COST-EFFECTIVENESS THRESHOLDS: METHODS FOR DEFINITION AND CASES AROUND THE WORLD

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ABSTRACT

INTRODUCTION: Cost-effectiveness thresholds (CETs) are used to judge if an intervention represents sufficient value for money to merit adoption in healthcare systems. The study was motivated by the Brazilian context of HTA, where meetings are being conducted to decide on the definition of a threshold. AREAS COVERED: An electronic search was conducted on Medline (via PubMed), Lilacs (via BVS) and ScienceDirect followed by a complementary search of references of included studies, Google Scholar and conference abstracts. Cost-effectiveness thresholds are usually calculated through three different approaches: the willingness-to-pay, representative of welfare economics; the precedent method, based on the value of an already funded technology; and the opportunity cost method, which links the threshold to the volume of health displaced. An explicit threshold has never been formally adopted in most places. Some countries have defined thresholds, with some flexibility to consider other factors. An implicit threshold could be determined by research of funded cases. EXPERT COMMENTARY: CETs have had an important role as a "bridging concept" between the world of academic research and the "real world" of healthcare prioritization. The definition of a cost-effectiveness threshold is paramount for the construction of a transparent and efficient Health Technology Assessment system.

KEYWORDS: Cost-Benefit Analysis; Cost-Effectiveness Analysis; Economics, Medical; Economics, Pharmaceutical; Expert Testimony; Review; Technology Assessment, Biomedical.

1 INTRODUCTION

Health technology assessment (HTA) relies on evaluations of the clinical, epidemiological and economic data to make decisions about the allocation of the scarce resources of public healthcare [1, 2, 3]. The centerpiece of a cost-effectiveness analysis (CEA) is the incremental cost-effectiveness ratio (ICER), which measures the differential cost for a unit of extra benefit gained from a new therapeutic strategy [2, 4, 5, 6, 7]. In most cases, new technologies that apply for public funding present higher costs and effectiveness than the technologies currently in use [8, 9, 10, 11, 12, 13]. For a new technology to be recommended based on economic assessments, several authorities have argued that the ICER must be compared to a cost-effectiveness threshold (CET) value that should represent the highest acceptable cost for an extra unit of benefit [2, 5, 7, 14, 15, 16, 17, 18].

Despite the economic evaluations being a mandatory part of the process of HTA in many countries, such as Brazil, USA, Canada and Australia, an explicit CET value has never been established for the

assessment of new technologies in their national health systems [19, 20, 21]. Many countries do not specify a threshold arguing that the benefits of doing so are controversial [5, 14, 15, 16, 18, 22, 23, 24, 25]. It has been suggested that the use of an explicit threshold could give manufacturers an incentive to "bid up" their price to the ICER level and that it could adversely affect the flexibility of decision makers, although there is little evidence of the latter [7, 13, 26, 27, 28]. In addition, an explicit CET might trigger a reevaluation of previous funding decisions [13]. The adoption of high threshold levels may contribute to the increase of health expenditures and decrease of coverage, especially among low- and middle-income countries (LMICs) [14, 29, 30]. Conversely, the establishment of appropriate methods for the definition of the threshold can be useful to the national health systems as a way to better negotiate prices, bring transparency into decision-making and improve value for money in public healthcare [15, 18, 23, 31, 32, 33].

The lack of a standard method for determining thresholds [34] appears to have given manufacturers a way to justify applications for new medicines with higher prices, which disproportionally affects LMICs [5, 14, 30, 35]. This study aims to review the methods to establish the threshold and present some examples of values implicitly or explicitly defined around the world. We discuss what would constitute an adequate and reasonable method to establish a threshold and the implications of an explicit CET to HTA. The study was motivated by the Brazilian context of HTA, where meetings are being conducted to decide on the explicit definition of a CET [36].

This objective was pursued through a literature review. An electronic search on the databases of Medline (*via* PubMed), Lilacs (*via* BVS) and Science Direct was performed to identify publications dealing with methods for the definition of CETs and cases of countries that have a standard value on which to base recommendations, followed by a complementary search in the references of included studies, Google Scholar and conference abstracts. The searches were performed on January 2017. The results were divided into three sections: the first describes the main methods for the definition of a CET; the second reports cases where the threshold has been defined or inferred around the world; and the third reflects on the implications of thresholds for HTA. We selected agencies and countries that were representative of a variety of healthcare systems.

2. METHODOLOGICAL APPROACHES FOR THE DEFINITION OF A COST-EFFECTIVENESS THRESHOLD

Most research on cost-effectiveness thresholds suggests its definition through three different approaches [13, 37, 38]: *the willingness-to-pay* (WTP) *method* for a unit of outcome, representative of the welfare economics theory; *the precedent method*, that is based in the value of an already funded technology; and *the opportunity cost method*, that links the threshold to the volume of health displaced by new technologies, considering the existence of restricted budgets. Other methods have been developed or adapted over the last few years. One of these is IQWiG´s efficiency frontier [39, 40].

2.1 The Willingness-to-Pay method

In this method, the threshold is estimated through preference data collected directly from the population with contingent valuation surveys, or indirectly, from the behavior of the individual in the market, WTP for a reduction of mortality or willingness-to-accept (WTA) for a risk [18, 41]. These methods are intended to elicit the maximum value that an individual would be willing to disburse to obtain a determined amount of health improvement, usually a small difference in utility aggregated to generate the value for a quality-adjusted life year (QALY) [41, 42]. Initially, the utility difference between two health states is estimated, commonly through time trade-off or standard gamble; and then the WTP is elicited for that difference [41, 43].

The contingent valuation method consists on the application of a structured questionnaire with all relevant information about the technologies and comparators, health conditions and context to inform respondents prior to the decision [42, 44, 45]. The WTP value can be elicited through a direct open-ended question; a bidding game, with a direct question followed by increases and decreases of value, until a point estimate is reached; payment cards, with values for the respondent to choose; and a discrete choice, where respondents answer a single "yes" or "no" question followed by statistical assessment of the data [42, 44]. The questionnaire should, preferably, be applied on face-to-face interviews and respondents must be reminded of the opportunity costs and therapeutic alternatives

[45, 46]. Bidding game and discrete choice are more common and reliable methods to assess the WTP [42, 44, 46, 47]. It is worth noting that WTP and WTA values, contrary to initial theoretical predictions, are substantially different from each other. This difference is a consequence of the *endowment effect*. The endowment effect is associated with loss aversion and failure to anticipate *ownership utility*. So, in terms of preferences, losses are weighted substantially more than gains [48, 49].

Individual preferences do not directly convert into affordability considering that individual valuation of health benefits is detached from the budget-setting process and can only very indirectly influence it [41, 50]. Consequently, WTP estimates on the CET usually return higher threshold values compared to the opportunity cost approach [18, 38]. Since the WTP threshold is not attached to the budget, these methods might not lead to maximization of health [3, 29, 51].

Contingent valuation might not provide an accurate assessment of WTP/QALY. Welfare states mostly rely on a social protection mechanism based on principles of social justice and solidarity [52, 53]. It has been shown that individuals might not be as willing to pay for other people's health as much as they would pay for their own. Shiroiwa *et al.* [43] observed differences for individual's valuation of WTP/QALY for society, oneself or family, with the order of preference being dependent on the context. The WTP/QALY depends on the severity, rarity and social stigma of the disease [5, 23, 25, 54, 55] and individuals might have little feel for choices which are so remote from their day to day experience and concerns. For example, Blumstein [56] states that people have a belief that democratic governments should protect life at any cost, yet, are unwilling to pay the price necessary to achieve that objective.

2.2 The Precedent method

Another way to estimate the threshold is based on the cost-effectiveness of an intervention that has already been approved for funding. The values of 50,000 USD/QALY in the USA or the updated values of 100,000 or 150,000 USD/QALY are examples of these [16, 25, 57, 58, 59]. The general idea is that if society already pays for some treatment, any alternatives with higher efficiency would be acceptable. This arbitrary threshold might be too high or too low, as there is no reason to suppose that previous decisions were taken rationally [2]. The value may, for example, be defined by a political decision rather than more evidence-based models, and be subject to exploitation, as seen with medicines for cancer and orphan diseases [16, 18, 60, 61, 62]. In addition, this approach does not take into consideration the affordability of interventions, running the risk of uncontrolled growth in healthcare costs [16, 59, 63, 64], and might lead to more losses than gains in terms of health outcomes [13, 29]. The precedent threshold values are usually fixed, not subjected to depreciation when efficient alternatives appear or adjustment for inflation [16, 59].

2.3 The Opportunity Costs method

The opportunity cost approach can be traced back to the work of Weinstein and Zeckhauser, in the 1970s, on the maximization of outcomes with resource constraints [3]. It assumes that the budget will be fully spent trying to obtain the maximum possible health returns by allocating from the most efficient to the least efficient interventions [3, 29]. The opportunity costs are measured in health benefits forgone [29], that should be expressed in units of health that associate mortality and morbidity (e.g. QALYs or disability-adjusted life years [DALYs]). The basic principles of the model are that the CET cannot be calculated independently of the health budget and the incorporation of new technologies, that imposes additional costs to the health system, might provoke displacement of already funded interventions [26, 29, 41]. Technologies with ICER values lower than the threshold should provide a positive balance between health benefits gained and lost [13, 17, 18, 29, 35, 38, 64]. Optimal reallocation would involve expansion the most cost-effective technologies by displacing the least cost-effective programs and services [13, 18, 37, 51]. Multiple thresholds may be required in systems where there are separate budgets for separate types of healthcare interventions within the same healthcare system [13, 29], although splitting health budgets can be shown to be in general suboptimal [18].

Some authors suggest that the opportunity cost threshold could be better estimated through a *league table* [41]. A *cost-effectiveness league table* lists alternative therapeutic strategies in order of desirability based on their ICERs and allocates them until the limit of the budget is reached [3, 29]. It

can be applied within specific conditions or across the entire system [65]. The CET would be the last accepted ICER [2, 16, 18, 57, 66]. The *bookshelf model* can be considered another way to represent the *league tables*. It consists of a bi-dimensional graph computing the Effectiveness-Cost Ratio (ECR) in the y-axis and the budget impact on the x-axis. The product of the axes would provide the health benefit of society with that technology. The alternatives should be allocated until the limit of the health budget. The Cost-Effectiveness Ratio (CER, inverse of the ECR) of the last funded technology corresponds to the CET [22, 29, 51].

The application of the *league table/bookshelf model* to express opportunity costs is difficult. The construction of the tables would require the existence of quality information on costs and benefits for all the technologies, that might not be available [26, 67], especially for new interventions in LMICs. All interventions have to be evaluated with the same method to allow direct comparisons. Another problem is that social preferences expressed by political decisions are not taken into account. The *league tables*, however, are capable of combining measures of efficiency with affordability, since the size of the list depends on the available budget [14, 16, 18, 24, 25, 56, 68], and have been used to rank interventions on HIV and cardiovascular disease [65]. If correctly constructed, a *cost per QALY league table* could provide information for decision-making [68].

Claxton *et al.* [17] aggregated the data on changes in overall English National Health Service expenditure, changes in mortality and age- and gender-adjusted quality-of-life to determine a CET from a supply side opportunity cost approach. If a technology's ICER is lower than the CET, then its funding would generate more utility gains than benefits foregone on average [17, 51]. This might be the best approach to set a CET so far [29] as it avoids the difficulty of having to analyze all technologies in the system, despite the difficulties with the reliability of data on quality-adjusted life expectancy and the partial ignorance of people's preferences.

There are controversies on whether the application of such thresholds improves health benefits conditionally, considering that the least cost-effective technologies would be displaced, or unconditionally, regardless of what might be displaced in actual practice. Approaching the displacement without concerns of which technologies will be displaced might lead to suboptimal reallocation [29, 51]. For scenarios of suboptimal allocation, Eckermann & Pekarsky [51] proposed the use of a shadow price and a CET to adjust the system towards allocative efficiency. If the cost of the new technology were adjusted to achieve the calculated CET then the net health benefits would be the same as the optimal reallocation process. Paulden *et al.* [69] claim that this approach is unlikely to be adopted in practice until there are processes to identify the least and most cost-effective technologies as budgets expand and contract.

Some limitations of this approach are that the healthcare decision-makers are considered maximizers of health, without regard for other objectives of the system (e.g. promotion of access to innovations and reduction of social inequalities) and measurement problems, such as imperfect or lack of information [69]. It also ignores society´s valuation of health improvements for threshold-setting purposes [41]. Optimal reallocation can involve eliminating effective technologies, which might be politically very difficult due to *internally ranked* interventions and the *endowment effect* [2, 29, 52, 70, 71]. Internally ranked interventions refer to technologies that might be more effective for some types of patients than others. Better targeting would be a strategy to reallocate the resources expended on them [29, 31].

The determinants of the threshold are the underlying demographics and disease burden, local environments, culture and social values, and the health budget [26, 29]. The threshold is also dependent on the perspective and context of the decision since different policy-makers are likely to have different budget constraints (e.g. government and other healthcare funders) [14]. Different perspectives (e. g. societal, third party, individual) might limit the comparability of values between countries. For instance, different countries assess the value and funding of new medicines for orphan diseases and cancer differently due to issues of unmet need, the perceived emotive nature of the disease and patient expectations [23, 60, 61, 62, 71].

3 COST-EFFECTIVENESS THRESHOLD VALUES AROUND THE WORLD

In most countries, an explicit cost-effectiveness threshold has never been formally adopted. Some countries defined a threshold to be used in the limits of their decisions with some flexibility to consider

other factors, such as the UK. In other countries, an implicit one could be determined by research on past decisions. A comparison of the implicit or explicit cost-effectiveness thresholds of the evaluated regions can be found in Supplementary Materials. In the remainder of this section we summarize our findings, first at the international level, and then for individual countries in Europe, Asia and the Americas.

3.1 International

The most commonly referred cost-effectiveness threshold at the international level is based on a year of perfect health referred by the Commission on Macroeconomics and Health and published by the WHO [14, 15, 16, 72]. The primarily objective seemed to be to connect the threshold to an objective national benchmark associated to affordability [18] and to suggest that the value of a utility-adjusted life year should reflect factors beyond market income, such as changes in longevity, pain and suffering [14]. In 2005, the responsible parties of the WHO's Choosing Interventions that are Cost–Effective project (WHO-CHOICE) suggested that therapeutic alternatives that add less than three GDP *per capita*/DALY should be considered cost-effective. This value has been applied as threshold in economic studies around the world [1, 14, 15, 16, 72, 73]. More recently, the WHO seems to be trying to dissociate themselves from this initial recommendation as it does not fit many contexts [1, 15, 16, 73].

This approach has major limitations and has been criticized by health economists [14, 30]. The GDP-based threshold is usually found to be above the opportunity cost threshold [15, 17, 35, 72], meaning that it offers a poor constraint to the incorporation of new technologies into the system. Consequently, it does not effectively discriminate between interventions that offer good from bad value for money [2, 16], exposes the system to the risk of unacceptable budget increases as new medicines are launched and might provoke more health losses than gains.

Woods *et al.* [35] used a method that relies on the definitions of income elasticity curves for the Value of a Statistical Life (VSL) to generate a range of values of threshold, based on the analysis of the National Institute for Health and Care Excellence´s (NICE) threshold and the difference in GDP *per capita* between countries, assuming that the curves would be stable across countries. They estimated a threshold of 3 to 116 USD/QALY for Malawi (1%–51% GDP *per capita*), 44 to 518 (4%–51% GDP *per capita*) for Cambodia, 422 to 1,967 (11%–51% GDP *per capita*) for El Salvador, 472 to 1,786 (14%–51% GDP *per capita*) for Indonesia, 4,485 to 8,018 (33%–59% GDP *per capita*) for Kazakhstan, 4,896 to 9,436 (31%–60% GDP *per capita*) for Chile, 25,292 to 31,915 (43%–93% GDP *per capita*) for Canada, 24,283 to 40,112 (46%–75% GDP *per capita*) for the USA, 43,211 to 93,736 (46%–75% GDP *per capita*) for Norway, and 43,092 to 143,342 (39%–129% GDP *per capita*) for Luxembourg.

Shiroiwa *et al.* [43] used contingent valuation, capturing data from six countries from an internet-based survey, to determine the CET in some countries in 2010. He found, for the estimation of WTP/QALY for the individual, family and society, values of 41,000 to 52,000 USD in Japan, 74,000 to 86,000 USD in Korea, 66,000 to 77,000 USD in Taiwan, 36,000 to 60,000 USD in the UK, 47,000 to 66,000 USD in Australia and 62,000 to 96,000 USD in the USA. The questionnaire was relatively simple and considered that the individual had a life-threatening condition that could potentially end his/her life instantaneously, which is methodologically undesirable. These publications [35, 43] exemplify the argument that WTP measures tend to lead to higher threshold values than opportunity cost approaches.

3.2 Brazil

The legislation in Brazil does not establish a CET [19, 20, 74, 75]. Nevertheless, it is very common to find mentions to one to three GDP *per capita*/QALY, as in the recommendations of Brazilian Guidelines [74]. Analyses of the decisions of the Brazilian HTA agency (CONITEC) found that the recommendations made were not largely influenced by the economic evaluations [76, 77, 78] and failed to derive a CET through a previous decision analysis [77, 78, 79, 80]. Economic evaluation seems to be a secondary criterion to the recommendations. However, Pichon-Riviere *et al.* [81] found through a research method based on health expenditures and life expectancy that the threshold for Brazil should be between 0.62-1.05 GDP *per capita*/QALY.

3.3 United States of America (USA)

A retrospective study failed to determine a cost-effectiveness threshold for Medicare decisions [82]. There is, although, a frequently referred precedent value of 50,000 USD/QALY in USA-based CEAs [82]. This value seems to have first been introduced to evaluate the interventions for end-stage renal disease patients of Medicare in the 1980s [25, 59] and gained widespread use in the 1990s [25]. More recently, the values of 100,000 to 150,000 USD/QALY have been used in publications [58]. The increase on the value of the threshold is advantageous pharmaceutical companies, who are subsequently able to seek higher prices for its innovations [16, 57, 58, 83].

3.4 England

Since 2004, NICE operates with an explicit value to be applied to candidate technologies for reimbursement with some flexibility that allows the system to take into account additional relevant factors, including social preferences [13, 17, 34]. A threshold of 20,000 GBP/QALY was set and could be increased to 30,000 GBP/QALY upon four considerations: certainty of ICER; inadequately evaluated health-related quality of life; innovation; and other non-health objectives of NICE [2, 84]. Technologies with an ICER up to 50,000 GBP/QALY could still be recommended if they were associated with life extending treatments as part of end-of-life care [2, 15, 17, 21, 84]. Claxton *et al.* [17] estimated, through an opportunity cost approach, a point estimate of 12,936 GBP/QALY for the CET. They strongly argue that the threshold value considered by NICE might be too high, given the restricted budget limits within the UK. It has also been argued that increasing the threshold value for other factors might be harming unidentified users that bear the opportunity cost [4, 84, 85].

3.5 Canada

The Canadian Agency for Drugs and Technologies in Health (CADTH) does not explicitly state a CET. Nevertheless, a value of 50,000 CAD/QALY based on precedent is often cited. Griffiths *et al.* [86] suggested, from retrospective analysis, that the value is considered when decisions state a need for reductions in prices (to achieve the ICER < 50,000 CAD/QALY) or to reinforce the decision (the ICER was under 50,000 CAD/QALY). Other interventions with higher ICERs were also recommended during the study period, demonstrating that the cost-effectiveness is not a *sine qua non* condition for recommendation. A review of past decisions of the Canadian Expert Drug Advisory Committee (CEDAC) from 2003 to 2007 reported a threshold of over 70,000 CAD/QALY or LYG [2].

3.6 Thailand

In 2007, Thailand regulators determined a threshold of 100,000 THB/QALY, equivalent to 0.8 GDP *per capita*. In time, this threshold been interpreted as becoming a powerful instrument for price negotiation [15]. More recently, the commissioners of health technology assessment recommended that the threshold should not be higher than 1.2 Gross National Income (GNI) *per capita*, which represented 160,000 THB/QALY in 2013 [87].

3.7 Australia

Australia was one of the first countries to place explicit emphasis on economic evidence as a decision criterion for funding health technologies [13]. The Australian Pharmaceutical Benefits Advisory Committee (PBAC) does not state an explicit CET for decision-making [13, 88, 89]. Harris *et al.* [33] showed that the incremental cost per QALY has a significant negative influence in the decisions, with increase of 10,000 AUD/QALY associated with a reduction of 0.06 on the chance of listing. The study was not able to define a threshold, but the results suggest a strong relationship between value for money and likelihood of public reimbursement of drugs [33].

3.8 Poland

In Poland, a general threshold of three GPD *per capita*/QALY or LYG was legally established in 2012 [15, 32, 90, 91]. A respective analysis conducted by Niewada *et al.* [92], published in 2013, found the CEA to be important for the explanation of negative recommendations from the Agency for Health Technology Assessment in Poland (AHTAPol), but they did not find a clear relationship between cost-effectiveness and budget impact for positive or negative recommendations. Clinical efficacy was

considered the most important criterion to guide decisions and cost-effectiveness seems to be perceived as a secondary factor [92].

3.9 Germany

The agency for HTA in Germany (IQWiG) uses an efficiency frontier model to issue recommendations on the reimbursement of new technologies [32, 39, 40, 93, 94]. Under IQWiG´s Efficiency Frontier (EF) approach, all the relevant interventions for a specific condition are identified and plotted in a cost-effectiveness plane on which costs are on the horizontal axis and health effects on the vertical axis [40, 94, 95]. Only interventions that lie on the efficiency frontier are considered. The CET for a new intervention is formed as an extension of the ICER between the two existing most effective interventions. The ICER for the entrant technology is formed by its comparison with the existing most effective technology. Alternatives under the efficiency frontier are absolutely or extendedly dominated [18, 39, 40, 94]. The slope of the frontier tends to decrease as benefits increase, representing diminishing marginal returns [40]. The perspective adopted considers the costs that citizens bear, including personal health costs that are usually excluded from health economic evaluations [40].

For IQWiG, the EF does not provide a decision rule. Decisions are taken on basis beyond efficiency [40]. The focus is on establishing relative health benefit in well-defined therapeutic areas, not setting priorities across the system [40]. In addition, it is predicated on the view that patients should not be excluded from treatment based on costs only [40], without assessment of opportunity costs and displacement of technologies. The economic evaluations only consider technologies judged to be superior on the benefit analysis [40], raising an issue with the impossibility of funding less effective technologies even if they are cheaper. Sculpher & Claxton [96] argue that the interpretation of the context of decision by the Panel that recommended the EF is too narrow, fails to define the concept of value, does not consider opportunity costs in the health sector or other areas, gives little attention to the way outcomes should be measured, and fails to examine the implications and to properly address the challenges to be met by the approach. The implementation of separate CETs for each area leads to suboptimal resource allocation [18].

3.10 Ireland

Irish regulators legally established a 45,000 EUR/QALY threshold for HTA of pharmaceuticals in 2012, after an agreement between government and the pharmaceutical industry [97, 98]. This value substituted the previous implicit threshold of 20,000 EUR/QALY. New medicines with ICERs below 45,000 EUR/QALY will have its reimbursement guaranteed, and the prices of other new medicines would be further negotiated. It has been argued that the value chosen has no empirical basis and should be revised to account for opportunity costs [97, 98].

3.11 Japan

In Japan, the CEAs acquired official status in 2016. So far, there is no consensus on the threshold with authors referring to NICE's threshold (20,000 to 50,000 GBP/QALY). More recent studies calculated the CET, through a WTP approach, being between 25,000 and 100,000 USD/QALY for different scenarios of disease status and end-of-life conditions [99].

3.12 Sweden

The implicit threshold for the Swedish Dental and Pharmaceutical Benefits Agency (TLV) is estimated to be between 700,000 and 1,220,000 SEK/QALY (80,000 and 135,000 EUR/QALY). Each 1000 SEK increase in the cost per QALY decreased the probability of subsidy in 0.06. Up to the cost per QALY of 500,000 SEK (56,500 EUR), which is considered a rule-of-thumb for the threshold in Sweden, the likelihood of approval would be 91 to 98% for non-severe and severe diseases, respectively [23].

3.13 New Zealand

The Pharmaceutical Management Agency (PHARMAC) has currently no explicit CET. PHARMAC operates under a fixed budget. The CEA is only one of nine criteria used to make decisions and a technology can only be considered cost-effective if it is prioritized against other proposals at the time [100, 101, 102].

3.14 Netherlands

Health economic assessments are routinely used for reimbursement decisions of new technologies in the Netherlands, supposedly with limited impact [71]. There is no formal CET. The Health Care Insurance Board (CVZ, now renamed Zorginstituut Nederland) suggests a range of threshold values to be applied on HTA studies of 10,000 to 80,000 EUR/QALY, depending on the severity of the disease [71]. This value is not a proper threshold since it is just indicative and not predictive of the decision. Their advice is based upon the balance of different criteria [71, 103]. Other values reported in the literature are 20,000 EUR/QALY [104, 105] and 20,000 to 50,000 EUR/QALY [106].

3.15 Norway

There is no official threshold value to be applied in HTA studies in Norway [107]. Nevertheless, a threshold value of 500,000 NOK/QALY is commonly cited in the literature [108, 109]. The third Norwegian Committee on Priority Setting in the Health Sector recently released a new framework for setting priorities in the health system based on maximization of health, burden of disease, equity, transparency, user participation, and systematic and effective analyses. The Committee recommended the determination of thresholds, through an opportunity cost approach, based on the health loss associated with the condition in three classes [55]. Therefore, the more health loss caused by the disease will make the threshold for the interventions higher and consequently drive up prices. The actual threshold values were not established.

4 CONSIDERATIONS ABOUT THE USE OF THRESHOLDS IN HEALTH TECHNOLOGY ASSESSMENTS

Medical innovations have made a great contribution to people's survival and quality of life. Nevertheless, healthcare systems are showing difficulties to fund premium-priced new drugs [102, 110, 111, 112]. The incremental relationship between costs and effectiveness of therapeutic alternatives is expressed as an ICER that must be compared to an acceptable threshold value to issue a recommendation. A well-established threshold can help improve transparency in HTA, diminish the arbitrariness in the decision process, support the sustainability of the health system, become a tool for price negotiation and increase the confidence that funding decisions are actually improving population health [13, 15, 21, 41, 57, 113].

The application of a fixed cost-effectiveness threshold set through WTP or a precedent decision can be contested [3, 18]. These approaches might lead to significant increases in healthcare spending and new technology prices [18, 41, 64]. Opportunity cost models commonly consider decision-makers as maximizers of health [3, 29, 50, 51, 114]. The basic underlying idea is that, given a budget constraint, policy-makers would take decisions focusing on maximizing health benefits by allocating technologies in the system from the most efficient to the least efficient until the limit of the budget is reached [3, 29]. The CER of the least efficient technology funded would correspond to the CET [22, 29, 51].

It has been suggested that pharmaceutical companies take the price of other approved medicines for the same diagnosis to set increasingly higher launch prices for their new medicines, which for instance has been leading to increasing costs for drugs for cancer treatment over the years [8, 12, 115, 116]. The process in which the manufacturers base the prices of new medicines on the price of already marketed medicines rather than associate it to the therapeutic benefit was described by Howard *et al.* [10] as *reference pricing*. The authors suggest that generous third-party coverage that make patients insensitive to prices, financial incentives to physicians and hospitals to adopt new technologies and the lack of substitute alternatives are some of the reasons that give manufactures the opportunity to charge higher prices for cancer pharmaceuticals even when they have very limited health gain over existing standards [9, 10, 11]. However, there are increasing concerns for price moderation among all key stakeholder groups in the US especially given recent publications suggesting that the cost of goods of some new cancer medicines can be as low as 1% of the selling price [115, 117, 118]. In addition, CETs defined above the value for a context with scarcity allow pharmaceutical companies to seek higher price levels, through *threshold pricing* [34]. The application of *value-based pricing* (VBP) in the healthcare system is already a reality [2, 5, 11]. VBP is a process in which new technologies are priced according to the added benefit to people´s health. There is a

tendency not to accept high prices for technologies that do not deliver value in comparison to existing alternatives, through transparent and valid methods [34].

The threshold and CEAs have an important role in VBP. When the ICER of a new technology is close to the cost-effectiveness threshold defined by opportunity costs, the system is paying the manufacturers the intrinsic value of the product. In that case, threshold pricing would be working in favor of efficiency. To pay more than that would be to pay more for the innovation than it is worth. Since the opportunity cost models work with the assumption that all the budget will be spent to achieve maximization of health and that the opportunity costs would be derived from the displacement of technologies to accommodate the new intervention into the system, to adopt higher prices would represent a negative balance in health benefits [26, 27, 29]. Arguably, the proximity between HTA, the threshold and VBP indicates that the same independent authority should assess the cost-effectiveness, determine prices and issue guidance to the health system [27].

VBP tends to lower the prices in the market and restrict the number of funded therapeutic alternatives. Because of it, only really innovative technologies, orphan drugs and cheaper generic drugs have shown increasing revenue over the last few years [31]. This is perhaps not surprising since only a small minority of new medicines are truly innovative, with the vast majority similar or marginally better than existing standards [11, 102, 119]. To avoid rejection, pharmaceutical companies would have to adopt other strategies including improved targeting and price deals [5, 31, 34, 120] although there are concerns with pricing deals [121].

Just as there is an increasing interest in the evaluation of thresholds through opportunity costs, the introduction of social values in the economic analysis have also been debated. The social values might influence decisions considering the appeal for equity, transparency, severity of illness, orphan conditions, wider social benefits, externalities and innovation [2, 13, 14, 18, 24, 29, 37, 55, 58, 59, 60, 61, 62, 63, 85, 102, 114, 122]. Altruistic motives may play an important role in systems based on solidarity [5, 23, 52, 54].

5 CONCLUSION

All methods for the establishment of a cost-effectiveness threshold have drawbacks. The precedent method does not have a solid scientific background and might generate overestimated or underestimated values. The WTP methodology might lead to an overestimated value of the threshold for public care also, and is not directly associated to affordability. Both methods might lead to uncontrolled health expenses and negative net health benefits. The opportunity cost methods are difficult to implement in practice since information is difficult to obtain, and the budget, the intervention costs and social preferences, might change over time. However, the opportunity cost approach allows the maximization of health benefits within budget constraints. Consequently, it might be the most recommendable approach to set thresholds in LMICs given their limited budgets despite the difficulties associated with data collection and reliability.

For most countries evaluated, it can be shown that the threshold value actually set and considered for decision making, when it exists, is typically less than three times GDP per capita/QALY or DALY. With that in mind, the use of WHO-CHOICE's initial threshold to issue recommendations on cost-effectiveness studies might justify requests of higher prices by pharmaceutical companies in HTA studies, recommend inefficient technologies for funding and lead to increasing healthcare spending. In the places where the threshold was calculated according to budgets, the various agendas of different stakeholders still have to be balanced for decision-making. Overall, the threshold values implicitly or explicitly defined, for the countries analyzed, seem not to be in accordance with the opportunity costs, since these values are usually higher than they should be for a context with budget constraints. Multinational analysis demonstrated a need for a greater focus on value for money in countries with fewer resources available for healthcare spending.

6 EXPERT COMENTARY AND FIVE-YEAR VIEW

What can this study tell us about the use of CETs in HTA? The concept of a CET has been long established, and has had an important role in academic thinking, and (perhaps to a lesser but still non-negligible extent) in the institutions of many countries' health systems. In this sense, CETs have

had an important role as a "bridging concept" between the world of academic research and the "real world" of healthcare prioritization as it actually happens through the healthcare system.

Nevertheless, as this study demonstrates, the concept of CET is not free from controversy. Most notably, there are multiple methods, reviewed in this paper, to determine the CET and they do not all produce the same answer. In general, one may expect that the supply-side methods such as the opportunity cost approach will produce lower estimates than demand-side methods such as willingness-to-pay. The stakes involved in getting a wrong estimate are significant: a CET estimate that is too low will result in patients being denied care and underspent or wasted budgets; whereas an estimate which is too high will result in exploding healthcare budgets and some patients loosing out within fixed financial budgets. Thresholds which are clearly far too high (such as the three times GDP per capita threshold) should be increasingly questioned since whilst new medicines could be nominally "cost-effective" according to this criterion, it is not the case that every new medicine achieving this is affordable, and decisions end up being made on the basis of implicit criteria and lobbying, which is not in the best interest of all key stakeholder groups.

We also highlight in this paper that there are considerable differences between countries in terms of their use of CET and cost-effectiveness information in general. In some countries, the use of CETs has been rejected because of poor fit with existing local legal or administrative cultures or because (especially in small and poor countries) of the high costs of checking each new technology against a CET. In other countries, however, the use of CETs has been rejected or constrained because of a genuine belief that the methodology does not fully take into account important social values, such as concern for the worst off.

We do believe that for large, and reasonably well-off countries with universal health systems (such as Brazil), the use of CETs is appropriate. With all their weaknesses, CETs do provide clarity and transparency on what the budget holders – in democracies, the citizens – are getting for their money, and do provide a stable environment for innovators to invest in new products, in confidence about the rules which will determine reimbursement. However, we appreciate the need to experiment with different ways of using CETs both at the national and (in countries which operate on a federal model) at the state level to arrive at processes and institutions which respect and are acceptable within the local context. This also includes issues of affordability as seen with the recent medicines for treating patients with hepatitis C since whilst cost-effective, funding all patients at initial requested prices would have increased total pharmaceutical expenditure within a country by up to four fold severely impacting on medicine availability for other patients [123]. Decision rules for determining pricing and reimbursement reflect important national values: the countries which have the most sophisticated and mature systems for using HTA have built their systems over many years through interaction between government, industry and academic stakeholders. Learning from international experience is essential, but there are no shortcuts.

In terms of our five-year outlook, we expect to see the following: firstly, we expect to see greater realism in setting CETs and greater linkage to what health systems can actually afford. In some jurisdictions, the CET may actually decline as demand pressures on the system increase and as populations age. How to manage the political consequences from a declining published CET is not a problem which any country has yet managed to effectively grapple with. Secondly, we expect to see greater use of multicriteria (MCDA) methods and perhaps also new wellbeing measures to capture a broader range of outcomes and ethically relevant factors in decision making. This happens in practice at the moment in many countries but the academic literature has so far not provided an appropriate frame for thinking about this, and it is neglected in the most authoritative HTA textbooks. Thirdly, we expect to see greater use of CET to look at existing practice: it is important to remember that what is cost-effective or not is not a technology *per se* but technology as it is used by a particular patient with a particular disease, medical history and prognosis. CETs can have an important role in optimizing treatment, for example in ensuring that technology is targeted on the subpopulation which presents the greatest (and most clearly cost-effective) opportunity to generate health benefits, perhaps by upscaling the use of out-of-patent technology with mass potential, such as lipid lowering agents. Such considerations, and the corresponding need for re-analysis and price re-negotiations, will grow as many standard medicines loose their patents and become available as low cost generics and biosimilars. Fourthly, we expect, quite simply to see greater use of CETs in countries around the world. For the foreseeable future, many countries will face demands rising faster than funding due to an ageing population, and a consequent need to focus minds on efficiency. Small countries are

banding together to ensure that they are able to secure the sorts of price transparency and reductions which are denied to them individually because of their scale. Poor countries, and hitherto poor but growing countries are expanding their universal coverage programmes and building analytic capacity but still face the need to explain to their populations why some new and effective technologies may not be available through the public system. All these factors predispose countries to use CETs in making decisions about what to fund and at what price.

The use of CETs for determining reimbursing healthcare technologies is replete with problems, as reviewed in this paper. However, the alternatives obscure the link between payment and health gained, and this link is essential if the funds which go into the healthcare system are to be spent wisely.

7 KEY ISSUES

- An increase on the value of the threshold enables the pharmaceutical industry to request higher prices for its products, but can have adverse effects for cost control in the public system. A well-defined threshold value has the power to drive prices to acceptable levels.

- It is difficult to understand how much the economic analysis really influences decisions. In some countries like Brazil and Germany, the economic analysis is considered a secondary criterion to effectiveness, efficacy and safety.

- The use of WHO-CHOICE's threshold to issue recommendations on cost-effectiveness studies might not justify the setting of higher prices by pharmaceutical companies. The incorporation of such inefficient health technologies overburdens the budgets of health systems.

- In countries where the threshold was calculated according to budgets, there are still other interests that have to be respected for decision making, for example concern for the worst off patients.

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