

6.3. Impact of using the wrong threshold

If the threshold used is lower than the empirical estimate, it may lead to potentially cost-effective (compared to the empirical threshold) technologies not being reimbursed. However, it should be noted that in situations where researchers suggested increasing the threshold [76], arguments were based on WTP/preference estimates. On the other hand, if the threshold used is higher than the empirical estimate reflecting health opportunity costs, each new technology approved (with a higher ICER than the empirical threshold) leads to loss in health outcomes. An example is NICE's end of life decision making scheme, where it was suggested that approving drugs with ICER higher than the NICE threshold of £20 000/QALY to £30 000/QALY resulted in substantial QALY losses [77]. Furthermore, Claxton et al [31] argue that the current NICE threshold (of £20 000/QALY to £30 000/QALY) is too high compared to the empirical estimates, suggesting that approving drugs lead to more health likely to be lost than gained.

6.4. Threshold and budget impact

If the budget impact of a new technology is substantial (i.e., non-marginal), the threshold used should be lower reflecting the size of the budget impact, as the new technology will displace a large proportion of the existing health services (see example in section 2.1) [78]. The recent hepatitis C drugs highlight this issue – whilst the new hepatitis C drugs were very cost-effective, their budget impact was quite substantial [79]. ICER in the US has a limit for budget impact ($915 million/year for 2017-2018) designed to alert policy makers that funding the new service may be difficult without displacing other needed services or increasing the health care insurance costs [35]. In UK, for cost-effective technologies with significant budget impact (NICE use a 'budget impact threshold' of £20 million per year, set by NHS England), special arrangements need to be agreed in dialogue with companies to better manage the introduction of these technologies in the NHS [80].

6.5. Threshold and inflation

Many have argued for a higher threshold, as the values used by NICE, PBAC, US etc. have remained the same since they were first introduced [81]. In the absence of an explicit health care budget constraint, inflation can potentially affect the WTP estimates of the threshold. However, if the threshold is linked to the efficiency of the health care system (i.e. cost-effectiveness of the displaced services), it is not related to inflation. If a health service became more efficient over time (i.e. the displaced activities become more cost-effective over time), the threshold will fall irrespective of inflation. This argument is also applicable for the transferability of thresholds between countries. Rather than relying on generic metrics such as GDP (e.g. WHO CHOICE guidelines for thresholds of one to three times the GDP) or exchange rates, the thresholds should be determined by estimating the efficiency of the health care system, as observed in section 4.

6.6 Threshold and capacity constraints

Published CEA often ignore the capacity constraints of resources (e.g. beds, nurses, equipment etc.), which may result in biased estimates of cost-effectiveness [82]. In principle, if perfect information was available, these capacity constraints can be added on top of the budget constraint into the optimisation problem to estimate the 'new' CE threshold that takes into consideration the scarcity of resources. However, this perfect information is not available in reality and thus, these capacity constraints are incorporated within in CE modelling to understand their impact the standard of care and the implementation of the new technology [83].

Where perfect information about capacity constraints does not exist, empirically estimated 'supply side' CE thresholds can be used to determine the expected value of reducing or removing such constraints either specific to interventions or across the health care system as a whole. This expected value can be used alongside information (e.g., based upon expert opinion) about the costs and benefits of removing different constraints to prioritise policies to reduce or remove constraints to scale up the implementation of interventions [61].

6.7 Priority setting process

Alongside the results of CEA, a number of other factors are often also considered as part of the appraisal process around whether to adopt or reject an intervention. A recent review of all HTA appraisals between May 2000 to May 2014 from NICE, PBAC, SMC and CADTH suggested that technologies with ICERs higher than the respective thresholds are sometimes recommended - the reasons included high clinical benefit over the standard of care, and addressing an unmet therapeutic need [84]. Similarly, even though some technologies (such as orphan drugs for rare diseases, or cancer treatments at end of life) have very high ICERs, NICE and most other health systems have found ways to fund those few technologies on the basis of evidence of benefit. On the other hand, some interventions are rejected even when the ICERs are below the threshold [46]. Indeed, it is acknowledged that there is need for some discretion in priority setting linked to legitimation of decisions rather than using the threshold alone.

7. Conclusions

This paper contributes to the literature on CE thresholds by providing a simple illustration of the CE threshold as the shadow price of budget constraint, providing a theoretical framework for how a CE

threshold could be employed in a hypothetical optimisation setting. Existing estimates of "thresholds" representing various definitions – from heuristics applied historically to more recent empirical estimates, whether willingness to pay for improvements in health or opportunity costs are then outlined. Among these, those that can be categorized as supply side estimates (i.e., from the UK, Australia, Spain and LMICs as presented in 4.1) may be considered more appropriate for judging the cost-effectiveness of new technologies where the aim of agencies is to inform whether or not a new technology is expected to improve population health. Finally, the future for CE thresholds is speculated upon where new policy questions have indicated further areas of research where thresholds will be relevant and useful for decision-making, in particular, the consideration of effects and costs on multiple sectors beyond health where opportunity costs are still relevant. Despite advances in this area of research, there remain misconceptions about CE thresholds, the assumptions involved and their implications, which this paper aimed to highlight. It is the responsibility of all of us to educate those who are involved in priority setting about these concepts of threshold in order to ensure efficient health care resource allocation.

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