# An International Review of Health Technology Assessment Approaches to Prescription Drugs and Their Ethical Principles

*Leah Z. Rand and Aaron S. Kesselheim*

Health technology assessment (HTA) organizations assess the economic value and make recommendations about reimbursement or coverage of prescription drugs and other health care products. The findings are then used by governments or other health insurers to negotiate prices, structure budgets, and decide whether to finance access to a drug or product. HTA is an important tool to control health care costs and determine the distribution of resources in society.[1]

Most high-income countries around the world use HTA as part of a negotiation process to establish drug prices, with the notable exception of the US.[2] While many high-income countries have experienced increases in prescription drug spending in the past decade, due to both increased volume and prices, rising health care costs and prescription drug prices in the US far exceed any other setting.[3] In response, the current US presidential administration and leading Congressional bills seek to rein in spending and excessive drug prices by linking US drug prices to those paid by other countries.[4] In 2019, House bill H.R.3 — the Elijah E. Cummings Lower Drug Costs Now Act — proposed pricing some of the most expensive drugs for Medicare and Medicaid Advantage at negotiated prices that may not exceed 120% of the average price in Australia, Canada, France, Germany, Japan, and the UK,[5] each of which uses HTA to negotiate prices for the country. H.R. 3 would also require negotiation for prices below the maximum level taking into consideration costs of drug development and production and information on the comparative effectiveness of the new drug.[6] The methods for this assessment have not been specified yet; other policy proposals may supplant H.R. 3, and so there is an opportunity to learn from the international example and shape the methods based on social and cultural values.

While HTA is an empirical process using economic and clinical evidence to arrive at a cost-effectiveness valuation of a drug, HTA is also fundamentally political; though grounded in evidence and validated modelling methods, the findings and recommendations reflect the political and social values of a country.[7] Though there are objections to HTA as an approach to determining coverage, its use in many countries signals a broad acceptance of a health economics approach to evaluating the value of drugs, so this paper focuses on HTA approaches. There are two key dimensions of every HTA organization that raise potential ethical concerns. The first is how HTA functions to generate the quantitative findings of cost-effectiveness. For example, some HTA bodies may choose to integrate modifications to the economic evaluation methods that change cost or effectiveness thresholds for a particular patient population, such as drugs treating rare diseases.[8] Such adjustments have important implications for patient access.

A second key feature with ethical ramifications is how cost-effectiveness is interpreted when the HTA organization makes a recommendation. When determining whether a drug is "worth it," the challenge for a health system is how to balance opportunity costs across the

**Leah Z. Rand, D.Phil.**, *is a post-doctoral fellow in the Division of Pharmacoepidemiology and Pharmacoeconomics in the Department of Medicine at Brigham and Women's Hospital and a research fellow at Harvard Medical School.* **Aaron S. Kesselheim, M.D., J.D., M.P.H.,** *is Professor of Medicine at Harvard Medical School, a faculty member of the Division of Pharmacoepidemiology and Pharmacoeconomics in the Department of Medicine at Brigham and Women's Hospital, the Director of the Program on Regulation, Therapeutics, and Law (PORTAL), and a primary care physician. He is the Editor-in-Chief of the* Journal of Law, Medicine & Ethics.



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system and for different patient groups. Opportunity costs arise because if resources are spent on one thing (a new drug), they are not available to be spent on something else (a different drug or service). These are population-level decisions, as opposed to decisions about the best treatment for an individual, so HTA averages outcomes and costs for groups. Determining whether a drug is worth spending limited resources on is a question of social values, the moral and ethical values and judgments of a particular society.[9]

As the US moves in the direction of referencing other countries' prices — or even setting up its own formal HTA process — our goal was to study the procedures used by leading HTA organizations around the world and shed light on how these different organizations address some of the key ethical dimensions in the application of HTA to prescription drugs. Their approaches to social and cultural values embedded in HTA methods could then inform the development of a US approach.

## Methods

*Cohort Selection*

We limited the analysis to the US and the six countries cited in House of Representatives bill (H.R. 3) because of their economic similarity to the US and transparent approaches to HTA: Australia, Canada, France, Germany, Japan, and the UK. We identified the primary national-level organization that conducts HTA of brand-name prescription drugs. In Australia, the Pharmaceutical Benefits Advisory Committee (PBAC) recommends which drugs should be covered by public subsidy.[10] The Canadian Agency for Drugs and Technologies in Healthcare (CADTH) provides information and recommendations to Canadian provinces, each with its own prescription drug coverage program and varying benefits.[11] France's National Health Authority (HAS) recommends to the government which prescription drugs should be included in the national insurance scheme and at what level of subsidy. Two committees inform these decisions: the Economics and Public Health Evaluation Committee conducts cost-effectiveness reviews, informing appropriate price for added value, and the Transparency Committee determines the effectiveness of the drug, and therefore the extent of subsidy.[12] The German Institute for Quality and Efficiency in Health Care (IQWiG) is commissioned to conduct HTAs by the Federal Joint Committee, which determines what drugs and at what price national insurers will cover.[13] In Japan, nearly all drugs with market authorization

Table 1

**HTA Organizations — organizations conducting national-level HTA of prescription drugs**

| Organization characteristics | Germany | France | Australia |
|---|---|---|---|
| **HTA Organization or committee** (acronyms are those used in each country) | Institute for Quality and Efficiency in Health Care (IQWiG)[80] | National Authority for Health (HAS)[81] | Pharmaceutical Benefits Advisory Committee (PBAC)[82] |
| **Year HTA started** | 2007 | 2008 | 1993[a] |
| **Recommendation status** | Advisory | Statutory decision maker | Advisory and sometimes statutory decision maker |
| **Recommendation use** | Inform price negotiations | Inform price negotiations; determine coverage | Determine coverage; Inform price negotiations |
| **Recommendation effects on access** | Price-setting: determination of appropriate price paid by insurance | Determines % of price covered by national insurance; remainder left to patients or alternate insurance | Determines inclusion in Pharmaceutical Benefits Scheme with AUS $41.00 co-pay. If not recommended, patients pay full price |
| **Drug selection for HTA** | G-BA commissions HTA, usually for drugs without comparators or when price negotiations have failed | All drugs submitted for national insurance coverage | All drugs that will be covered by a national insurance subsidy; HTA conducted at manufacturer's request |

[a] PBAC was established in 1953 but did not start conducting HTA until 1993 when it was required to consider cost-effectiveness and additional benefit of new drugs.[87]



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are reimbursed through national health insurance, but in 2016 the Central Social Insurance Medical Council (Chuikyo), which regulates prices, began conducting HTA on a pilot basis with plans to apply findings to the repricing of drugs, and we focus on this new process.[14] In the UK, the National Institute for Health and Care Excellence (NICE), conducts HTAs and makes recommendations the National Health Service of England must follow to finance coverage of drugs.[15]

There is no government-endorsed HTA organization in the US, so we included the Institute for Clinical and Economic Review (ICER), an independent nonprofit organization that conducts HTA, has transparent guidelines and published reports, and has gained traction as US insurers and pharmaceutical benefits managers have used its reports to make coverage decisions.[16] Table 1 summarizes the cohort of HTA organizations.

*Data Sources and Extraction*

For six of the HTA organizations, we reviewed methods and guidance documents available in English on the organization website. We used peer-reviewed published articles on methods written by members of the Chuikyo because of limited publicly available English information.

| Canada | UK—England | Japan | ICER |
|---|---|---|---|
| Canadian Agency for Drugs and Technologies in Healthcare (CADTH)[83] | National Institute for Health and Care Excellence (NICE)[84] | Central Social Insurance Medical Council (Chuikyo)[85] | Institute for Clinical and Economic Review (ICER)[86] |
| 1989 | 1999 | 2016 | 2006 |
| Advisory | Statutory decision maker | Statutory decision maker | Advisory |
| Inform price negotiations and coverage decisions | Determine coverage | Sets reimbursement price | Inform price negotiations and coverage decisions |
| Indirect — left to provincial systems to determine coverage.<br>May recommend not to cover a drug | Determines inclusion in the NHS with £9 co-pay. If not recommended, patients pay full price | Price-setting: determines reimbursement price for national insurance list | Indirect — use by insurers and benefits managers |
| Manufacturer submissions on a first-come-first-served basis; provincial plans request for advice on a drug (prioritized) | Drugs likely to have significant health benefit, impact on resources or regional variation in access | Drugs with high price premiums (vs. comparators) and sale rates | Budget impact, policy priorities, potential to improve health, address variation, or links with health reform initiatives |


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We analyzed the guidance documents to identify differences in two dimensions of HTA with explicit ethical implications: the HTA methods and HTA interpretation. Regarding the first dimension (HTA methods), we focused on methodological differences in cost-utility analysis, often called the cost-effectiveness of a drug. Cost-effectiveness is frequently measured with the incremental cost-effectiveness ratio. This ratio compares the cost difference between the new drug and its comparator divided by the difference in effectiveness:

$$\frac{Cost_{drug} - Cost_{comparator}}{Effectiveness_{drug} - Effectiveness_{comparator}}$$

The smaller the incremental cost-effectiveness ratio, the more cost-effective the drug and the more likely its price will be considered appropriate, increasing the likelihood that coverage is recommended. Therefore, we identified differences in methods that would affect the calculation of the incremental cost-effectiveness ratio.

Regarding the second dimension (HTA interpretation), we sought statements in guidance documents that directed the organizations to consider additional, non-quantified issues that could affect the interpretation of cost-effectiveness or the organization's recommendation. For example, PBAC decisions may be influenced by "less-readily quantifiable factors," such as "Implicit equity and ethical assumptions, such as age, or socioeconomic and geographical status, may vary for different submissions."[17]

In each case, one author (LZR) extracted differences in the methods and non-quantified recommendation considerations. Both authors then analyzed these differences, categorizing them, and identifying their ethical implications.

*Limitations*

One limitation of this study is that the effects of HTA on price negotiation are not publicly known, since most of the countries negotiate confidential discounts.[18] Published prices are often not the actual prices paid, which may be significantly lower. A further limitation is that the organizations may deviate from their published methods and guidelines when conducting HTA. For example, though IQWiG guidance states that QALYs may be used in analysis,[19] in practice they have never been used. An important feature of the HTA organizations reviewed is that most make recommendations informed by health economic evaluation and deliberation on those findings and other considerations. We discuss some of the qualitative considerations in that deliberation but note that the guidance does not fully describe the extent of that decision-making and its effect on HTA recommendations.

## Results

*Variations in HTA Methods*

We identified six important features related to cost-effectiveness calculations with ethical implications that differ across HTA organizations, summarized in Table 2. Most of the included HTA organizations receive evidence as submissions from manufacturers, which are then internally reviewed.[20] These submissions include cost-effectiveness findings, and the organization may dispute them or offer alternative analyses. While the HTA organizations specify what information should be included, some supplemental analyses, like supplementary costs, are often not submitted and therefore would not be considered for the recommendation.

OUTCOME MEASURES

The primary outcome measure for HTA is the quality-adjusted life year (QALY), a measure that combines the length of life with quality of life. QALYs are calculated by multiplying the years of life gained by a utility score that captures health-related quality of life and ranges from 0 (death) to 1 (full health). Utility scores are average population preferences determined with standardized surveys. All seven HTA organizations use QALYs, but only IQWiG encourages alternative outcome measures; the other organizations require a justification when QALYs are not used as the outcome measure in the primary analysis.[21] IQWiG is also different from the others because it determines utility scores not from the general population but from patients who have experienced the condition.[22]

In addition to using QALYs as an outcome, ICER and HAS always perform separate analysis with the alternative outcome of length of life or life years gained. Life years gained result in a larger net health benefit for treatments that extend but do not improve quality of life.[23]

*Cost-Effectiveness Thresholds or Efficiency Frontiers*

Five of the seven HTA organizations (NICE, CADTH, Chuikyo, ICER, and PBAC) use explicit or implicit cost-effectiveness thresholds, summarized in Table 2. If a drug's cost-effectiveness is below the threshold, it is found to be good value for money. NICE applies a threshold range of £20,000-30,000/QALY ($26,000-39,000/QALY)[24] and may refuse placement on the national formulary for drugs exceeding the upper limit.[25] CADTH issues cost-effectiveness recommendations based on a CA $50,000/QALY (US


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Table 2
**HTA organization cost-effectiveness thresholds or efficiency frontiers**

| Germany | France | Australia | Canada | UK—England | Japan | ICER |
|---|---|---|---|---|---|---|
| No threshold. Efficiency frontier compares cost-effectiveness of comparators for a condition[88] | No threshold. Efficiency frontier compares cost-effectiveness of comparators[89] | No explicit threshold | Threshold: CAD $50,000 per QALY ($38,000/QALY), but the threshold is an advisory reference only[90] | Threshold: £20-30,000/QALY ($26-39,000/QALY)[91] | Threshold: no adjustment ≤ ¥ 5,000,000/QALY ($45,000/QALY); maximum adjustment for ≥ ¥ 10,000,000/QALY ($91,000/QALY); some adjustment for values in range[92] | Threshold: $100-150,000 per QALY[93] |

Note: Currency conversion using Xe.com on January 15, 2020 and rounded to nearest 1,000.

$38,000/QALY).[26] PBAC uses incremental cost per QALY in its analyses, but it does not subscribe to a threshold and retrospective attempts to infer one have varied conclusions.[27]

In France and Germany, the HTA organizations construct "efficiency frontiers" that map the cost per benefit of each therapeutic option for a specific condition. There is no cost-effectiveness cut-off or threshold. Instead, the organizations judge whether the cost increase is proportionally appropriate for the additional benefit and compare it against other drugs for the same condition.[28]

### SUPPLEMENTARY COSTS

Six HTA organizations in the cohort — all except NICE — conduct additional analyses that include a supplementary cost: patient productivity, defined as the lost economic output from illness or decreased economic costs from returning a person to work as a result of treatment. Productivity may be counted at a societal level (economic impacts) or an individual level (lost wages).[29]

Six HTA organizations — all except IQWiG — conduct additional analyses that include the productivity losses (or gains from treatment) of informal caregivers, usually patients' family members. Impacts on the health of caregivers from providing care may also be counted.[30]

HAS was distinctive in considering the time it takes patients to travel to and from treatment, using a standardized model to capture those costs.[31]

### LONG-TERM EFFECTS

All HTAs apply a discount rate to costs and benefits after one year, which reduces the value of future benefits and costs. However, they range in how much of a discount rate they use, from 1.5% (CADTH) to 5% (PBAC), with most rates around 3%.[32] Choice of discount rate has the greatest effect on the cost-effectiveness of drugs that are administered once or a few times but have clinical effects for many years, since the effects but not the upfront costs will be discounted. NICE and HAS reduce the discount rate (from 3.5% to 1.5% and from 4% to 2%, respectively) for drugs that provide a benefit of at least thirty years.[33] Japan's Chuikyo raises the cost per QALY thresholds for drugs with pediatric indications.[34]

Single or short-course interventions — such as gene therapy "cures" — are an extreme example of this long-term effects issue. Only ICER has modified its methods for potentially curative drugs. ICER conduct two analyses: one splits health system savings from shifting to a one-off rather than continuous, intensive treatment for a severe condition 50-50 between the drug effects and the health system, the other caps health system savings at $150,000 per year and assigns the balance to the manufacturer.[35]

### TREATING TERMINAL CONDITIONS

NICE increases the threshold for drugs treating end-of-life conditions with a life-expectancy of less than 24 months and treatment that extends life by at least three months; for such conditions, QALYs may be weighted as worth up to 1.7 times more, a threshold of £51,000/QALY ($67,000/QALY).[36] No other HTA organization has a similar method.

### AFFORDABILITY

In addition to cost-effectiveness, HTA organizations include a budget impact analysis, which estimates the


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total cost of the drug based on eligible patients and likely uptake. In France, HTA is required for drugs likely to increase spending by more than €20,000,000 in their second year on the market.[37] In Australia, if PBAC recommends a drug that will cost more than AUD $20,000,000 per year, approval is escalated up the government to the Cabinet.[38] ICER includes budget impacts if predicted drug costs would increase health spending over five years by an amount greater than economic growth since this is likely to cause system affordability and individual access problems, like increased premiums or restrictions.[39]

*Variations in HTA Interpretation*

We identified three features with ethical implications that differ across HTA bodies related to how recommendations are made.

EFFECT ON INNOVATION

Only NICE guidance directs HTA committees to consider the value of innovation to the health system that a drug provides.[40] The other HTA organizations consider innovation as part of clinical effectiveness. For highly cost-effective and innovative drugs, Chuikyo will raise the price paid if the drug has an ICER below ¥2 million/QALY ($18,192/QALY) and is highly innovative and proven to be more effective than the comparator.[41] Distinct from its HTA process, Chuikyo sets prices with a premium for innovation that can range from 5-120% of the comparator's price.[42]

NEED AND SEVERITY

QALYs gained from the drug indicate what clinical benefit it provides but not how badly off patients were initially, so several HTA organizations additionally consider patients' need and the severity of a condition to inform recommendations. In France, HTA informs price negotiations, but the proportion of drug costs that national insurance pays, rather than patients or private insurance, is determined by the effectiveness and added benefit of the drug, which are evaluated with criteria that include severity of the condition.[43] PBAC, CADTH, and NICE guidance require consideration of the degree of patient need, particularly significant, unmet need.[44] ICER reports absolute QALY shortfall, the absolute amount of health patients are expected to lose without the treatment, and the proportional QALY shortfall, the proportion of remaining life lost or with low quality due to the untreated condition. These findings are not incorporated into cost-effectiveness or effectiveness findings, but are used to consider whether those findings may under or overvalue health gains.[45]

EQUITY

Several guidance documents stated that committees making recommendations should consider health inequities and the effect of the drug in exacerbating or mitigating them. PBAC, for example, considers patient affordability — whether patients could pay for the drugs themselves or will require a government subsidy — when it lists drugs.[46] To control costs, PBAC has used this flexibility to de-list drugs from general coverage while still covering them for indigenous groups with a higher burden of illness and challenges accessing health services.[47] NICE's guidance prohibits different recommendations based on features like socioeconomic status or race that are independent of demonstrable, different clinical benefit.[48]

Chuikyo adjusts the calculation of cost-effectiveness to reflect social and ethical concerns: if an "ethical and social influence perspective" is adopted, the incremental cost-effectiveness ratio is reduced for the relevant patient subgroup by 5% before all subgroup averages are combined to determine an overall cost-effectiveness ratio.[49]

*Carve-Outs*

Finally, we identified two cases of disease conditions that certain HTA organizations carve out, both applying different methods and interpreting the results differently in making recommendations.

ULTRA-RARE CONDITIONS

For ultra-rare conditions affecting 2-3 people per 100,000, NICE and Chuikyo increase the cost-effectiveness threshold: NICE by 3.33 times from £30,000/QALY to £100,000/QALY ($39,000/QALY to $130,000/QALY), and Chuikyo by 1.66 times from ¥5-10 million/QALY to ¥7.5-15 million/QALY ($45,000-91,000/QALY to $68,220-136,440/QALY).[50] ICER formerly extended the upper threshold from $150,000/QALY to $500,000/QALY but no longer applies a special threshold for rarity.[51]

PBAC and CADTH include deliberative considerations for recommendations specific to ultra-rare conditions. For example, PBAC adopts a "rule of rescue" that applies when four conditions are true: (a) no alternative treatment exists; (b) the condition is severe, progressive, and will lead to premature death; (c) the condition applies to a small number of patients; (d) the drug provides a worthwhile clinical benefit. Conditions (b) and (c) narrow the potential application of the rule, and PBAC guidance states that it should not be frequently invoked to justify covering non-cost-effective drugs.[52]


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If PBAC determines that a drug is not cost-effective and should not be listed, the drug may be covered under the Life Saving Drug Program, a separate committee that considers these non-listed drugs and may choose to fund them. Sixteen drugs are currently listed through this program, most for inherited metabolic disorders.[53]

France makes no adjustments to HTA for rare diseases, but in Germany the additional benefit of the drugs is assumed, and HTA only undertaken if sales in the last year exceeded €50 million ($56 million).[54]In Japan, the parent organization overseeing HTA separately handles reimbursement for drugs treating ultra-rare conditions.[55]

#### CANCER

NICE and CADTH both carve out separate procedures for evaluating cancer drugs. NICE usually evaluates them with the standard HTA methods, possibly applying the end-of-life premium. If more evidence is needed to make a confident recommendation, the drug can be funded through the Cancer Drugs Fund, which provides two years of funding while collecting evidence from patients to inform future HTA.[56] CADTH conducts HTA of cancer drugs through the pan-Canadian Oncology Drug Review, which uses the same methods as the Common Drug Review (all other drugs CADTH reviews) and the same recommendation considerations, except that patient preferences are included in the evidence and deliberative framework.[57]

By contrast, PBAC does not make exceptions for cancer drugs, and its guidance emphasizes waiting for evidence that can support a funding decision rather than offering early access.[58]

Chuikyo does not apply a separate process for cancer drugs, but it does treat them as a special consideration and applies higher cost per QALY thresholds, the same as those for rare or pediatric indications.[59]

## Discussion

Our analysis identified important differences in three areas central to HTA for prescription drugs: the methodologies used, the way results are interpreted, and the populations or drugs carved out from standard HTA assessment. These choices have important ethical implications related to access to drugs and lead HTA organizations reach different conclusions and make divergent recommendations. The HTA organizations of different countries are each situated in their own cultural, social, and political contexts, so the ethical implications should be seen as value choices reflective of that context.[60]

One of the most important differences we observed was in the ways HTA organizations calculate cost-effectiveness. Across the organizations, there is an underlying consequentialist assumption to maximize population health and well-being with the resources available, but how that is determined and what become priorities depends on the approach taken to cost-effectiveness. For example, if supplementary costs, like productivity, are included, then the analysis is likely to favor drugs for patient groups who work rather than those unable to work due to disability or age. While including productivity may disadvantage the young, reducing the discount rate for long-term effects favors drugs for conditions affecting young people and makes them more likely to be cost-effective. These choices in the methods reflect decisions about whether to include a broader scope of societal economic costs, like lost productivity and upfront payments for long-term benefit, or individual costs and benefits, lost wages and lasting health effects.

We also identified substantial variations in how HTA recommendations are made. For example, HTA organizations vary in how they consider the context of a finding that a drug is not cost-effective. Though QALYs are currently the best tool for comparing health states and health gain from treatment, the incremental cost-effectiveness ratio accounts for absolute QALY gain, not how badly off a patient group is to start. Both a move from 0.2 to 0.3 QALYs and from 0.9 to 1.0 QALYs involve the same QALY gain of 0.1, but one group has worse health than the other. HTA organizations differ in how they seek to meet the needs of the worst-off, an important ethical value. ICER has attempted to do this quantitatively with QALY shortfall reporting, and other organizations include need or severity as a qualitative consideration when making recommendations.

Similar challenges arise with attempts to quantify equity concerns. The HTA organizations we reviewed emphasized concern about not increasing health inequities and identifying equity concerns the HTA may raise.[61] However, none of the organizations attempt to redress health inequities by applying weightings to QALYs, with the exception of Chuikyo's vague 5% discount for "social and ethical perspective" subgroups. Partly this is a methodological challenge, but it is also a broader ethical question about whether the health care system should aim to address a broad set of inequities through drug access for some groups. PBAC has decided to cover access for indigenous groups and not others; CADTH has considered similar measures but worries about unintended consequences.[62]


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Table 3

**Differences in methods and considerations for recommendations among HTA organizations**

| Ethical consideration | Germany | France | UK—England | Canada | Australia | Japan | ICER |
|---|---|---|---|---|---|---|---|
| **Outcome measures** Use of non-QALY outcome measures regularly included in reference case | ✓ | ✓ | ✗ | ✗ | ✗ | ✓* | ✓ |
| **Supplementary costs** Inclusion of patient productivity costs | ✓ | ✓* | ✗ | ✓* | ✓* | ✓* | ✓* |
| Inclusion of informal caregiver costs | ✗ | ✓* | ✓* | ✓* | ✓* | ✓* | ✓* |
| **Long-term effects** The method is modified for curative drugs or ones with long-lasting effects | | ✓ | ✓ | | ■ | ✓ | ✓ |
| **Treating terminal conditions** End-of-life conditions are treated differently | | | ✓ | | | | |
| **Affordability** Budget impact analysis included | ■ | ■ | ✓* | | ■ | | ✓ |
| **Effect on innovation** Innovation is considered in the HTA or recommendation independently of clinical effect | | | ■ | | | ✓ | ■ |
| **Need and severity** The method or considerations for recommendations include severity or need | | ■ | ■ | ■ | ■ | | ■ |
| **Equity** Health or other inequities are considered in the HTA or recommendation | | | ■ | ■ | ■ | ✓ | ■ |
| **Ultra-rare conditions** The method is modified for drugs for ultra-rare conditions | □ | □ | ✓ | ■ | ■ | ✓ | ✗ |
| **Cancer** The method or considerations for recommendations include a carve-out for cancer | | | ✓ | | ✗ | ✓ | |

Key

| | |
|---|---|
| ✓ | The method includes a quantified adjustment in the reference case for this consideration such that it affects cost-effectiveness findings. |
| ✓* | The method sometimes includes a quantified adjustment for this consideration either in certain circumstances or as a separate analysis. |
| ✗ | The method excludes this consideration from analysis. |
| ■ | This consideration is included in a non-quantitative stage of HTA, such as deliberations for recommendations. Note: if an organization includes this consideration in both a quantitative stage and a qualitative one, it is marked with a green check. |
| □ | The consideration is not considered by the HTA organization, but the overseeing government body (e.g. Ministry of Health) separately makes coverage and reimbursement decisions relevant to it. |
| | The methods and guidance do not explicitly say anything about this consideration. It is not included in reference case. |



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This review has important lessons for US policymakers considering setting up an HTA-like system to negotiate drug prices in Medicare. The choices in HTA approaches are inherently value judgments that will affect coverage and access to drugs, and therefore should be reflective of American values. First, the health outcome most used in HTA, the QALY, introduces the potential for variation in cost-effectiveness calculations since utility scores for health conditions vary by country: even in similar countries, like Canada and the US, there are differences in how people rate the utility of health states.[63] Therefore, a robust US HTA method needs to use fair and representative US-specific utility scores. AHRQ has so far published one such data set that captures a nationally-representative sample of scores.[64]

Another choice US policymakers will have to face is whether to use a cost-effectiveness threshold or efficiency frontier, two different ways of defining when a drug is good value for money. Notably, HTAs that use thresholds to identify the opportunity costs of introducing a new drug set them too high to accurately capture opportunity costs. In the UK, the actual opportunity cost threshold has been estimated at £13,000/QALY: if more than £13,000 is spent on producing one QALY, more than one QALY will be lost elsewhere in the health system.[65] However, NICE uses a threshold of £20-30,000/QALY. ICER uses an upper threshold of $150,000/QALY, but the most generous estimate of an actual US threshold for private plans is $84,000/QALY.[66] ICER accounts for this difference by addressing opportunity costs with its budget impact analysis, alerting decision makers when a drug would unsustainably increase health spending.[67] By contrast, efficiency frontiers — the approach adopted in Germany and France — are more consistent with what US private insurers do when they negotiate with manufacturers for a better price on a drug. As the US government considered implementing HTA assessments, efficiency frontiers would allow Medicare to identify an appropriate and proportional price for a new drug without having to apply a cut-off, which would help overcome political resistance to cost-controls and limit-setting via cost-effectiveness.

We identified two groups of carve-out conditions with special methods or considerations for HTA. Drugs for cancer have become increasingly expensive and are politically sensitive for HTA organizations, which grapple with questions of how much small gains in life expectancy are worth.[68] Different procedures or standards for cancer drugs and ultra-rare diseases, like Germany's assumption that drugs for rare diseases offer benefit or the UK's Cancer Drugs Fund and higher threshold for rare diseases, treat some people's health gains as worth more than others. Such an approach may make sense in the context of a market failure. Treatments for ultra-rare conditions have tended to be very expensive because the small patient populations mean small markets for manufacturers to recoup upfront development costs and make a profit.[69] This results in higher costs for treatments for ultra-rare conditions, so the drugs are less likely to be cost-effective. While some HTA organizations consider rare diseases to be a special case, the inverse is never true: lower thresholds are not applied to drugs with a wide market that will impact health system affordability, though modifications to cost-effectiveness analysis to account for this have been proposed.[70] For example, sofosbuvir (Sovaldi), an extremely effective treatment for hepatitis C virus infection, was cost-effective despite a high initial price per course of therapy,[71] but in the US its budget impact meant that not all patients could be treated without exceeding the budget of health systems.[72] Therefore, some countries, including US Medicaid programs, imposed non-evidence based guidelines to prioritize patients.[73] If context, like a small patient population, is a reason for weighting QALYs as worth more, then one could argue that a similar contextual feature, a large patient population, should also receive special consideration when assessing cost-effectiveness. Budget impact analysis also plays an important role in setting an upper limit on how much a health system should spend on a single drug.

It is not clear that special carve-outs would be required in the US for rare diseases or cancer drug innovation. In the US, the 1983 Orphan Drug Act introduced a tax credit to incentivize drug development and granted seven-year market exclusivity to manufacturers of such drugs, which, combined with the high prices charged, make many drugs for ultra-rare diseases profitable.[74] ICER changed its approach to rare diseases and stopped applying a higher threshold in its HTAs because of the changed contextual features (profitability) and ethical concerns about giving special consideration to rarity.[75] Similarly, the US government supports innovation through federally funded research and tax incentives, much of which goes to research on cancer.[76] In the US, with its government and public sector support for research and the development of drugs for cancer or rare diseases, it would magnify the special treatment if HTA also includes carve-outs.

Carve-outs for rare diseases and cancer, consideration and calculations for innovation, terminal conditions, long-term effects, productivity, or equity — these are all social value judgments about what matters most and how to allocate public or private resources for health care. NICE guidance states "an additional


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QALY should receive the same weight regardless of other characteristics of the people receiving the health benefit."[77] However, each methods choice, like whether to raise a threshold or include productivity, means shifting the calculation of cost-effectiveness and makes additional QALYs receive different weights for different patient groups. The HTA organizations make arguments for why these issues are relevant to consider, and their decisions reflect judgements about economic and social values specific to the country. The US has its own social values, so a US-based HTA process for insurers and federal payers should base its methods on the particular context. There has already been some work exploring people's values and preferences in designing health insurance and potential limits to benefits; other research has focused on particular questions of age, severity, and productivity in the context of allocating organ transplants.[78] ICER solicited public input on its recent updates to its HTA framework, and other countries can provide examples of how to solicit and incorporate public, social values into HTA.[79] While ICER offers one American approach to HTA, other value frameworks have been proposed, it is not clear the extent to which it reflects social value judgments and whether it should be the defining approach in the US. For a US HTA method to reflect American social values, more research needs to be done into public values on the issues raised in HTA and the choices that need to be made to make recommendations. For Medicare, which enrolls millions of Americans across the country, broad public representation will be important.

## Conclusion

Current proposals to rein in US drug spending tie drug prices to those paid in other countries that use HTA organizations, so we should consider how those calculations are made and what values are embedded in the recommendations. Our analysis identified differences in the HTA methods of the countries proposed as benchmarks in H.R. 3 with important ethical implications that affect cost-effectiveness. The differences in methods and their ethical implications point to the need for US policy to take into account the value judgments inherent in HTA and design a method that best reflects American values and health system aims.

Current proposals to rein in US drug spending tie drug prices to those paid in other countries that use HTA organizations, so we should consider how those calculations are made and what values are embedded in the recommendations. Our analysis identified differences in the HTA methods of the countries proposed as benchmarks in H.R. 3 with important ethical implications that affect cost-effectiveness. The differences in methods and their ethical implications point to the need for US policy to take into account the value judgments inherent in HTA and design a method that best reflects American values and health system aims.

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