OHE

International Cost-Effectiveness Thresholds and Modifiers for HTA Decision Making

CONSULTING | REPORT
MAY 2020

Kyann Zhang
Martina Garau

ohe.org

OHE

MAY 2020

International Cost-Effectiveness Thresholds and Modifiers for HTA Decision Making

Kyann Zhang
Office of Health Economics, London

Martina Garau
Office of Health Economics, London

Please cite this report as:
Zhang, K. and Garau, M., 2020. International cost-effectiveness thresholds and modifiers for HTA decision making. OHE Consulting Report, London: Office of Health Economics. Available at: https://www.ohe.org/publications/international-cost-effectiveness-thresholds-and-modifiers-hta-decision-making

Corresponding Author:
Kyann Zhang
kzhang@ohe.org

OFFICE OF HEALTH ECONOMICS **CONSULTING**

For further information please contact:

Martina Garau
Director, OHE

Tel +44 (0)207 747 8867
Email mgarau@ohe.org

About OHE Consulting Reports

Many of the studies OHE Consulting performs are proprietary and the results are not released publicly. Studies of interest to a wide audience, however, may be made available, in whole or in part, with the client's permission. They may be published by OHE alone, jointly with the client, or externally in scholarly publications. Publication is at the client's discretion.

Studies published by OHE as OHE Consulting Reports are subject to internal quality assurance and undergo a rapid external review, usually by a member of OHE's Editorial Panel. Any views expressed are those of the authors and do not necessarily reflect the views or approval of the OHE's Editorial Panel or Research and Policy Committee, or its sponsors.

Funding and Acknowledgements

This consulting report was commissioned and funded by The Association of the British Pharmaceutical Industry (ABPI).

Table of Contents

Executive Summary

OHE Consulting conducted a literature review, supplemented with expert interviews, to identify cost-effectiveness thresholds (CETs) used in a selected number of countries in their decision-making process for Health Technology Assessments (HTAs). The review finds that, out of the 15 selected countries, only four specify an *explicit* CET in their official HTA guidelines. For the rest, an '*implicit*' threshold – a value that is informally accepted by the decision-makers, or one based on past decisions – is used.

In most of the countries reviewed, additional considerations – here termed 'modifiers' – are incorporated when making funding and reimbursement decisions. The two main modifiers identified were severity and rarity of the disease in question. In some cases, such modifiers lead to an (upward) adjustment in the applied threshold for interventions that meet specific requirements. On the other hand, some HTA processes prefer to maintain more flexibility and apply modifiers in a 'qualitative' manner – that is, allowing decision committees to consider them as part of a deliberative process. In these cases, it is not necessarily clear the degree of influence that modifiers may have in determining whether or not an intervention is approved.

1 Introduction

Many countries conduct Health Technology Assessments (HTAs) as a means of judging value for money when making recommendations on the funding and reimbursement of new health interventions. A number of these countries have employed cost-effectiveness analysis – which seeks to estimate the additional cost incurred to gain one quality-adjusted life-year (QALY) – as part of their HTAs. This may then be compared against a certain level – a cost-effectiveness threshold (CET) – above which the new technology would be deemed to be not cost-effective.

OHE Consulting conducted a review of CETs applied in a selected number of countries to provide an understanding of the HTAs decision-making process around the world. We explored to what extent these thresholds are *explicit* (i.e. stated in official documents such as methods guidelines) or *implicit* (derived from previous reimbursement decisions or recommendations, or informally accepted by decision makers). In addition, this review sought to determine which factors (here termed '*modifiers*') other than – and in some cases, given priority over – cost-effectiveness are considered when deciding which interventions should be recommended.

2 Methods

We conducted a targeted literature review to identify published literature – such as reviews and existing analyses – on the levels of CETs used in practice in different countries. A general search was carried out using search terms including: 'cost-effectiveness', 'cost-effectiveness thresholds', 'ICER thresholds', 'HTA thresholds' along with a combination of these terms with specific country names. Only thresholds expressed as cost per QALY gained were considered. Therefore, the countries selected for inclusion are those where the QALY is used to measure health gains. These are Australia, Canada, Czech Republic, England and Wales, Ireland, Japan, the Netherlands, Norway, Poland, Scotland, South Korea, Sweden, Taiwan, Thailand, and the United States. For the United States, we considered the methods of the Institute for Clinical and Economic Review, which conducts technology assessments but do not have a formal mandate from a public payer or private insurer. We included the Institute for Clinical and Economic Review in the review because of its increasing influence in the US and internationally.

Key papers identified as a result of the first search and selection process included Cameron, Ubels and Norström, (2018), Griffiths et al., (2015), Schwarzer et al., (2015), Wang, Gum and Merlin, (2018), Skedgel, Wranik and Hu, (2018), Dakin et al., (2015) and Appleby et al., (2009). Follow-up searches were done where relevant references were identified from these articles. In addition, OHE consulted country-specific guidelines regarding HTA methods (where available) to determine whether any indication of a threshold against which interventions should be evaluated had been given.

For countries that have not specified an explicit threshold – that is, a level or range as defined in a methods guide or other official document – we explored whether a threshold has been used by decision-makers in an informal capacity ('as given'), to be applied systematically (or at least frequently). This type of CET will be referred to here as an '*implicit/informal*' threshold. There are also studies that have attempted to infer a threshold through an empirical analysis of past HTA decisions. We refer to this type of CET here as '*implicit/empirical*' thresholds. However, results from these studies do not necessarily inform future decisions, as they are not generally formally referenced by HTA agencies as a basis in the decision-making process. To compile results, we have used a combination of these methods, depending on data availability.

In addition to the literature search, OHE conducted a number of semi-structured interviews with local experts in the included countries to validate and supplement our review results. The interviewees were drawn from a mix of representatives of national trade associations, and biopharmaceutical companies' local and global functions. Out of nine potential contacts, four agreed to be interviewed, one sent responses by email and one declined. No response was received from the remaining three. We developed an interview guide to structure the discussion and obtain information related to the CETs used in decision making, and any flexibility around it that decision-making committees may apply. A copy of the interview guide is available on request. Phone interviews were then conducted with contacts from Canada, Norway, Sweden, and the Netherlands.

For ease of comparison, a conversion of thresholds to USD (2018) has been included. Two of the papers identified in the literature review (Cameron, Ubels and Norström, (2018) and Schwarzer et al., (2015)) have attempted to make international comparisons by converting the thresholds to a common currency and relating them to an external measure, such as GDP or total health expenditure. The question of whether the 'right' values of thresholds were selected, and whether the methods applied for these conversions were appropriate, requires further investigation that is beyond the scope of this study, and are not further discussed here.

3 Results

3.1 Thresholds

The table below presents the findings of CETs for the selected countries. Where a range or multiple values for thresholds were found, the lower bound (of explicit thresholds) or most-used value (for implicit thresholds) was included. Theoretically, new technologies that demonstrate an Incremental Cost-Effectiveness Ratio (ICER) lower than this value would be approved by the HTA agency. However, it should be noted that other considerations – economic and otherwise – may still have the potential to affect the final decision. Situations in which higher thresholds apply – that is, where the above-mentioned 'modifiers' become a factor for consideration – will be discussed in the next section.

Table 1 presents the results of both our literature review and interviews. Where we obtained different threshold values from the two sources, we have reported the information in two rows (referring to the same country). This is the case, for example, of Canada as explained below. Please see the Appendix for a list of the relevant HTA agencies in each of the included countries.

TABLE 1 COST-EFFECTIVENESS THRESHOLDS (MOST QUOTED OR LOWER BOUND), BY COUNTRY

Country	Threshold (per QALY gained)	Currency	*Note*	Threshold stated in guideline	USD (2018)[1]	Reference
Australia	50,000	AUD		No	$ 37,351	Wang, Gum and Merlin, 2018
Canada	80,000	CAD	*See table note a*	No	$ 61,722	Paris, Valerie and Belloni, Annalisa, 2013
	50,000 (non-oncology) 100,000 (oncology)	CAD		No	$ 38,576 $ 77,153	Interview
Czech Republic	1,355,826	CZK	*3xGDP per capita (2016 LCU[2])*	No	$ 62,394	Gulácsi et al., 2014
England and Wales	20,000	GBP	*See table note b*	Yes	$ 26,676	NICE, 2018
Ireland	45,000	EUR		Yes	$ 53,108	HIQA, 2019
Japan	5,000,000	JPY		No	$ 45,274	Shiroiwa et al., 2013
Netherlands	20,000	EUR		Yes (but not considered explicit)	$ 23,604	Care Institute Netherlands, 2017

[1] *OECD annual exchange rate used with the exception of Taiwan and Thailand*
[2] *Local Currency Unit*

Country	Threshold (per QALY gained)	Currency	*Note*	Threshold stated in guideline	USD (2018)[1]	Reference
Norway	500,000	NOK		Yes (but not considered explicit)	$ 61,464	Ottersen et al., 2016
	275,000	NOK		Yes (but not considered explicit)	$ 33,805	Interview[3]
Poland	146,937	PLN	*3 x GDP per capita (2016 LCU)*	Yes[4]	$ 40,680	Gulácsi et al., 2014
Scotland	20,000	GBP		No	$ 26,676	Scottish Medicines Consortium, 2012
South Korea	25,000 000	KRW	*1 x GDP per capita*[5]	No	$ 22,716	Bae et al., 2018
Sweden	700,000	SEK		No	$ 80,549	Svensson, Nilsson and Arnberg, 2015
	500,000	SEK		No	$ 57,535	Interview
Taiwan	1,199,237	NT	*1 x GDP per capita (2016 LCU)*	No	$ 38,598	Tang et al., 2019
Thailand	160,000	THB		Yes	$ 5,237	HITAP, 2014
United States	50,000	USD		Yes	$ 50,000	Institute for Clinical and Economic Review, 2018

a. *The Patented Medicines Price Review Board (PMPRB) has proposed new Guidelines to implement changes from the newly amended Patented Medicines Regulations in Canada, which will come into effect in July 2020[6]. The thresholds indicated are those considered before the mentioned reforms.*

b. *Note that this is the lower bound of the NICE CET range (£20,000 - £30,000 per QALY gained). For decisions on technologies with an ICER above £20,000 per QALY gained, judgements about their acceptability as an effective use of NHS resources will take into account additional factors (outlined in section 6.3.3 of the NICE Methods Guide[7]).*

Australia: Commonly quoted values are around AUD50,000 per QALY gained. Identifying a threshold is made more difficult by the fact that the summaries from the Pharmaceutical Benefits Advisory Committee (PBAC) do not specify the ICER/s of the interventions appraised, only the range into which it falls, with the lowest category starting at AUD15,000. However, this is not interpreted to be a threshold.

[3] *Severity of illness and priority setting in Norway. Summary of a working group report (November 2015). Available from: https://www.regjeringen.no/contentassets/d5da48ca5d1a4b128c72fc5daa3b4fd8/summary_the_magnussen_report_on_severity.pdf*

[4] *Stated in Reimbursement Act (cited by Badora et al., 2017)*

[5] *Conversion as given in Bae et al (2018)*

[6] *https://www.canada.ca/en/patented-medicine-prices-review/services/consultations/draft-guidelines.html*

[7] *https://www.nice.org.uk/process/pmg9/chapter/the-appraisal-of-the-evidence-and-structured-decision-making#decision-making*

Canada: HTA decisions appear to be largely based on precedent, with an implicit threshold generally assumed to be around CAD50,000 per QALY gained (based on individual testimony). The supplementing interview indicated that this threshold is outdated and currently applies mostly to non-oncology drugs. A threshold of CAD100,000 is generally accepted for oncology drugs, for which a specific programme had been created. It was noted that these values are not recorded as part of any guideline but are usually taken as the 'accepted' levels for threshold. This is generally in line with the literature reviewed that indicates CAD80,000 as a general threshold. We did not find any formal evidence that threshold values are cited in decision making.

Under proposed new Guidelines by the Patented Medicines Price Review Board (PMPRB), the maximum rebated price (net price) of patented medicines with yearly sales or annual treatment costs above a certain value will be set using market size and pharmacoeconomic factors of treatment cost, incremental cost and incremental QALYs valued using a CET of CAD60,000 per QALY gained. Note that this threshold is *not currently* in use as the Guideline is still under development and due to come into force in July 2020 (Patented Medicines Prices Review Board, 2019).

Czech Republic: No legally binding CET applies, but a 'generally accepted willingness-to-pay threshold' is set at 3 times GDP per capita per QALY gained.

England and Wales: Guidelines set by NICE specify an explicit cost-effectiveness range of £20,000 to £30,000 per QALY gained.

Ireland: The Republic of Ireland has an explicit threshold of EUR45,000 per QALY gained. This threshold applies only to pharmaceutical interventions.

Japan: An HTA process was only very recently implemented (April 2019). While a JYP5,000,000 threshold has been proposed, it has not been imposed by policymakers. However, it is implied that decision makers may still follow this as an implicit threshold.

The Netherlands: While no official threshold value is used, The National Health Care Institute (Zorginstituut Nederland, ZiN) has set three burden-of-illness categories with increasing 'acceptable' ICERs based on the severity of the disease. The lowest threshold set by these categories is EUR20,000 applied to conditions with a low burden of illness. This is interpreted here as the 'implicit' baseline threshold.

Norway: Previously, Norway has had an explicit threshold of NOK500,000, which was considered indicative and not always been adhered to. Since January 2018, a stepwise system based on severity has been used to set thresholds. Similar to the Netherlands, we used the ICER level associated with the lowest severity category (NOK275,000) as the 'implicit' baseline threshold. See section on Modifiers for an explanation.

Poland: The Reimbursement Act states a legally binding CET of 3xGDP per capita per QALY gained. The same threshold applies to all medical technologies claiming public funding.

Scotland: No formal threshold is given. The Scottish Medicines Consortium (SMC) refers to the NICE (England and Wales) threshold of £20,000 to £30,000, which can be considered an *implicit/informal* threshold.

South Korea: No explicit threshold is given, but CET is usually assumed to be approximately equal to GDP per capita per QALY gained.

Sweden: Currently there is no official threshold for the health sector. Data from previous appraisals show that the implicit threshold appears to be between SEK700,000 and SEK1,220,000. During our interviews, it was noted that over the past five years, pharmaceutical appraisals with ICERs up to SEK500,000 have always been approved.

Taiwan: At present, there is no consensus on an official CET for Taiwan. A value of between 1 to 3 times GDP per capita per QALY gained has been quoted as a possible threshold, based on past WHO recommendations.

Thailand: The threshold was stated in the HTA guideline by The Journal of Medical Association of Thailand to be THB160,000 per QALY gained, which is roughly equal to Thailand's GDP per capita (World Bank, 2018).

United States: A threshold of between USD50,000 and USD150,000 is recommended by the Institute for Clinical and Economic Review (Institute for Clinical and Economic Review, 2018).

Only four out of the 15 countries considered in this analysis (England and Wales[8], the Republic of Ireland, Poland, and Thailand) state an explicit threshold in a methods guide (or another official document). While the Institute for Clinical and Economic Review in the US also recommends an explicit threshold range, it is not an official HTA body and does not have an official mandate from payers, therefore it has not been included in this category.

The rationale for the lack of an explicit threshold differs between the remaining countries. Reasons given include the complexities associated with using a specific methodology for threshold-setting, ethical concerns, and political sensitivities (Schwarzer et al., 2015). In some countries – such as Norway and Sweden – payers generally prefer not to disclose what they consider to be acceptable ranges for the ICER prior to reaching an agreement with the manufacturer.

3.2 Modifiers

While recognising that cost-effectiveness is an important consideration for HTAs, we find it is not the only consideration upon which decisions are based. This is consistent with the observation that explicit CETs are not used by most countries with a formal HTA process, this suggests any such boundary is subject to modification where circumstance requires.

A number of modifiers were identified in the literature review, and through interviews. These are characteristics – relating to either the intervention, the targeted indication(s), or population(s) – that are given priority by decision makers. Where one or more modifiers are applicable to the intervention under appraisal, approvals may be granted despite an ICER that exceeds the CET. The literature review and interviews both suggest that modifiers can be applied in a 'quantitative' or 'qualitative' manner. 'Quantitative' modifiers may lead to an (upward) adjustment in the applied threshold for interventions that meet specific requirements. That is, it is assumed that that the QALY gains accrued by certain populations should be valued more than others. In the case of 'qualitative' modifiers, a deliberative process allows the decision-making committee to consider different considerations – both economic and otherwise – and exercise judgement to reach a decision.

Modifiers identified and presented in Table 2 include:

[8] *Counted as one here as they both follow NICE guidelines*

Severity of illness: Countries including the Netherlands, Sweden and Australia have approved interventions for disease classified as 'severe', although different definitions and approaches to measure it have been applied:

- Burden of illness:
  - In Norway, cost-effectiveness thresholds are stratified into 'health-loss' classes based on 'absolute shortfall', which measures the amount of future health – both in terms of length and quality of life – that will be lost as a result of the disease (Ottersen et al., 2016). There is a total of 6 categories, the threshold for the lowest severity category is NOK275,000, and NOK825,000 for the highest.
  - In the Netherlands, it is accepted that priority in health care should be given to those who stand to lose the largest proportion of their QALY expectancy if left untreated (the 'proportional shortfall' approach). The lowest category has a threshold of EUR20,000 per QALY gained (as shown in Table 1 above), and the highest category of BOI has a maximum threshold of EUR80,000.

- ***Disease category:*** In Canada, oncology medicines are appraised in a separate process to non-oncology drugs. While there is no explicit threshold for either category, the difference in processes may be a factor when determining whether or not a medicine is recommended. As noted above, the threshold for oncology medicines is notably higher than that for non-oncology medicines. The estimate reported in Table 2 was provided by an *empirical* study of past decisions (rather than the *implicit/informal* reported in Table 1). Unlike some other countries, Canada does not currently have a policy regarding rare diseases[9]. It was noted that this has resulted in most interventions for these disease areas to be rejected due to the high ICERs typical for such indications.

- ***End-of-life***: In England and Wales, treatments that meet end-of-life criteria are subject to a threshold of £50,000 per QALY gained, instead of the standard £20,000 - £30,000 range.

Rare diseases: Interventions that are granted orphan designation and also considered ultra-rare may be given priority for approvals since it is generally recognised that drugs in this category are unlikely to meet any pre-existing cost-effectiveness threshold (Griffiths et al., 2015). For a distinction between orphan and ultra-orphan medicines see Towse and Garau, (2018).

- In Scotland, flexibility is granted for rare indications, with a separate appraisal route used for ultra-rare indications. While medicines for rare diseases do not automatically qualify for a higher threshold, the SMC may accept more uncertainty in the economic case for drugs licensed for treating ultra-rare diseases (defined as having a prevalence of less than 1 in 50,000 in Scotland (Scottish Government, 2019)). This is in recognition of the fact that evidence on efficacy for such diseases is typically limited.

- For Norway, it was indicated that, along with the severity of disease, rarity was also taken into consideration. Authorities may be willing to pay more – that is, above the threshold for the highest severity category – for drugs that target ultra-rare diseases. However, it is not publicly known how *much* more above the highest severity category they will be willing to pay.

[9] We note that the new PMPRB guidelines propose to use a CAD90,000 per QALY for orphan drugs. As with the rest of this report, these guidelines are not included here as they are not currently in place (due to be implemented in July 2020).

- In Sweden, severity and rarity of disease are considered as a part of HTA decisions. Interventions for indications considered more severe are usually approved for ICERs up to one million SEK. Interventions with ICERs beyond this level have also been granted approval for cases considered most severe. In recent years, drugs for rare disease indications have been approved where the ICER exceeded two million SEK.

- In the US, the Institute for Clinical and Economic Review modifies its approach to value assessments for conditions classified as ultra-rare. It is suggested a higher CETs (up to USD500,000) should be applied for such conditions (Institute for Clinical and Economic Review, 2018).

- In Japan, for drugs with rare disease indications, paediatric indications or which are anti-cancer agents, the threshold is generally 50% higher.

- Ireland has a 'notional' threshold of EUR100,000 for medicines for ultra-rare indications, however, this is not an explicit level.

- *Highly specialised technology (HST)*: in England and Wales, treatment for very rare conditions evaluated as part of the HST programme are assessed against a threshold of £100,000 per QALY gained; in cases where it can be shown the technology achieves a substantial increase in health gains, an additional weighting factor between 1 and 3 may be applied to the QALY gain. The highest weighting is given to technologies that show compelling evidence of achieving a (lifetime) QALY gain of 30 or more, effectively resulting in a cost-effectiveness threshold of £300,000.

Equity: Along with the number of QALYs gained from new interventions, there appears also to be consideration given to the way these are distributed to ensure that the intervention does not lead to an exacerbation in inequity. For example, willingness-to-pay might be higher for treatments that target diseases mainly prevalent in socio-economically disadvantaged populations. However, there does not appear to be a systematic manner in which this is applied:

- Most reviews of CETs in different countries include this as a point for consideration when appraisal decisions are being made – for example, Australia (Taylor and Jan, 2017) and Thailand (HITAP, 2014). However, the way by which this is incorporated into the decision – for example, when weighed against the other modifiers identified here – are mainly qualitative, and often need to be put in context of ethical and political considerations.

- Guidelines for Ireland note that equity is an important consideration in health care decisions. However, it does not include any equity weightings as part of QALY calculations due to methodological difficulties.

Availability of alternatives: In exceptional circumstances where there are no alternative treatments for the disease in question, new health technologies that exceed the usual threshold may be approved

- In Australia, the PBAC can resort to the 'rule of rescue', which may influence the decision to accept a higher ICER where four conditions are met (PBAC, 2016):
  - There is no alternative (pharmacological or otherwise);
  - The condition is severe, progressive and expected to lead to premature death;
  - The condition applies to only a small number of patients; and

  - The proposed drug provides a worthwhile clinical improvement sufficient to qualify as a rescue from the medical condition.

We note that some of these criteria are likely to be met by orphan medicines.

- In Scotland, the SMC considers cost per QALY gained as part of a wider judgment of value for new medicines. Final decisions will take into account a range of modifiers (Scottish Medicines Consortium, 2012) including:
  - Evidence of substantial improvement in life expectancy with sufficient quality of life;
  - Evidence of a substantial improvement in quality of life;
  - Evidence that a subgroup of patients may derive specific or extra benefit (for medicines that can be targeted to this subgroup);
  - Absence of other therapeutic options for the disease in question;
  - Possible bridging to another definitive therapy in a defined proportion of patients;
  - The emergence of a licensed medicine as an alternative to an unlicensed product that is established in clinical practice in NHS Scotland.

Innovation factor: While the issue of 'innovation' is mentioned frequently in the literature, there does not appear to be any formalised method by which it is measured in practice. Relative to clinical effectiveness considerations, innovation factors do not appear to feature as prominently as consideration for special priority. It is also noted that this affects a relatively small proportion of HTA cases.

- In the Czech Republic, drugs applying for reimbursement under the special category of 'highly innovative medicinal projects' (defined by their clinical characteristics) are exempt from having to prove cost-effectiveness to be granted a temporary reimbursement, for a maximum of 3 years.

TABLE 2 COST-EFFECTIVENESS THRESHOLDS (COMMONLY OBSERVED RANGES, WITH MODIFIERS) BY COUNTRY

Country	Threshold	Currency	Modifiers (quantitative[10])	Modifiers (qualitative)	Reference
Australia	Not specified	-		Rule of rescue / unmet needs, Equity	Taylor and Jan, 2017
Canada	140,000	CAD		Oncology	Skedgel, Wranik and Hu, 2018
Czech Republic	Not specified	-		Innovation, Severity	Skoupá, 2017
England and Wales	50,000 100,000 - 300,000	GBP	End of Life, HST, Ultra-rare		NICE, 2018
Ireland	100,000	EUR	Ultra-rare		Interview
Japan	7,500,000	JPY	Rare, Paediatric, Oncology		Towse, 2019
Netherlands	20,000-80,000	EUR	Severity (proportional shortfall)		Reckers-Droog, van Exel and Brouwer, 2018
Norway	1,000,000	NOK		Ultra-rare	Ottersen et al., 2016
	275,000 - 825,000	NOK	Severity (absolute shortfall)		Interview[11]
Poland	n/a				
Scotland	Not specified	-		See SMC modifiers list (above)	Scottish Medicines Consortium, 2012
South Korea	Not specified	KRW	Severity, Availability of substitutes		Bae et al., 2018
Sweden	1,220,000	SEK		Severity, Rare	Persson et al, 2012
	2,000,000	SEK			Interview
Taiwan	n/a				
Thailand	Not specified	THB		Equity	HITAP, 2014
United States	500,000	USD	Ultra-rare		Institute for Clinical and Economic Review, 2018

[10] Where a specific value is attached to the modifier (e.g. £300,000 for HST in England and Wales)
[11] Severity of illness and priority setting in Norway. Summary of a report from a working group, November 2015: Available from: https://www.regjeringen.no/contentassets/d5da48ca5d1a4b128c72fc5daa3b4fd8/summary_the_magnussen_report_on_severity.pdf

4 Discussion

For England and Wales, NICE specifies an explicit CET of £20,000 to £30,000 per QALY gained for most HTAs. Reviews of past NICE decisions suggest the 'in practice' threshold is around £35,000 to £40,000 per QALY gained (Griffiths et al., 2015). Previous modelling of these decisions also suggests that technologies with an ICER of £40,000 per QALY gained have a 50% chance of being rejected by NICE (Dakin et al., 2014). We note that these studies might capture the effect of the end-of-life criteria (introduced in 2009) and potentially of other social value judgements.

In the case of implicit thresholds, we found that despite numerous attempts over time to derive a cost-effectiveness threshold for HTAs – through measures such as willingness-to-pay, opportunity cost, and league tables – no definitive method has been officially endorsed by most HTA decision makers (Appleby et al., 2009). Most implicit thresholds are largely based on existing literature, agency publications and inference from previous decision-making trends (Griffiths et al., 2015). For example, the value typically quoted for the US – USD50,000 – is said to be based on the cost of end-stage renal disease in the 1970s. However, this has not been officially verified, nor is there any justification given as to why this should be used as a cost-effectiveness threshold (Cameron, Ubels and Norström, 2018).

It is observed that there is often a discrepancy between what is commonly quoted to be an implicit threshold, and what HTA decisions are based on in reality. For example, while a number of papers cite the implicit threshold in Canada to be CAD50,000 per QALY gained, reviews of HTA decisions show that approvals have been granted when the ICER was much higher (Griffiths et al., 2015). While cost-effectiveness forms part of the decision-making criteria, it is not the only consideration in the appraisal of new health technologies. This suggests that modifiers are likely to have significant influence over the application of the threshold.

In many cases, the use of modifiers is applied in a qualitative sense. That is, while the aforementioned issues of rarity or severity of disease are mentioned in decision-making guidelines, it is not always clear how they are taken into consideration, or what relative weight they have on final recommendations. While countries such as Canada have an implicit understanding of different thresholds being applied to oncology and non-oncology drugs, these are not officially formalised. This makes the price negotiation process less predictable for pharmaceutical manufacturers, as it is unclear which cost-effective ranges are acceptable. In some cases – such as in Canada – previous approvals may be treated as a benchmark when approvals are given. This can potentially lead to 'threshold creep', thereby increasing the threshold over time. It was indicated by interviewees from a number of countries (including Sweden and Norway) that the threshold is not typically referenced when appraisal decisions are announced, thus making it difficult to decipher which level of the threshold was used, or how the economic factors were weighed in the final decision.

In addition to this, it was noted that in some countries where an explicit threshold is not specified (including Canada and the Netherlands), the overall budget impact is an important factor in whether a new intervention is approved. In such cases, if it is determined that the total budget impact of the intervention is too large, the intervention might not be approved even when the ICER is within what would generally be considered the 'acceptable' threshold. On the other hand, for some countries (e.g. the Netherlands and Ireland), a full economic evaluation may not be considered necessary if the overall budget impact is judged to be sufficiently low.

4.1 Limitations

While effort has been made to be comprehensive in detail and coverage, there are a number of limitations to this review. First, only a small number of people were interviewed. This may potentially mean the review has not captured full details of every country we sought to include, particularly with respect to specific details on modifiers (e.g. how frequently they are used, the degree of influence they have on final decisions and the way in which this differs between countries). We also note that our sample of interviewees included only industry representatives – from either companies or trade associations – and the inclusion of a broader range of stakeholders and experts could have brought different perspectives. More detailed understanding around these points would be useful for future analyses.

Also, we converted the threshold values found using a USD (2018) conversion to present results in a common currency. However, it should be noted that direct comparisons should not be made on this value alone, as other factors – such as health system expenditure in each country – need to be taken into consideration when comparing threshold values. What is appropriate in one country may not necessarily be so in another. As noted above, the aim of this review was to identify HTA systems using explicit vs implicit cut-off values for decision making, and to what extent – and on what basis – flexibility around these values are allowed. A comparison of CETs between different countries is beyond the scope of this review, and should be considered for further research.

Finally, while this paper presents an overview of cost-effectiveness thresholds for selected countries, it does not provide an examination of whether the thresholds accepted – or the manner by which they are applied – are in fact appropriate for the relevant health system. Research has shown that if a threshold is not set at the appropriate level, there will be an inefficient allocation of limited health sector resources. Others have argued that decisions leading to efficient health spend might not reflect society preferences. Determining the optimal threshold level is a highly complex matter, and there are different perspectives regarding the appropriate way to defining and estimating it. For further discussion of this topic, please see Cubi-Molla, et al (2020). The same applies to the analysis of modifiers. We did not investigate the extent to which considerations beyond cost-effectiveness were informed by specific evidence of public preferences, and thus did not discuss the merits of the approaches used to apply them in decision-making.

5 Conclusion

The key findings from this review are as follows:

- Most countries currently engaging an HTA process do not operate with an **explicit CET**. Only four out of the 15 selected countries (England and Wales[12], the Republic of Ireland, Poland, and Thailand) specify a CET value in their official HTA guidelines.

- In countries where an explicit threshold is not specified, a range of **'implicit' values** may be used. These may be values that are informally accepted by the HTA agencies ('implicit informal'), or those that have been observed through previous reviews ('implicit empirical').

- In four countries (Canada, Sweden, Norway and the Netherlands), interviewees indicated that there is an assumed level at which new technologies are considered cost-effective. However, it is not always certain how the thresholds are applied in individual circumstances. For example:

  - While Canada has a generally accepted implicit CET, decisions on appraisals do not cite a particular level that was applied to reach the relevant outcomes.

  - Similarly, while Norway has published a range of threshold *categories*, the actual value applied in each case is not made known to pharmaceutical manufacturers to avoid potentially influencing pricing negotiations.

- The Institute for Clinical and Economic Review in the US has published explicit threshold ranges, but it is not included in this category as it does not have formal mandate from a public payer or private insurer.

- In addition to a threshold (explicit *or* implicit) there are usually a number of considerations – here termed 'modifiers' – which allow certain new technologies to be approved despite having an ICER above the typical threshold. The two main considerations are:

  - The **severity** of the condition treated by the new technology: the measurement for this varies from country to country; and

  - The **rarity** of the condition: significantly higher thresholds may be used in the case of interventions for ultra-rare conditions.

- In seven out of the 15 countries reviewed, at least one of these two factors is taken into consideration in the decision to use a higher CET:

  - The Netherlands and Norway appear to prioritise **severity** in decision making. Proportional shortfall and absolute shortfall are adopted (respectively) by these two countries to measure disease severity, and the threshold is adjusted upwards accordingly. We note that severity is captured in terms of both life expectancy and quality of life impacts of the condition on patients, rather than focusing exclusively on the former as in the case of the end-of-life criteria by NICE.

[12] *Counted as one here as they both follow NICE guidelines*

  - In England, some interventions for **ultra-rare** diseases may be approved through the HST route if certain requirements are satisfied. However, not all interventions in the ultra-rare category are appraised through this approach.

- Although it was not part of the remit of this review, we note that in the included Nordic countries (Norway and Sweden) a societal perspective is used as part of the reference case. This may affect ICER values resulting from the appraisal – for example, when evaluating treatments with large, prolonged impacts on carers and the informal care sector.

- Interviewees from countries both with 'quantitative' and 'qualitative' modifiers were able to provide examples of medicines that were approved with an ICER significantly higher than the level typically accepted, on the basis that they were indicated for rare diseases. While the number of such cases is very limited (only one or two in each country), this supports the notion that there is willingness on the part of HTA agencies to make concessions for specific cases based on some broadly defined decision-making criteria.

Finally, it was noted that in some countries (including Canada and the Netherlands), **budget impact** is also an important factor in whether a new intervention is approved. In such cases, if it is determined that the total budget impact of the intervention is too large, the intervention might not be approved even when the ICER is within what would generally be considered the 'acceptable' threshold. This reinforces the notion that even where a cost-effectiveness threshold is generally acknowledged to be in use – formally or otherwise – other factors are taken into consideration when determining whether an intervention is approved.

6 References

Appleby, J., Devlin, N., Parkin, D., Buxton, M. and Chalkidou, K., 2009. Searching for cost effectiveness thresholds in the NHS. *Health Policy*, 91(3), pp.239–245. 10.1016/j.healthpol.2008.12.010.

Badora, K., Caban, A., Rémuzat, C., Dussart, C. and Toumi, M., 2017. Proposed changes to the reimbursement of pharmaceuticals and medical devices in Poland and their impact on market access and the pharmaceutical industry. *Journal of Market Access & Health Policy*, 5(1), p.1381544. 10.1080/20016689.2017.1381544.

Bae, E.-Y., Kim, H.J., Lee, H.-J., Jang, J., Lee, S.M., Jung, Y., Yoon, N., Kim, T.K., Kim, K. and Yang, B.-M., 2018. Role of economic evidence in coverage decision-making in South Korea. *PLOS ONE*, 13(10), p.e0206121. 10.1371/journal.pone.0206121.

Cameron, D., Ubels, J. and Norström, F., 2018. On what basis are medical cost-effectiveness thresholds set? Clashing opinions and an absence of data: a systematic review. *Global Health Action*, 11(1), p.1447828. 10.1080/16549716.2018.1447828.

Cubi-Molla, P., Errea, M., Zhang, K. and Garau, M., 2020. *Are Cost-Effectiveness Thresholds fit for Purpose for Real-World Decision Making? | OHE*. [online] Available at: https://www.ohe.org/publications/are-cost-effectiveness-thresholds-fit-for-purpose.

Dakin, H., Devlin, N., Feng, Y., Rice, N., O'Neill, P. and Parkin, D., 2014. The Influence of Cost-Effectiveness and Other Factors on Nice Decisions. *Health Economics*, 24(10), pp.1256–1271. 10/f7qscg.

Dakin, H., Devlin, N., Feng, Y., Rice, N., O'Neill, P. and Parkin, D., 2015. The Influence of Cost-Effectiveness and Other Factors on Nice Decisions: FACTORS INFLUENCING NICE DECISIONS. *Health Economics*, 24(10), pp.1256–1271. 10.1002/hec.3086.

Griffiths, E., Hendrich, J., Walsh, S. and Stoddart, S., 2015. Acceptance of health technology assessment submissions with incremental cost-effectiveness ratios above the cost-effectiveness threshold. *ClinicoEconomics and Outcomes Research*, p.463. 10.2147/CEOR.S87462.

Gulácsi, L., Rotar, A.M., Niewada, M., Löblová, O., Rencz, F., Petrova, G., Boncz, I. and Klazinga, N.S., 2014. Health technology assessment in Poland, the Czech Republic, Hungary, Romania and Bulgaria. *The European Journal of Health Economics*, 15(S1), pp.13–25. 10.1007/s10198-014-0590-8.

HIQA, 2019. *Guidelines for the Economic Evaluation of Health Technologies in Ireland*. Available at: https://www.hiqa.ie/sites/default/files/2019-07/HTA-Economic-Guidelines-2019.pdf.

HITAP, 2014. *Guidelines for Health Technology Assessment in Thailand (Second Edition)*.

Institute for Clinical and Economic Review, 2018. *A Guide to ICER's Methods for Health Technology Assessment*.

NICE, 2018. *NICE technology appraisal guidance | NICE guidance*. [CorporatePage] NICE. Available at: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance.

Ottersen, T., Førde, R., Kakad, M., Kjellevold, A., Melberg, H.O., Moen, A., Ringard, Å. and Norheim, O.F., 2016. A new proposal for priority setting in Norway: Open and fair. *Health Policy*, 120(3), pp.246–251. 10.1016/j.healthpol.2016.01.012.

Paris, Valerie and Belloni, Annalisa, 2013. *Value in Pharmaceutical Pricing*. [OECD Health Working Papers] 10.1787/5k43jc9v6knx-en.

Patented Medicines Prices Review Board, 2019b. *PMRPB Guidelines 2019*. [online] Ottawa: PMRPB. Available at: https://www.canada.ca/content/dam/pmprb-cepmb/documents/consultations/draft-guidelines/draft-guidelines-en.pdf.

PBAC, 2016. *PBAC Guidelines | 5.4 Basis for any claim for the 'rule of rescue'*. Available at: https://pbac.pbs.gov.au/section-5/5-4-basis-for-any-claim-for-the-rule-of-rescue.html.

Persson, U., 2012. *Value Based Pricing in Sweden: Lessons for Design*? Seminar Briefings. [online] Office of Health Economics. Available at: https://ideas.repec.org/p/ohe/sembri/000141.html [Accessed 17 Jul. 2018].

Reckers-Droog, V.T., van Exel, N.J.A. and Brouwer, W.B.F., 2018. Looking back and moving forward: On the application of proportional shortfall in healthcare priority setting in the Netherlands. *Health Policy*, 122(6), pp.621–629. 10.1016/j.healthpol.2018.04.001.

Schwarzer, R., Rochau, U., Saverno, K., Jahn, B., Bornschein, B., Muehlberger, N., Flatscher-Thoeni, M., Schnell-Inderst, P., Sroczynski, G., Lackner, M., Schall, I., Hebborn, A., Pugner, K., Fehervary, A., Brixner, D. and Siebert, U., 2015. Systematic overview of cost–effectiveness thresholds in ten countries across four continents. *Journal of Comparative Effectiveness Research*, 4(5), pp.485–504. 10.2217/cer.15.38.

Scottish Government, 2019. *Ultra-orphan medicines pathway: guidance*. [online] Available at: https://www.gov.scot/publications/ultra-orphan-medicine-pathways-guidance/ [Accessed 18 Mar. 2020].

Scottish Medicines Consortium, 2012. *SMC modifiers used in appraising new medicines*. [online] Available at: https://www.scottishmedicines.org.uk/media/3565/modifiers.pdf [Accessed 18 Mar. 2020].

Shiroiwa, T., Igarashi, A., Fukuda, T. and Ikeda, S., 2013. WTP for a QALY and health states: More money for severer health states? *Cost Effectiveness and Resource Allocation*, 11(1), p.22. 10.1186/1478-7547-11-22.

Skedgel, C., Wranik, D. and Hu, M., 2018. The Relative Importance of Clinical, Economic, Patient Values and Feasibility Criteria in Cancer Drug Reimbursement in Canada: A Revealed Preferences Analysis of Recommendations of the Pan-Canadian Oncology Drug Review 2011–2017. *PharmacoEconomics*, 36(4), pp.467–475. 10.1007/s40273-018-0610-0.

Skoupá, J., 2017. Drug Policy in the Czech Republic. *Value in Health Regional Issues*, 13, pp.55–58. 10.1016/j.vhri.2017.08.002.

Svensson, M., Nilsson, F.O.L. and Arnberg, K., 2015. Reimbursement Decisions for Pharmaceuticals in Sweden: The Impact of Disease Severity and Cost Effectiveness. *PharmacoEconomics*, 33(11), pp.1229–1236. 10.1007/s40273-015-0307-6.

Tang, C.-H., Cheng, W.F., Jiang, J.-H., You, S.L., Huang, L.-W., Hsieh, J.-Y., Mukherjee, P., Van Kriekinge, G. and Lee, C., 2019. Cost-Effectiveness Analysis of Human Papillomavirus Vaccination in Adolescent Girls in Taiwan. *Asian Pacific Journal of Cancer Prevention*, 20(5), pp.1377–1387. 10.31557/APJCP.2019.20.5.1377.

Taylor, C. and Jan, S., 2017. Economic evaluation of medicines. *Australian Prescriber*, 40(2), pp.76–78. 10.18773/austprescr.2017.014.

Towse, A., 2019. HTA in Japan: Failing to Meet International Good Practice? *HTA in Japan: Failing to Meet International Good Practice*?. Available at: https://www.ohe.org/news/hta-japan-failing-meet-international-good-practice [Accessed 17 Jan. 2020].

Towse, A. and Garau, M., 2018. *Appraising Ultra-Orphan Drugs: Is Cost-Per-QALY Appropriate? A Review of the Evidence*. Consulting Reports. [online] Office of Health Economics. Available at: https://ideas.repec.org/p/ohe/conrep/001978.html [Accessed 17 Jul. 2018].

Wang, S., Gum, D. and Merlin, T., 2018. Comparing the ICERs in Medicine Reimbursement Submissions to NICE and PBAC—Does the Presence of an Explicit Threshold Affect the ICER Proposed? *Value in Health*, 21(8), pp.938–943. 10.1016/j.jval.2018.01.017.

Appendix

HTA agencies (or relevant decision makers) in countries included in this review

Country	HTA agency (medicines)	Abbreviation
Australia	Pharmaceutical Benefits Advisory Committee	PBAC
Canada	Canadian Agency for Drugs and Technologies in Health	CADTH
Czech Republic	State Institute for Drug Control (Státní ústav pro kontrolu léčiv)	SUKL
England and Wales	National Institute for Health and Care Excellence	NICE
Ireland	Health Information and Quality Authority	HIQA
Japan	Central Social Insurance Medical Council	Chuikyo
Netherlands	The National Health Care Institute (Zorginstituut Nederland)	ZIN
Norway	Norwegian Institute of Public Health	NIHR
Poland	Agencja Oceny Technologii Medycznych I Taryfikacji	AOTMiT
Scotland	Scottish Medicines Consortium (Healthcare Improvement Scotland)	SMC
South Korea	National Evidence-based Healthcare Collaborating Agency	NECA
Sweden	Swedish Agency for Health Technology Assessment and Assessment of Social Services (Statens beredning för medicinsk och social utvärdering)	SBU
Taiwan	Center for Drug Evaluation	CDE
Thailand	The Health Intervention and Technology Assessment Program	HITAP
United States	Institute for Clinical and Economic Review	ICER

About us
Founded in 1962 by the Association of the British Pharmaceutical Society, the Office of Health Economics (OHE) is not only the world's oldest health economics research group, but also one of the most prestigious and influential.

OHE provides market-leading insights and in-depth analyses into health economics & health policy. Our pioneering work informs health care and pharmaceutical decision-making across the globe, enabling clients to think differently and to find alternative solutions to the industry's most complex problems.

Our mission is to guide and inform the healthcare industry through today's era of unprecedented change and evolution. We are dedicated to helping policy makers and the pharmaceutical industry make better decisions that ultimately benefit patients, the industry and society as a whole.

OHE. For better healthcare decisions.

Areas of expertise

- Evaluation of health care policy
- The economics of health care systems
- Health technology assessment (HTA) methodology and approaches
- HTA's impact on decision making, health care spending and the delivery of care
- Pricing and reimbursement for biologics and pharmaceuticals, including value-based pricing, risk sharing and biosimilars market competition
- The costs of treating, or failing to treat, specific diseases and conditions
- Drivers of, and incentives for, the uptake of pharmaceuticals and prescription medicines
- Competition and incentives for improving the quality and efficiency of health care
- Incentives, disincentives, regulation and the costs of R&D for pharmaceuticals and innovation in medicine
- Capturing preferences using patient-reported outcomes measures (PROMs) and time trade-off (TTO) methodology
- Roles of the private and charity sectors in health care and research
- Health and health care statistics

CONSULTING | REPORT
MAY 2020

ohe.org

The Office of Health Economics A Company Limited by Guarantee of Registered No. 09848965
OHE Consulting Ltd Registered Company No. 09853113
OHE is a Charity Registration No. 1170829
Registration Office Southside, 105 Victoria Street, London SW1E 6QT