The Use of Incremental Cost-Effectiveness Ratio Thresholds in Health Technology Assessment Decisions

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ABSTRACT: The incremental cost-effectiveness ratio (ICER) is used to determine the cost-effectiveness of new health care interventions. A literature review was conducted to determine the ICER thresholds used by different countries in their healthcare reimbursement decisions, the extent to which they are used, and how they may have changed over time to reflect inflation and medical progress. Treatments that received contrasting approval decisions from different health technology assessment (HTA) bodies were identified. Countries use both static and dynamic thresholds for approval processes, and static ICER thresholds are not regularly updated. Between 2012 and 2015, eight therapies received different reimbursement approval decisions in different countries. ICERs established for type 2 diabetes (T2DM) and non-small-cell lung cancer (NSCLC) were compared and were found to vary significantly. The author’s findings suggest that ICER thresholds may be outdated and may not account for innovation in technology, inflation, and increased research and development costs. Furthermore, it may be more appropriate for different ICER thresholds to be set for therapies for different disease states to account for differences in value assessment.

KEY WORDS: incremental cost-effectiveness ratio, literature review, health technology assessments.


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Cost-effectiveness analysis is an economic evaluation tool applied to assess the costs and outcomes of different health care interventions in order to arrive at an overall valuation for those options. One method for analyzing the cost-effectiveness of a health care intervention is to estimate the incremental cost-effectiveness ratio (ICER), which is typically expressed as the additional cost associated with a given unit of measure—for example, quality-adjusted life-year (QALY)—to quantify the improvement in outcome associated with that cost. ICERs are used to assign a quantifiable value to the healthcare intervention; an intervention with a low ICER is considered more favorable for drug reimbursement decisions by healthcare programs.

Health technology assessment (HTA) bodies in many countries have set an ICER threshold, above which an intervention is considered to be not cost-effective, in order to aid their respective processes of decision-making. Some of these ICER threshold were established as long ago as 1982. Over the past few
decades, there has been extraordinary growth and progress in medical technologies and drug discovery. Examples include antiretroviral therapies, biologics, and immunomodulators that have enhanced quality of life and improved survival in numerous therapeutic areas.\(^5\)–\(^8\) However, these more effective therapies tend to be associated with higher costs.\(^9\) Additionally, inflation has led to higher healthcare costs as well as an increase in healthcare expenditures other than treatment costs.\(^10\) In light of these developments, the present applicability of ICER thresholds established 20–30 years ago are greatly debated. It has not been systematically evaluated whether or how ICER thresholds have evolved over time to respond to the changing landscape of healthcare options.

Another concern raised by researchers is that, when used as the only or main decision-making tool, ICER thresholds fail to account for aspects of non-monetary-based value of the product, such as the extent to which the treatment is addressing previously unmet needs, the severity of disease treated by the treatment, and the population size to be impacted by the new treatment.\(^11\) The variability in ICERs for therapies for different disease states has not, to date, been systematically evaluated.

Different countries evaluate new technologies using different decision-making tools and ICER thresholds, leading to varying approval decisions.\(^12\) A better understanding of how ICER thresholds have been set and used in the past decades is needed to contribute to the ongoing debate on whether ICER thresholds and their current role in assessing new drugs and technologies are appropriate.

The purpose of this study was to evaluate the landscape of ICER thresholds and to gain insight on the past and current use of ICER thresholds in HTA processes for making reimbursement decisions for new drugs and technologies. A systematic literature review was conducted in order to document the ICER thresholds set in different countries, to determine changes that may have occurred since inception of the initial ICER thresholds, assess whether and how reimbursement decisions by countries with different ICER thresholds may have differed, and to determine the discrepancies between ICERs of treatments for different disease states. The future recommendations of other researchers relating to the use of ICER thresholds in healthcare decision-making are also discussed.

### METHODS

**Current Landscape of ICER Thresholds**

First, we conducted a targeted literature review using the PubMed database to determine: (1) the initially established ICER thresholds in countries that use them as part of their HTA assessment process; and (2) whether current ICER thresholds differ from originally established ICER thresholds. Search terms included “ICER threshold” and its variations (Table 1). The titles of studies published in the English language, between January 1970 and January 2015, were reviewed with no geographic limitations. Additionally, we conducted a grey literature search using Google Scholar with similar search terms. Subsequently, a secondary manual search of bibliographies of the included studies was conducted. Studies that provided information on the above criteria were selected and added to the list of included studies. Finally, key information was collated using descriptive data from the studies included.

The yield was 1857 studies, of which 44 titles and abstracts qualified for full text review. The grey literature search did not yield any additional studies. Of the 44 full texts that were reviewed, 10 were excluded because they did not provide data on any of the following: (1) the established ICER thresholds; (2) updates or changes to previously established ICER thresholds; or (3) recommendations or expectations provided by researchers relating to the use of ICER thresholds in the healthcare decision-making process. In addition, two studies were obtained from the secondary manual search of bibliographies of the included studies. The 36 studies included in the analysis were published between 1992 and 2015 and provided data about Australia, Belgium, Canada, Ireland, the Netherlands, New Zealand, Poland, Spain, Sweden, the United Kingdom, and the United States.

### Differences in Coverage Decisions in Countries with Different ICER Thresholds

Second, we reviewed HTA decisions to determine whether products received different coverage decisions from different countries (Canada and the United Kingdom) and whether this was due to differences in ICER thresholds. A search was conducted on the official websites of the national HTA bodies in Canada (Canadian Agency for Drugs and Technologies in Health (CADTH)) and in the UK (The National Institute for Health and Care Excellence (NICE)).

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**Table 1. PubMed Search Strategy for Targeted Literature Search Regarding ICER Thresholds in Different Countries.**

<table>
<thead>
<tr>
<th>Search Terms</th>
<th>Filters</th>
<th>Date Accessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>(&quot;ICER threshold&quot;[All fields]) OR (&quot;cost effectiveness threshold&quot; [All fields]) OR (&quot;incremental cost-effectiveness ratio&quot;[All fields]) OR (&quot;incremental cost effectiveness&quot;) OR &quot;cost benefit analysis&quot; [All fields]) AND (&quot;threshold&quot;[All fields]) OR (&quot;ICER value&quot; [All fields]) AND (1970/01/01[PDAT] : 2015/01/01[PDAT])</td>
<td>Language: English; Publication date: 01/01/1970 to 01/01/2015</td>
<td>August 3, 2015</td>
</tr>
</tbody>
</table>

Abbreviations: ICER, incremental cost-effectiveness ratio.

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For nine studies,18–26 cost conversions were not possible.

Comparing ICERs Across Therapeutic Areas
Third, we compared ICERs of drugs across two disease states, chosen because of their varying attributes, to sample the variability in ICERS. Type 2 diabetes mellitus (T2DM) and non-small cell lung cancer (NSCLC) were selected for the informal analysis due to the differences in the levels of unmet need, disease severity, quality of life, etc. Two systematic literature reviews were conducted to identify empirical cost-effectiveness and cost-utility studies for T2DM and for NSCLC treatments. The search terms used were (1) disease-related (“Type 2 diabetes mellitus” and “Non-small cell lung cancer”, with variations); and (2) study type-related (“Cost-effectiveness analysis”, “Cost-utility analysis”, with variations). The search was limited to studies published between January 2012 and January 2015 reporting ICERs in T2DM and NSCLC. The search strategy is summarized in Table 2.

A total of 288 studies related to ICERs for T2DM therapies were identified, of which 20 titles and abstracts qualified for full text review. Of the 20 full texts that were reviewed, 2 were excluded. Data were extracted from 18 studies. A total of 91 studies related to ICERs for NSCLC therapies were identified, of which 24 titles and abstracts qualified for full-text review. Of the 24 full texts that we reviewed, 7 were excluded. ICERs were extracted from the 17 identified studies in the currency in which they were originally reported.

Extracted ICERs were converted into 2015 USD ($) and 2015 GBP (£) using the Campbell and Cochrane Economics Methods Group (CCEMG) tool recommended by Cochrane.13,14 We calculated the median (range) ICER for each therapy area in order to compare them. For nine studies,18–26 cost conversions were not possible since they reported ICERs in currencies other than their own (Euros); the CCEMG tool uses original “country” and “year” during conversion and does not incorporate “currency” into the conversion.

RESULTS

Current Landscape of ICER Thresholds
Data regarding ICER thresholds used to make reimbursement decisions by HTA bodies internationally were extracted from 36 studies. Belgium, Poland, and Sweden do not use any formal ICER thresholds in their decision-making processes.15,16 In countries that use ICER thresholds for HTA decisions, thresholds vary widely (Table 3). Converted into USD, ICER thresholds ranged from $13,000 (New Zealand) to $104,000 (Canada). In Australia, Canada, the Netherlands, ranges are used rather than a defined threshold.

The ICER thresholds in the UK and the US have not undergone changes since their inception, and thus can be considered “static.” New Zealand, the Netherlands, Australia, and Canada use dynamic ICER threshold values that vary periodically and are determined from past resource allocation decisions, but these ICER thresholds are not officially established.2

Differences in Coverage Decisions by Countries with Differing ICER Thresholds
The rationale of reviewing reimbursement approval decisions by CADTH and NICE was to understand the disparities in patient access across countries resulting from the dissimilar processes and nature of tools used in decision-making. To determine the extent to which differences between countries’ ICER thresholds are associated with differences in reimbursement coverage decisions, we evaluated HTA reports to identify products that received differential reimbursement decisions from different countries.19 HTA reports were reviewed related to reimbursement approval decisions by CADTH and NICE. Between the years 2012 and 2015, eight unique products were identified as receiving differential reimbursement approval decisions from different countries.19 HTA reports were reviewed related to reimbursement approval decisions by CADTH and NICE. Between the years 2012 and 2015, eight unique products were identified as receiving differential reimbursement approval decisions from different countries.19

Table 2. Search Strategy for Systematic Literature Search Regarding ICERs for T2DM and NSCLC Treatments

<table>
<thead>
<tr>
<th>Search Terms</th>
<th>Filters</th>
<th>Date Accessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>(“Diabetes Mellitus, Type 2/therapy”[Mesh]) OR (“Diabetes Mellitus, Type 2/drug therapy”[Mesh]) AND (“Diabetes Mellitus, Type 2/economics”[Mesh]) OR (“cost effectiveness”[title/abstract]) OR (“cost utility”[title/abstract]) AND (“English”[language])</td>
<td>Publication date: 01/01/2012 to 01/01/2015</td>
<td>August 4, 2015</td>
</tr>
<tr>
<td>(“Carcinoma, Non-Small-Cell Lung”[Mesh]) OR (“Carcinoma, Non-Small-Cell Lung/drug therapy”[Mesh]) OR (“Carcinoma, Non-Small-Cell Lung/therapy”[Mesh]) AND (“Carcinoma, Non-Small-Cell Lung/economics”[Mesh]) OR (“cost effectiveness”[title/abstract]) OR (“cost utility”[title/abstract]) AND (“English”[language])</td>
<td>Publication date: 01/01/2012 to 01/01/2015</td>
<td>August 4, 2015</td>
</tr>
</tbody>
</table>

Abbreviations: ICER, incremental cost-effectiveness ratio; NSCLC, non-small cell lung cancer; T2DM, type 2 diabetes mellitus.
consideration. One exception with NICE is an initiative to evaluate life-extending technologies through an elaborate set of “end-of-life” criteria, in which therapies with ICERs above £30,000 will be considered.17 As a result, some treatments were rejected (and, for some, later approved) by NICE but were approved by CADTH.

Comparing ICERs Across Therapeutic Areas
We compared ICERs of drugs across two disease states—T2DM and NSCLC—chosen because of their varying attributes, to sample the variability in ICERs. The individual ICERs reported by the 35 included studies (18 for T2DM and 17 for NSCLC) are listed in Supplemental Table 1 and Supplemental Table 2. The median (range) of the adjusted ICERs revealed that the ICERs of treatments for T2DM ($19,535 per QALY2$42,000–76,000 AUD per QALY46) or £13,284 per QALY (€778–47,642 per QALY4) was approximately two-fold greater than that of treatments for NSCLC ($54,020 per QALY ($1,001–464,681 per QALY) or £36,734 per QALY (£681–315,983 per QALY)).

DISCUSSION
The literature contains little evidence that the ICER thresholds being used have been modified since their inception. The $50,000 per QALY threshold currently used in the US was established in 1982 based on the cost-effectiveness of hemodialysis for the treatment of end-stage renal disease.4,16 The £20,000–30,000 per QALY threshold currently used in the UK was established in 1999 and has no reported basis.27,28 The absence of a justification for the arbitrarily set thresholds likely stemmed from the lack of policy related decision-making context or precedent at that time. Currently, adjustments to account for inflation, innovation, increasing cost of research and development, satisfying unmet needs, or for severe diseases, may not be adequately addressed. Our findings were comparable to those by Claxton and associates,11 who used a similar targeted literature review approach, although they focused on NICE and implications for the National Health Service. They found that many institutions set “hard thresholds” and referred to literature that conveys the dissatisfaction with a “hard threshold” that does not reflect the following considerations: the benefits of a new treatment; the argument for using multiple thresholds; and the need for an update of ICER thresholds based on reasons such as increased NHS budget, inflation, advancements in technology, and congruency with societal willingness-to-pay.11

Researchers have published their concerns with the stagnant and unique ICER threshold value being used. There is concern that the static thresholds become outdated because

<table>
<thead>
<tr>
<th>Country</th>
<th>HTA Body</th>
<th>ICER Threshold</th>
<th>Year Established</th>
<th>Changed Since Inception?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>Pharmaceutical Benefits Advisory Committee (PBAC)</td>
<td>69,000 AUD per QALY2–42,000–76,000 AUD per QALY46</td>
<td>Based on past resource allocation decisions</td>
<td>Yes</td>
</tr>
<tr>
<td>Canada</td>
<td>Canadian Agency for Drugs and Technologies in Health (CADTH)</td>
<td>20,000 CAD per QALY16 Range of rejection: 32,000–137,000 CAD per QALY4</td>
<td>Based on past resource allocation decisions</td>
<td>Yes</td>
</tr>
<tr>
<td>Ireland</td>
<td>The Health Information and Quality Authority (HIQA)</td>
<td>€45,000 per QALY47</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Pharmaceutical Care Committee (CFH)</td>
<td>No formal threshold48 €10,000–80,000 per QALY49 €20,000–80,000 per QALY15</td>
<td>Based on past resource allocation decisions</td>
<td>Yes</td>
</tr>
<tr>
<td>New Zealand</td>
<td>Pharmaceutical Management Agency (PHARMAC)</td>
<td>No formal threshold50 Varies annually51 20,000 NZD per QALY2</td>
<td>Based on past resource allocation decisions</td>
<td>Yes</td>
</tr>
<tr>
<td>Spain</td>
<td>The Spanish Agency for Health Technology Assessment, in collaboration with agencies of regional governments</td>
<td>€30,000 per QALY52,53</td>
<td>200352</td>
<td>NR</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>National Institute for Health and Care Excellence (NICE) and Scottish Medicines Consortium (SMC)</td>
<td>£20,000–30,000 per QALY2,33,34,35,39,54–65</td>
<td>199927</td>
<td>No</td>
</tr>
<tr>
<td>United States</td>
<td>NA</td>
<td>$50,000 per QALY4,10,36,37,43,59,64,65</td>
<td>19824,10,16,59</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: AUD, Australian dollar; CAD, Canadian dollar; HTA, health technology assessment; NA, not applicable; NR, not reported; NZD, New Zealand dollar; QALY, quality-adjusted life-year.
they fail to account for a number of factors including the evolving medical landscape in terms of both diagnosis and management. In the past three decades, treatments for diseases that had no cure have now been developed and are currently in use. New technologies have been discovered that improve life expectancy for cancers or quality of life for viral infections, immune disorders, and rare diseases significantly. As an example, in 2011 two new technologies were discovered that offered better cure rates for Hepatitis C, a disease that affects approximately 150 million people.29,30 Several other new technologies under investigation have the potential for significantly improved quality of life and longer survival.31 With increased and earlier access to screening and healthcare, more patients can be diagnosed and treated at an earlier point in disease progression, leading to better health and economic outcomes.

The experience in using the thresholds over the past decades could appropriately inform decision makers to revisit the initially established thresholds since ICER thresholds play a significant role among other factors in the decision-making process in many countries. Some researchers recommended that the ICER thresholds be reevaluated regularly to account for inflation, per capita-income, disease burden, innovation in diagnosis and treatment, and patient

### Table 4. Different Reimbursement Decisions by CADTH and NICE for the Same Products

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>CADTH Reimbursement Status</th>
<th>Year of Decision</th>
<th>ICER (CAD per QALY)</th>
<th>Adjusted ICER (2015 USD)*</th>
<th>NICE Reimbursement Status</th>
<th>Year of Decision</th>
<th>ICER (£ per QALY)</th>
<th>Adjusted ICER (2015 USD)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiraterone</td>
<td>Metastatic, castration-resistant prostate cancer</td>
<td>Approved66</td>
<td>2013</td>
<td>&gt;175,00066</td>
<td>&gt;147,115</td>
<td>Initially rejected, later approved67,68</td>
<td>2012</td>
<td>&lt;50,00069</td>
<td>&lt;77,876</td>
</tr>
<tr>
<td>Aflibercept</td>
<td>Metastatic colorectal cancer</td>
<td>Rejected69</td>
<td>2014</td>
<td>NR69</td>
<td>-</td>
<td>Rejected70</td>
<td>2014</td>
<td>51,00070</td>
<td>76,179</td>
</tr>
<tr>
<td>Bosutinib</td>
<td>Philadelphia-chromosome-positive CML</td>
<td>Approved71</td>
<td>2015</td>
<td>NR71</td>
<td>-</td>
<td>Rejected72</td>
<td>2013</td>
<td>58,000–60,00072</td>
<td>88,614–91,670</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>NSCLC with ALK fusion gene</td>
<td>Initially rejected, later approved73,74</td>
<td>2013</td>
<td>NR73,74</td>
<td>-</td>
<td>Rejected75</td>
<td>2013</td>
<td>50,200 and &gt;100,00075</td>
<td>76,697 and &gt;152,783</td>
</tr>
<tr>
<td>Everolimus</td>
<td>Advanced HER2 negative, hormone receptor positive breast cancer</td>
<td>Approved76</td>
<td>2013</td>
<td>162,04976</td>
<td>136,228</td>
<td>Rejected77</td>
<td>2013</td>
<td>68,00077</td>
<td>103,893</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>Non-squamous NSCLC</td>
<td>Approved78</td>
<td>2013</td>
<td>170,272–173,86478</td>
<td>143,141–146,160</td>
<td>Rejected79</td>
<td>2014</td>
<td>74,50079</td>
<td>111,281</td>
</tr>
<tr>
<td>Trastuzumab emtansine</td>
<td>Metastatic HER-2 positive breast cancer</td>
<td>Approved80</td>
<td>2014</td>
<td>NR80</td>
<td>-</td>
<td>Rejected81</td>
<td>2014</td>
<td>166,00081</td>
<td>247,956</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>Locally advanced or metastatic melanoma</td>
<td>Approved82</td>
<td>2013</td>
<td>221,668–275,70782</td>
<td>186,347–231,776</td>
<td>Initially rejected later approved83,84</td>
<td>2012</td>
<td>44,000–51,80084</td>
<td>68,531–80,679</td>
</tr>
</tbody>
</table>

*Calculated using the CCEMG tool, recommended by Cochrane.13,14

**Abbreviations:** ALK, anaplastic lymphoma kinase; CADTH, Canadian Agency for Drugs and Technologies in Health; CML, chronic myelogenous leukemia; HER2, human epidermal growth factor receptor 2; NICE, National Institute for Health and Care Excellence; NR, not reported; NSCLC, non-small-cell lung carcinoma.
preferences;10,27 be increased to reflect societal willingness-to-pay, increased healthcare funding, and inflation;10,32–35 be raised to $200,000 or more per QALY;10,36,37 or be set $109,000–297,000 per QALY.38 Others recommend that ICER thresholds be lowered and not raised; these recommendations are based on theoretical concepts such as opportunity costs and value of precedents of previously funded technologies.39,40

Although some ICER thresholds can be considered “static” (UK, US), some countries use a “dynamic” threshold (Australia, Canada, Netherlands, and New Zealand) that varies periodically. In such cases, ICER thresholds are not the sole decision-making criteria in the HTA process. Another evolution that has occurred since the inception of ICER thresholds is the development of real-world data. Various countries use real-world data to a different extent and fashion.41 HTA processes are becoming more dynamic and embracing different types of assessments that help inform real-world value of new technologies.42

Our findings regarding varying reimbursement approval decisions by different HTA bodies result from differences in the extent to which ICER thresholds are considered within that HTA process. Some researchers recommended that the ICER thresholds incorporate other important criteria, rather than a rigid implementation of only one single, quantitative criterion during resource allocation decisions.2,3 Other recommendations point to the need for an update to the ICER threshold based on increase in budget, inflation, advancements in technology, and congruency with societal willingness-to-pay; as well as the establishment of multiple thresholds for varying situations. Studies suggest that ICERs are subjective to specific contexts at a specific time point and conditions; hence, they are inherently dynamic in nature, implying that ICER thresholds need to be updated regularly due to changing settings.2,27,44 Based on these findings, ICER thresholds appear to have a place within the HTA decision-making process but should be regularly updated to account for budgetary changes, inflation, advancements in technologies, and payer and societal willingness-to-pay. Additionally, decision-makers should reflect on the evidence that points toward the inclusion of factors other than cost-effectiveness, such as innovation, unmet need, disease severity, and target population size, when determining the “value” of a healthcare intervention.

**CONCLUSIONS**

To the best of our knowledge, this is the first summary of the landscape of ICER thresholds and provides insights into previously reported recommendations while also providing case studies of approval decisions across two HTA bodies. The targeted literature review approach inherently introduces a level of bias; however, our research questions were structured to directly address previously raised issues and to be the least susceptible to bias. Future research should consider evaluating the impact of alternative methodologies on the healthcare decision-making process.

The future recommendations and expectations elucidated by previous researchers relating to the use of ICER thresholds in healthcare decision-making vary significantly. These recommendations and expectations set forth by researchers mainly point to the need for an update to the ICER threshold based on increase in budget, inflation, advancements in technology, and congruency with societal willingness-to-pay; as well as the establishment of multiple thresholds for varying situations. Studies suggest that ICERs are subjective to specific contexts at a specific time point and conditions; hence, they are inherently dynamic in nature, implying that ICER thresholds need to be updated regularly due to changing settings.2,27,44 Based on these findings, ICER thresholds appear to have a place within the HTA decision-making process but should be regularly updated to account for budgetary changes, inflation, advancements in technologies, and payer and societal willingness-to-pay. Additionally, decision-makers should reflect on the evidence that points toward the inclusion of factors other than cost-effectiveness, such as innovation, unmet need, disease severity, and target population size, when determining the “value” of a healthcare intervention.

**Supplemental data are available online at www.jcponline.com.**

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