Sebastian Salas-Vega, Annika Bertling and Elias Mossialos

A comparative study of drug listing recommendations and the decision-making process in Australia, the Netherlands, Sweden, and the UK

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A Comparative Study of Drug Listing Recommendations and the Decision-Making Process in Australia, the Netherlands, Sweden, and the UK

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ABSTRACT

Drug listing recommendations from health technology assessment (HTA) agencies often fail to coincide with one another. We conducted a comparative analysis of listing recommendations in Australia (PBAC), the Netherlands (CVZ), Sweden (TLV) and the UK (NICE) over time, examined interagency agreement, and explored how process-related factors—including time delay between HTA evaluations, therapeutic indication and orphan drug status, measure of health economic value, and comparator—impacted decision-making in drug coverage. Agreement was poor to moderate across HTA agency listing recommendations, yet it increased as the delay between HTA agency appraisals decreased, when orphan drugs were assessed, and when low-value medicines (immunosuppressants, antineoplastics) were removed from the sample. International differences in drug listing recommendations seem to occur in part due to inconsistencies in how the supporting evidence informs assessment, but also to differences in how domestic priorities shape the value-based decision-making process.

INTRODUCTION

Health technology assessment (HTA) is frequently used to inform value-based decision-making. Since it involves systematically evaluating health economic evidence, HTA is supported by a growing number of digital resources and regulatory initiatives that promote the sharing of clinical data. In the US, for instance, all applicable clinical trials must submit results to the publicly searchable registry clinicaltrials.gov,(1) making submitted data available for use by international appraisers. Regulators, including England's National Institute for Health and Care Excellence (NICE), may also require manufacturers to submit all clinical data within the company's possession anywhere in the world prior to drug review.(2) Evidence from recent comparative studies indicates that a similar set of clinical trials are in fact made available to drug appraisals,(3,4) which might lead one to anticipate significant overlap in value-based decision-making on drug coverage around the world.

Contrary to this expectation, a growing body of literature has found that the HTA-based decisions on whether to recommend public reimbursement of new medicines rarely coincide with one another.(5,6) The literature has generally examined this issue from the perspective of the last available listing recommendation, and has suggested that international differences are accounted by social determinants, including preferences for treatment, disease severity and rarity (7,8) and local clinical practice;(4) as well as methodological factors, including HTA design and sufficiency of pharmacoeconomic evidence,(7,9) and use of comparative data.(4) As has been previously argued, however, HTA is a complex process that cannot be fully understood if the perspective concentrates exclusively on final listing decisions.(10) Rather, social and methodological factors may impact final listing decisions, but only to the extent that they influence complex HTA processes that occur over time.

These complex processes are reflected in HTA agency listing recommendations, which may evolve as time passes. Periodic reassessment of cost-effectiveness may be mandated,(11) but it may also result from an appeal against initial opinions on listing,(12,13) *ad hoc* reassessment initiated by the emergence of new health economic evidence,(14) or risk-sharing agreements.(2) In England, for instance, public guidance may be reviewed and re-issued if there is significant new evidence that is likely to change opinions on drug listing.(2) Australian listing recommendations can also be deferred for further review or appealed on 'procedural' or 'merit-based' grounds. Sponsors are also allowed an unlimited number of resubmissions should new information become available, and can request an independent review of negative recommendations.(15) Australian authorities in fact highlight that a decision not to recommend or change listing status "does not represent a final … view about the merits of the medicine", but rather contributes to an "improved understanding of the listing process".(16)

Therefore, to better understand the causes of disagreement in HTA-based decision-making, we conducted a comparative analysis of drug listing recommendations emerging over time from Australia, England, the Netherlands, and Sweden. Within this framework, we examined interagency agreement in drug listing, and how social and methodological factors pertaining to the assessment process—including therapeutic indication and orphan drug status, time delay between HTA evaluations, health economic value, and comparator—influenced listing recommendations. This analysis found that international differences in drug listing recommendations exist in part due to inconsistencies in how the supporting evidence informs assessment, but also to differences in how domestic priorities shape the value-based decision-making process.

METHODOLOGY

Inclusion Parameters

This study examined HTA review processes and drug listing decisions from four HTA agencies in Australia (PBAC), England (NICE), the Netherlands (CVZ; 'Zorginstituut Nederland' since 2014), and Sweden (TLV) between 2009 – 2013. These were selected as leading examples of agencies that make similar use of HTA to inform value-based decision-making in drug coverage **(Table 1)**. The five-year period Jan 2009 – Dec 2013 was chosen in order to pragmatically optimize the size of our sample while also capturing contemporary HTA practice.

Data Extraction

HTA Appraisal Documents

A stepwise approach was used to identify all drugs that were appraised by the four HTA agencies. This process first identified all unique molecules that were assessed by NICE between 2009 – 2013 (n=102). Of these, reviews for 67 drugs were publicly available as of July 2014 from the PBAC, of which 56 were also found to have been appraised by the CVZ. Of those 56 drugs, the TLV was found to have assessed 43 through July 2014. Since appraisals were publicly available for those 43 drugs from Australian, Dutch, Swedish, and UK HTA agencies, they were used as a common sampling frame in this study. Drug name, indications, listing recommendations, year of assessment, incremental cost-effectiveness ratios (ICERs), and review comparators were then extracted from all appraisal documents corresponding to each of the 43 drugs. If multiple HTA evaluations existed for drug-indication pairs, data was extracted from both the first and last appraisal that had been published through June 2014. For example, Australia's PBAC evaluated the clinical- and cost-effectiveness of sorafenib for renal cell carcinoma in 2006, 2008, 2012, and 2013—the evaluation conducted in 2006 was taken as the 'first' appraisal, while the one published in 2013 was classified as the 'last' available appraisal.

Listing recommendations were classified into four categories: 'List' (L), 'list with restrictions' (LWR), 'deferral' (D) and 'do not list' (DNL). Base case analyses defined restrictions on listing decisions by the presence of any constraint on use in the approved indication that would limit the population eligible for reimbursement. For the TLV, positive approvals that were assigned a '*Generell Subvention*' (general subsidy) were categorized as 'L', while those given a '*Begränsad Subvention'* (limited subsidy) were classified as 'LWR'. System-specific restrictions—e.g. physician prescription, reimbursement authority requirements—were not considered.

Summary ICER measures were also extracted for each drug-indication pair. These consisted of discrete, one-sided directional, or a range of values. If agencies accepted more than one ICER for individual drug-indication pairs—e.g. to reflect treatment across patient subgroups—an inclusive ICER range was derived using the lowest and highest ICER values approved by the agency. Furthermore, if different ICERs were provided for different comparators, the ICER value corresponding with comparators used by other agencies was recorded to permit cross-agency comparison; otherwise, an ICER range was constructed to encompass all comparators that were used. ICERs were converted to U.S. dollar equivalents using historical currency conversion rates from OANDA that corresponded to the year of evaluation.(17) Nominal ICER values were also converted to constant 2013 U.S. dollars using price inflation indices from the World Bank.(18) To permit comparison, analyses were restricted to ICERs that were measured in terms of cost per QALY.

Supplementary Sources

Anatomical Therapeutic Chemical (ATC) classifications for therapeutic main groups of drug-indication pairs were obtained from the WHO Collaborating Centre for Drug Statistics Methodology's ATC/DDD Index 2014. Orphanet was also used to obtain EU drug 'orphan' status for the corresponding indication.(19)

Analysis

Two analytical endpoints were included within the main analyses: an assessment of the distribution of listing recommendations across the four national HTA agencies, and inter-country agreement in listing decisions. Both endpoints were further stratified across potential drivers of international discrepancies in drug listing recommendations.

Listing Recommendations and HTA Agency Associations

HTA agency listing rates were calculated by dividing the number of drug-indication pairs given an 'L' or 'LWR' recommendation by the total number of drug-indication pairs evaluated in each country. Pearson's χ^2 test for independence and odds ratios were used to test for, and measure the strength of, association between listing recommendations and issuing HTA agency. Correspondence analysis was used to visually examine the association between first and last available listing recommendations and issuing HTA agency in low-dimensional space.(20)

Agreement in the Overall and Stratified Sample

Agreement in drug-indication pair listing recommendations from the four HTA agencies was measured using Cohen's kappa coefficients. These were categorized into different levels of agreement using previously established thresholds.(21) Building on the available literature on factors that may explain levels of agreement in listing recommendations, these were stratified by: ATC groupings for treatment indications and orphan drug status; time delay (years) between assessments from NICE and the other HTA agencies, categorized as ≤3 years, ≤2 years, ≤1 year, 0 years; and agreement in ICER and selection of comparator. This allowed us to consider the impact of social factors (preferences for treatment, disease severity and rarity) and methodological factors (evidence or pricing developments, health technology assessment) on the process of HTA-based decision-making.

Listing Recommendations and Assessments of Value

Finally, this analysis examined the association between final available listing recommendations and ICERs, a health economic measure of value. This analysis included all drug-indication pairs for which ICER estimates were given in terms of cost per QALY gained. The bound to one-sided directional ICER estimates and ICER range midpoints were used if discrete ICER values were not reported. Any drug-indication pair that was found to be dominated by its comparator was excluded.

RESULTS

Table 1 summarizes the policy context related to health technology assessment and drug listing in Australia, the Netherlands, Sweden, and the UK. Though there is much overlap in the overall review process used by all four HTA agencies, there are differences in how health economic evidence is used, and in the factors that are considered during appraisal.

In sum, all four countries provide public guidance for health technology evaluations, and most rely primarily on manufacturer-submitted health economic analyses. NICE reviews manufacturer-submitted health economic evidence, as other agencies do, but it also works with Technology Assessment Groups (TAGs) to independently assess the value from treatment. NICE is also the only HTA agency to use explicit willingness-to-pay thresholds when determining whether to recommend treatment coverage through the National Health Service. Although the CVZ does not apply a "hard limit" to willingness-to-pay thresholds, it does operate within a suggested "bandwidth". All countries nevertheless claim that they consider severity of disease, health needs, and availability of alternative treatment when issuing listing recommendations. As the Netherlands and UK show, orphan drug status may also be considered. Australia's PBAC and the Dutch CVZ explicitly indicate that budget impact is considered when developing HTA-based listing recommendations, whereas Swedish and UK authorities do not. Implementation of Swedish and Australian listing recommendations is prescriptive under certain circumstances, while those from the Netherlands and the UK are left at the discretion of higher authorities. Differences in the design and priorities of HTA may reflect different policy and social objectives, and could therefore contribute to differences in drug listing recommendations. Comparative analyses of drug listing recommendations are now used to explore this issue.

[INSERT TABLE 1]

Listing Recommendations and HTA Agency Associations

Appraisals for a total of 231 drug-indication pairs were considered in this analysis across the four HTA agencies. NICE evaluated 72 drug-indication pairs for the 43 drugs that were included in our sample. Appraisals for 61 drug-indication pairs were available from PBAC documents, 52 from TLV documents and 46 from CVZ documents published through July 2014. The difference in number of drug-indication pairs evaluated across the four agencies may reflect differences in HTA dissemination strategies, duration of regulatory review, and market launch strategies.(22,23) Of the 72 drug-indication pairs obtained from NICE, antineoplastic agents (39%) and immunosuppressants (28%) were the two largest therapeutic classes represented. See Supplementary Material **(eFigure 1)** for a full breakdown of these 72 drug-indication pairs by ATC groups.

For the medicines that were included in our sample, the TLV was most likely to issue a positive final listing recommendation, with a final listing rate of 0.92 across all drug-indication pairs that it considered. This was followed by the CVZ (0.89), PBAC (0.84) and NICE (0.75). Even though it appraised the highest number of drug-indication pairs, NICE nevertheless issued a larger number of positive listing recommendations compared to the other HTA agencies (**Figure 1**). For both NICE and the PBAC, however, listing rates were lowest after the first available assessment, and subsequently increased after last available review **(Figure 1)**. This finding was most dramatic for the PBAC, whose listing rate increased from 0.46 to 0.84 in its final evaluation of drug-indication pairs. NICE listing rates followed a similar, albeit less dramatic, increase (0.69 to 0.75). Increases in listing rates may reflect improvements in the perceived value from drug treatment—likely spurred on by new clinical or economic evidence supporting the submission—as well as mechanisms for drug review. For instance, of all four HTA agencies, the PBAC published multiple evaluations for the largest number of drug-indication pairs (n=36). This likely reflects the fact that the PBAC is the only agency of the four considered that may defer a listing recommendation pending cost negotiations or further investigations into clinical safety or efficacy.

[INSERT FIGURE 1]

The null hypothesis of independence between HTA agency and listing recommendations was rejected for both the first and last available appraisals (First: $\chi^2 = 74.94$; $p < 0.01$; Last: $\chi^2 = 54.66$; $p < 0.01$). Local odds ratios were therefore used to measure the association between HTA agencies and initial and final available listing recommendations **(Table 2)**. The TLV and CVZ were most likely to issue positive listing recommendations; negative listing recommendations from the PBAC frequently became positive with time; and NICE was, generally speaking, most restrictive in the positive listing recommendations that it issued.

[INSERT TABLE 2]

These results were consistent with correspondence analysis **(eFigure 2)**. The principal dimension in correspondence analysis biplots for first and last available assessments appeared to consistently highlight opposition in listing recommendations. However, while this appeared to initially represent opposition between positive (L) and negative (DNL/D) outcomes, opposition appeared to better reflect a choice between listing with or without restrictions in last available assessments. In settings where listing recommendations can change over time, this may suggest that HTA agencies generally become more accommodative and transition from considering 'whether or not to list' to 'whether or not to list with restrictions'.

The association between HTA agency and listing rates however varied by drug indication. To draw inference, we limited our analysis to ATC subgroups with a sample size of at least 5 drug-indication

pairs (antithrombotics, antineoplastics, and immunosuppressants). For each HTA agency, immunosuppressants were associated with a final listing rate that exceeded that of the entire sample **(Figure 2)**. Apart from the CVZ, a similar phenomenon was observed for antithrombotic agents. In contrast, antineoplastics had a lower listing rate than the overall institutional average for NICE, PBAC and the TLV; the CVZ's listing rate for antineoplastics was above the agency's average **(Figure 2)**. Please see the appendix for more information on all remaining indications **(eFigure 3).**

[INSERT FIGURE 2]

Agreement in the Overall and Stratified Sample

Consistent with previous findings, there was poor to fair agreement in listing recommendations across all agency to agency pairings **(Table 3)**. NICE listing recommendations most often agreed with those from the PBAC, while the lowest level of agreement was observed between PBAC and TLV listing recommendations. The overall level of agreement in listing outcomes generally increased as the delay between agency assessments decreased and when orphan drugs were assessed. Inter-rater agreement was lower for antineoplastics and immunosuppressants than that observed for the entire sample **(Table 3)**. Removing L01- (antineoplastics) and L04-indicated (immunosuppressants) drug products tended to increase the overall level of agreement between listing recommendations from NICE and the PBAC, TLV, and CVZ **(eTable 1)**. Agreement in listing recommendations also generally decreased between first and last available assessment, and there was poor to fair agreement in listing recommendations across the other factors that were considered **(Table 3)**.

[INSERT TABLE 3]

Listing Recommendations and Assessments of Value

Final NICE listing rates decreased as ICERs increased. The agency approved all drug-indication pairs with an ICER of less than US$45,000 per QALY gained (n = 27), and most of those (0.93) with ICERs ranging between US$45,001 – US$60,000 (n = 14). Lower listing rates were observed for the six drug-indication pairs with ICERs between US$60,001 – US$75,000 (0.67), and for the 24 drug-indication pairs with an ICER above US$75,001 (0.25). Antineoplastics (L01) were disproportionately associated with higher ICER values, and in the set of drugs that received a negative listing recommendation from NICE **(ure 3.** I**)**.

[INSERT FIGURE 3]

Although the PBAC, TLV and CVZ less frequently published ICER data, there appeared to be a similar, albeit generally weaker, relationship between drug listing recommendations and ICER observations where data existed **(eFigure 4-6)**. In light of earlier findings, these data suggest that NICE and the PBAC are less likely than the TLV and CVZ to recommend funding of medicines that are deemed to provide low value, many of which are indicated for cancer.

DISCUSSION

HTA-Based Practices in Drug Listing

All drugs appraised by England's NICE between 2009-2013, and also evaluated by the Australian PBAC, Dutch CVZ, and Swedish TLV through July 2014, were included in this study (n = 43). This drug sample corresponded to a total of 231 drug-indication pairs with drug listing recommendations across the four agencies, of which the largest share came from NICE (n = 72). Antineoplastics and immunosuppressants were the largest therapeutic indications represented, together accounting for 67% of all drug-indication pairs considered by NICE.

Drug listing rates varied across Australian, Dutch, Swedish, and English HTA authorities. The Swedish TLV was the most generous of the four HTA agencies, with 92% of evaluated drug-indication pairs ultimately receiving a positive (restricted + unrestricted) listing recommendation. This was followed by the Dutch CVZ (89%), the Australian PBAC (84%), and England's NICE, which eventually approved 75% of the drug-indication pairs that it considered.

However, listing recommendations changed over time in some cases, which could point to differences in the ability of public agencies to take in new evidence, or their procedures for drug evaluation and cost negotiation. This was most dramatic for the Australian PBAC, where domestic authorities gave 46% and 84% of drug-indication pairs a positive listing recommendation after first and last available review, respectively. A similar, yet less dramatic, trend was observed for England's NICE. While negative recommendations are believed to reflect insufficiencies in the supporting evidence, restrictions on use may represent an attempt to increase the cost-effectiveness of treatments.(24) That the number of restricted drug listing recommendations increase over time in Australia and England may therefore indicate that both countries use the regulatory process to improve value-for-money in drug spending.

Generally speaking, these findings point to different regulatory approaches to inform value-based decision-making, limit budget impact, or optimize value-for-money in pharmaceutical spending by patients and payers. Let us take Australia as a case study: this analysis finds that Australia's PBAC often issues a 'do not list' recommendation following initial review, but becomes more likely to grant a permissive recommendation over time ('list with restriction'). The agency is responsible for issuing recommendations on whether to list medicines onto Australia's Pharmaceutical Benefits Scheme (PBS), the first national pharmaceutical reimbursement program to explicitly consider 'value-for-money' as a prerequisite for formulary listing.(25) The PBAC is known to have at times issued controversial decisions regarding listing status, even for indications such as cancer where treatment availability may be socially mandated, and the agency only recommends public listing of medicines that are priced at a premium over comparable drugs if the scientific data demonstrably shows clinically significant improvements in effectiveness or reductions in toxicity.(25) The PBAC may also limit the number of subsidized indications for a given drug, or may require "stepped therapy" or a "continuation rule" for subsidized use.(25) The mandate to ensure value-for-money in pharmaceutical spending may therefore be supported by a regulatory process that institutionalizes deferral of listing decisions and repeated review.

From another perspective, an extensive review process that better informs value-based decision-making or improves efficiency in pharmaceutical spending may nevertheless delay patient access. Recent evidence in fact suggests that Australians wait longer than most other OECD nations to access new medicines.(26) Future comparative studies should examine health outcomes as well as unit-level availability, pricing, and spending for new medicines in Australia, Sweden, the Netherlands, and the UK to explore the potential trade-offs from different approaches to pharmaceutical regulation and appraisal.

Convergence in Drug Listing Recommendations

This analysis found poor to modest agreement in the listing recommendations that were issued by Australian, Dutch, Swedish, and English HTA agencies. The overall level of agreement was highest for listing recommendations from Australia and the UK, and lowest for those issued by Australian and Swedish HTA agencies. Agreement also tended to decrease between first and last available listing recommendations. Since it has focused on the latter, this finding may suggest that the available literature underestimates the level of agreement in drug listing recommendations from HTA agencies, particularly for the period soon after initial market entry.

To also examine how the available evidence, social and institutional preferences, and processes for health economic assessment are associated with agreement in drug listing recommendations, this study stratified its sample by the delay occurring between health technology assessments, therapeutic indication and orphan status, and agreement in ICERs and health economic comparators.

Increasing the delay between HTA evaluations was associated with a decrease in the level of agreement between listing recommendations from NICE and the PBAC and TLV. This finding may suggest that HTA agencies differ in how they incorporate new evidence, and that this can in turn impact agreement across their respective listing recommendations. Agreement also tended to increase when the sample was limited to orphan medications, particularly for listing recommendations from NICE and the TLV and CVZ. These findings may suggest that common health needs and preferences can have a converging effect on drug listing recommendations.

Within our sample, the divergence observed across all international drug listing recommendations was driven by disagreement on listing recommendations for L01- (antineoplastics) and L04-

(immunosuppressants) indicated drug products. Considered alongside the finding that antineoplastics and immunosuppressants are also often associated with comparatively low levels of assessed health economic value, these findings may suggest that considerations of value-for-money strongly influence drug listing decisions—particularly in the UK and Australia—and that they are an important source of discrepancy in international listing recommendations.

Health economic evaluations are an important component to technological assessments. To examine how these influence listing decisions across countries, we evaluated the association between drug listing recommendations and a health economic measure of value, the incremental cost effectiveness ratio (ICER). 40-60% of commonly evaluated drug-indication pairs that provided ICER estimates received similar ICER assessments across agency pairings, though the proportion of ICERs in agreement generally decreased between first and last available assessment. Methodological differences in how value is assessed may therefore partly account for drug listing discrepancies—perhaps particularly in final listing recommendations—though the extent to which this is true varies by setting. This, however, reaffirms our earlier findings suggesting that methodological features of health economic assessments are not the only cause of international disagreement in whether to publicly reimburse medicines. Any influence on international agreement in listing recommendations from features of HTA appears to be compounded by differences in institutional priorities, insofar as how they shape the regulatory process and value-based decision-making. To gauge the appropriateness of differences in listing recommendations, additional work is therefore needed to examine how institutional priorities and practices reflect societal needs and preferences for treatment.

CONCLUSION

Consensus in global HTA has become an important health policy objective, as it represents an opportunity to both reduce duplication of regulatory effort and improve transparent, value-based decision-making in drug coverage. To better understand the causes of disagreement in HTA-based recommendations on whether to include medicines on publicly reimbursable drug lists, this study conducted a comparative analysis of drug listing recommendations emerging over time from Australia, the Netherlands, Sweden, and the UK. Although final drug listing rates in these countries are generally high, they vary considerably across settings and tend to increase over time in Australia and the UK. Still, there is poor to moderate agreement in the drug listing recommendations from these four highly-developed health systems, though this is associated with the time delay between health technology assessment, orphan drug status, and with medicinal classes that are deemed to provide low value-for-money (immunosuppressants, antineoplastics). Poor to moderate agreement in listing decisions is also compounded by HTA-based value assessments that rarely coincide with one another. International differences in drug listing recommendations therefore seem in part due to early inconsistencies in how the supporting evidence informs appraisal, but also to differences in how domestic priorities shape the regulatory process and value-based decision-making. Moving forward, additional work is needed to examine how well drug review processes and outcomes reflect social values regarding the trade-off between publicly subsidized drug coverage and use of resources.

EXHIBITS

Table 1. Health Technology Assessment and value-based decision-making in drug coverage

	Australia	Netherlands	Sweden	UK
Drugs appraised	All seeking reimbursement	Out-patient and expensive inpatient	All out-patient	Based on priority
Final Listing Authority	Yes/No: Advises Ministry of Health and Ageing and/or federal cabinet. Federal government may list drugs with (+) rec, but cannot list drugs with (-) recs	No: Provides solicited and unsolicited advice to the Ministry of Health	Yes/No: (+) listing recs must be implemented by county councils. Discretion in implementations is permitted for (-) recs	No: TAGs inform independent NICE Technology Appraisal Committees. NICE guidance is advisory – NHS makes final decision
Guidelines	√	√	√	√
Literature review	√	X	X	√
Study design	Preferred: Direct, H/H RCTs	Preferred: Direct, H/H RCTs	Preferred: Direct, H/H RCTs	Preferred: Direct, H/H RCTs
Source of evidence	External: Manufacturer. Economic evidence interpreted, assessed by PBAC Economics Sub-Committee	External: Manufacturer. Economic evidence evaluated by Committee on Pharmaceutical Care (now, Scientific Pharmaceutical Advisory Commission)	External: Manufacturer. Economic evidence evaluated by internal TLV project teams	External: (1) Manufacturer evidence reviewed (2) NICE-associated Technology Assessment Groups (TAGs)
Appraisal of clinical evidence	√	X	X	√
Data synthesis	Meta-analysis of key clinical outcomes + supplement with indirect comparisons	X	X	Meta-analysis of key clinical outcomes + supplement with indirect comparisons
Perspective	Societal	Societal	Societal	Public payer (NHS, Personal Social Services), or societal (excluding productivity costs) for non-reference cases
Analytic methods	CEA, CUA, CBA, CMA accepted (preference for CUA)	CEA CUA	CEA, CUA recommended CBVA, CBA analysis if QALYs unavailable CMA with constant health status	CEA, CUA preferred
Clinical comparator	Treatment most likely to be replaced	Standard treatment, defined as first-choice in daily practice with proven effectiveness (comparison with listed drugs mandatory)	Routine practice, non-medical intervention, therapeutic group alternatives (second & fourth ATC level)	Therapies customarily prescribed (including current best alternative or routine care)
Clinical value	Number QALYs gained.	Preferably valued in terms of QALYs, where relevant. CEA may use “cost per year of life” or cost per measure of effectiveness	QALYs gained. Cost effectiveness ratio determines price (premium)	QALYs gained.
Utility	EuroQol 5D, Health Utility Index Mark 2, Health Utility Index Mark 3 all acceptable MAUI + TTO or SG accepted to apply utility weights	MAUI or direct elicitation of utility. Visual analogue scale also accepted as a method to obtain utility weights	Direct or indirect (e.g. EuroQol 5D) + TTO or SG to apply utility weights. Patient rather than public preferences to determine weights	EuroQol 5D as the MAUI + TTO approach to apply utility weights
Costs considered	Direct medical, social services and indirect costs. Often only direct med costs or only drugs costs considered	All relevant costs and revenues, irrespective of payer/beneficiary	All relevant costs and revenues, irrespective of payer/beneficiary. Wider social impacts incorporated into costs/QALY	Probable direct and indirect resource cost to NHS and spending on PSS
Resource use data	X	X	X	Systematic literature review and other data searches
Model validation & Uncertainty analysis	Disease natural history data, systematic literature review, use of plausible values from trials or published literature	X	X	Impact of structural uncertainty in model, justification of uncertain distributions based on published literature
Subgroup analysis	X	X	If differences in cost-effectiveness expected	Relevant if biologically/clinically probable
Budget impact	Explicitly considered (no explicit limit and budget impact threshold)	Taken into consideration by the Health Insurance Board when making reimbursement recs; less weight than CEAs	Not considered (diverging restrictions can occur at the county council level)	Not explicitly considered (though recs correlated with potential budget impact)
ICER thresholds & decision-making	No explicit threshold. Implicit threshold, ~A$45,000–75,000. “Rule-of-rescue” under certain criteria (approval possible despite unfavorable cost-effectiveness) and “Life Saving Drug Program”	“Bandwidth” with suggested max ICER bound of €80,000 (“no hard limit”). Orphan drugs accepted with higher ICERs. “Highest need” considered in appraisal but not in economic evaluation.	No explicit threshold. Severity of disease, not rarity, primary consideration in decision-making.	Explicit range: £20,000–£30,000. Implicit premium: “end of life” (£40,000) and orphan drugs (£200,000– £300,000) accepted

Overview of policies related to the implementation of health technology assessment and its use in value-based decision-making in drug coverage.

Sources: Adapted from (14,15,27–38)

Figure 1. HTA agency listing recommendations, by first or last available assessment

[FIGURE 1 - SEPARATE FILE]

Listing recommendations across agencies, by first and last available appraisal for drug-indication pairs evaluated by NICE between 2009-2013. Number of drug-indication pairs falling within each recommendation category are provided within each bar. Positive listing rates (L + LWR) are provided to the right of each stacked bar.

Table 2. Measure of association between listing recommendations and HTA agencies, by first or last available assessment

	First		Last	
	L vs LWR	LWR vs DNL	L vs LWR	LWR vs DNL
NICE vs PBAC	0.654	2.667	0.563	0.519
NICE vs TLV	0.149	0.571	0.115	0.889
NICE vs CVZ	0.137	0.893	0.103	1.429

Local odds ratios to measure the strength of association between HTA agencies and first **(Left)** and last **(Right)** available listing recommendations. Since Australia is the only country of the four to defer the issuance of listing recommendations, deferrals are not considered. Definitions: L = List; LWR = List With Restrictions; DNL = Do Not List.

Figure 2. HTA agency listing recommendations, by ATC group

[FIGURE 2 – SEPARATE FILE]

Number of drug-indication pair recommendations issued for therapeutic groups with ≥5 drug-indication pairs (antithrombotics, antineoplastics, immunosuppressants), by first (F) and last (L) available appraisals across the four HTA agencies considered. Positive listing rates (L + LWR) are provided to the right of each stacked bar.

Table 3. Agreement across HTA agency listing recommendations, with sample stratifications

		First available evaluation			Last available evaluation		
		PBAC	TLV	CVZ	PBAC	TLV	CVZ
Reference Agency	NICE	κ = 0.232***	κ = 0.123*	κ = 0.111	κ = 0.198**	κ = 0.058	κ = 0.043
		SE = 0.08	SE = 0.081	SE = 0.079	SE = 0.087	SE = 0.075	SE = 0.075
		n = 57	n = 49	n = 45	n = 61	n = 52	n = 46
	PBAC		κ = -0.027	κ = 0.116**		κ = -0.053	κ = 0.116
			SE = 0.064	SE = 0.068		SE = 0.088	SE = 0.092
			n = 50	n = 43		n = 50	n = 43
	TLV			κ = 0.135			κ = 0.076
				SE = 0.122			SE = 0.12
				n = 40			n = 40
Reference Agency = NICE	Years between assessment						
	≤ 3	κ = 0.253***	κ = 0.168**	κ = 0.113	κ = 0.158*	κ = 0.106	κ = 0.026
		SE = 0.08	SE = 0.093	SE = 0.09	SE = 0.098	SE = 0.09	SE = 0.085
		n = 52	n = 42	n = 39	n = 52	n = 43	n = 41
	≤ 2	κ = 0.257***	κ = 0.219**	κ = 0.110*	κ = 0.159*	κ = 0.135*	κ = 0.068
		SE = 0.079	SE = 0.106	SE = 0.08	SE = 0.102	SE = 0.102	SE = 0.081
		n = 50	n = 38	n = 35	n = 48	n = 38	n = 36
	≤ 1	κ = 0.275***	κ = 0.225**	κ = 0.080	κ = 0.174*	κ = 0.167*	κ = 0.040
		SE = 0.09	SE = 0.106	SE = 0.069	SE = 0.113	SE = 0.108	SE = 0.073
		n = 40	n = 36	n = 31	n = 38	n = 34	n = 28
	0	κ = 0.378***	κ = 0.348**	κ = 0.126**	κ = 0.265*	κ = 0.391***	κ = 0.000
		SE = 0.155	SE = 0.166	SE = 0.063	SE = 0.204	SE = 0.157	SE = 0
		n = 16	n = 19	n = 17	n = 17	n = 20	n = 14
	Same comparator						
		κ = 0.162*	κ = 0.114	κ = 0.449***	κ = 0.250**	κ = 0.026	κ = 0.344**
		SE = 0.103	SE = 0.151	SE = 0.173	SE = 0.111	SE = 0.15	SE = 0.172
		n = 34	n = 19	n = 14	n = 35	n = 19	n = 14
	Same ICER						
	5% Margins	κ = 0.174*	κ = 0.071	κ = 0.000	κ = 0.073	κ = -0.091	κ = 0.000
		SE = 0.117	SE = 0.132	SE = 0	SE = 0.14	SE = 0.096	SE = 0
		n = 21	n = 13	n = 7	n = 19	n = 9	n = 7
	10% Margins	κ = 0.159*	κ = 0.071	κ = 0.290*	κ = -0.012	κ = -0.091	κ = 0.385*
		SE = 0.115	SE = 0.131	SE = 0.205	SE = 0.1304	SE = 0.096	SE = 0.279
		n = 22	n = 13	n = 9	n = 22	n = 9	n = 8
	Same ICER and comparator						
	5% Margins	κ = 0.055	κ = 0.000	κ = 0.000	κ = 0.200	κ = -0.136*	κ = 0.000
		SE = 0.158	SE = 0.141	SE = 0	SE = 0.158	SE = 0.1	SE = 0
		n = 13	n = 6	n = 5	n = 12	n = 5	n = 5
	10% Margins	κ = 0.055	= 0.000	κ = 0.333	κ = 0.133	κ = -0.136*	κ = 0.333
		SE = 0.158	SE = 0.141	SE = 0.304	SE = 0.161	SE = 0.1	SE = 0.304
		n = 13	n = 6	n = 6	n = 13	n = 5	n = 6
	Orphan drugs						
		κ = 0.000	κ = 0.221*	κ = 0.184	κ = 0.022	κ = 0.114	κ = 0.149
		SE = 0.149	SE = 0.146	SE = 0.168	SE = 0.156	SE = 0.132	SE = 0.188
		n = 11	n = 10	n = 8	n = 11	n = 10	n = 8
	ATC group (n ≥ 5)						
	B01 antithrombotics	κ = 0.000	κ = 0.000	κ = 0.000	Insufficient rating categories or observations	κ = 0.000	κ = 0.000
		SE = 0	SE = 0	SE = 0		SE = 0	SE = 0
		n = 8	n = 8	n = 7		n = 8	n = 7
	L01 antineoplastics	κ = 0.015	κ = -0.032	κ = 0.205**	κ = 0.006	κ = -0.032	κ = 0.143
		SE = 0.118	SE = 0.135	SE = 0.106	SE = 0.134	SE = 0.135	SE = 0.1
		n = 22	n = 16	n = 18	n = 22	n = 16	n = 18
	L04 immunosuppressants	κ = 0.217	κ = 0.013	κ = -0.154*	κ = 0.000	κ = 0.000	κ = -0.184**
		SE = 0.178	SE = 0.029	SE = 0.108	SE = 0.167	SE = 0	SE = 0.107
		n = 15	n = 13	n = 10	n = 18	n = 16	n = 10

Agreement across agency listing recommendations, standard error and sample size. Levels of agreement are measured with kappa (**κ**) scores across all agency– agency pairs (top), and in sample stratifications comparing NICE and other HTA agencies (bottom). Kappa thresholds are defined as per Landis & Koch (1977) (21) – poor agreement: **κ** ≤ 0.00, slight agreement: **κ** = 0.01–0.20, fair agreement: **κ** = 0.21–0.40, moderate agreement: **κ** = 0.41–0.60, substantial agreement: **κ** = 0.61–0.80, near perfect agreement: **κ** = 0.81–1.00. Statistical testing: *p < 0.10, **p < 0.05, ***p < 0.01.

Figure 3. Incremental cost-effectiveness ratios for NICE drug-indication pairs, by ATC group and listing recommendation

[FIGURE 3 – SEPARATE FILE]

Final available incremental cost effectiveness ratios (ICER) for NICE drug-indication pairs, by ATC group (x-axis), listing recommendation, and sorted by ATC group average ICER (USD/QALY). Sample includes all drug-indications pairs for which ICERs were available. Where ATC group has >1 observation, 95%CI are provided around group average ICER. All values presented in constant 2013 USD.

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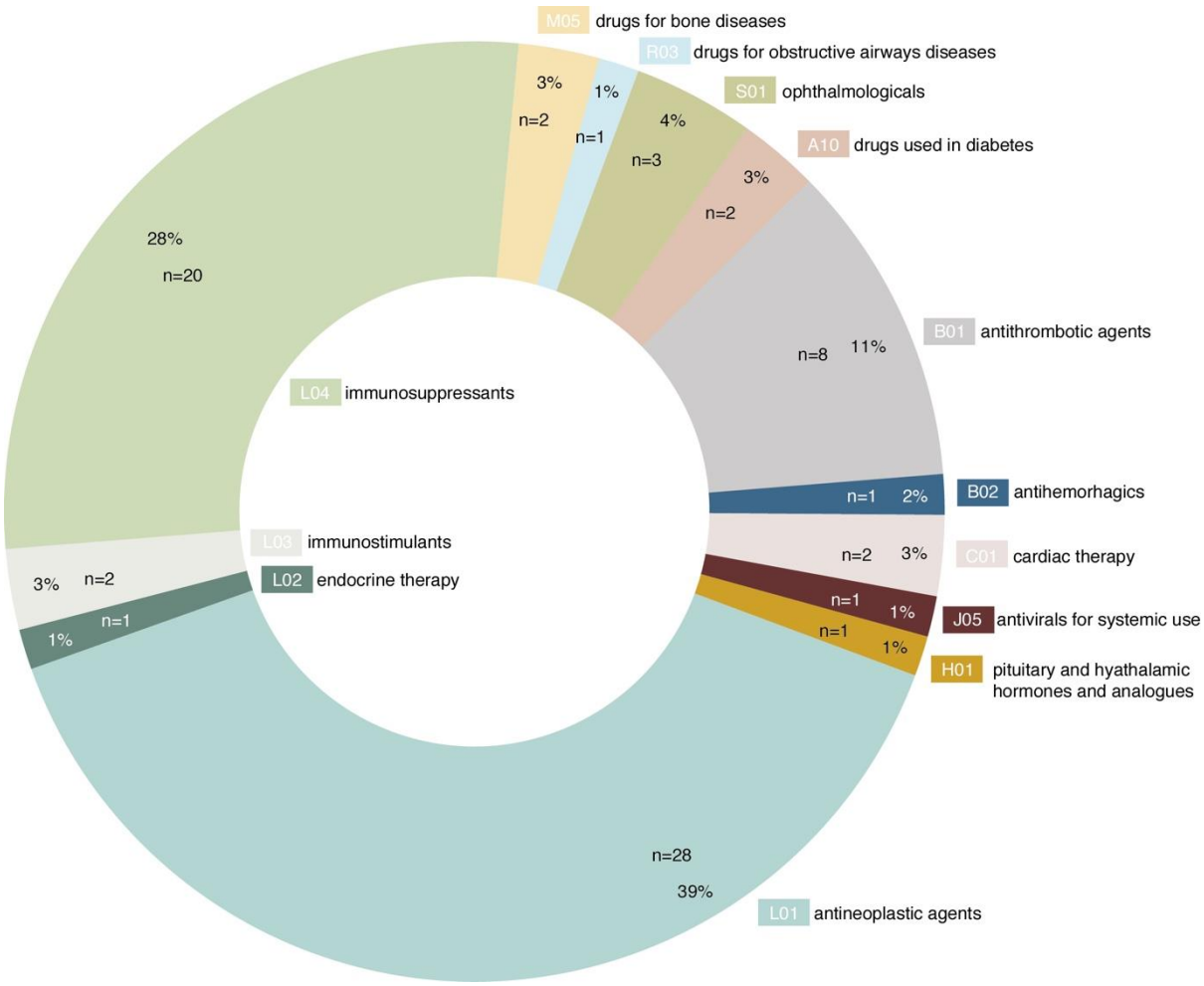
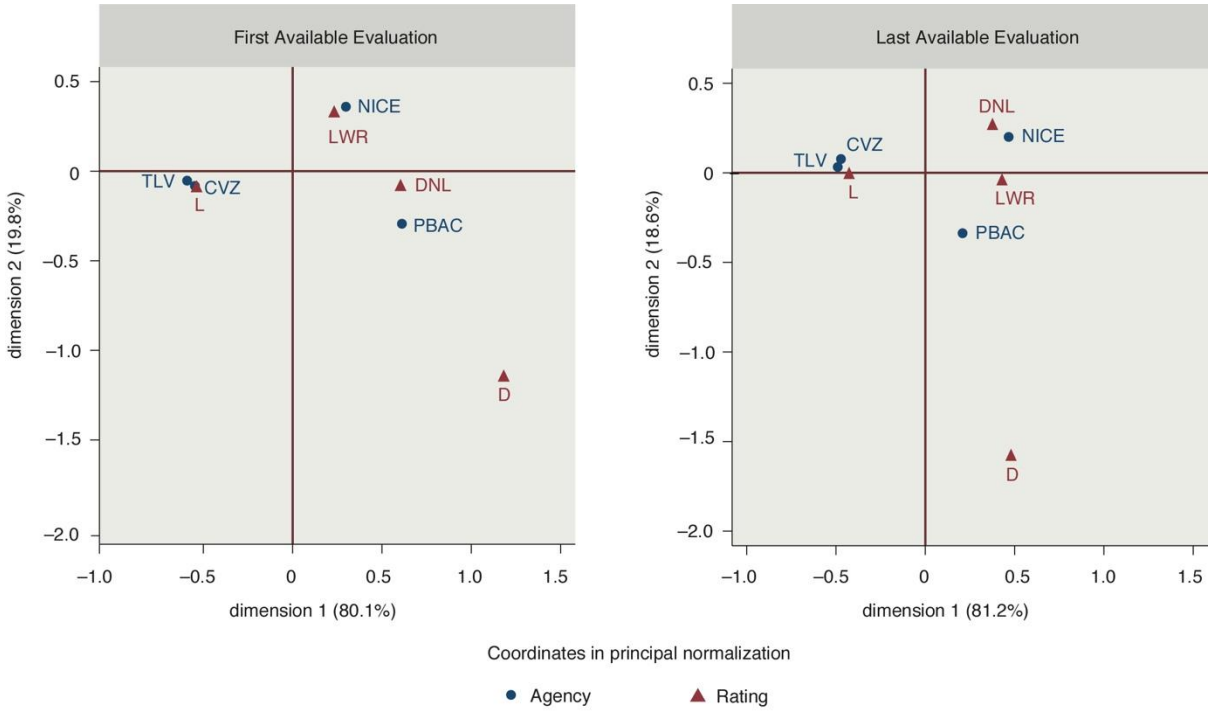
SUPPLEMENTARY MATERIAL

eFigure 1. Drug-indication pairs evaluated by NICE between 2009-2013, by class of indication



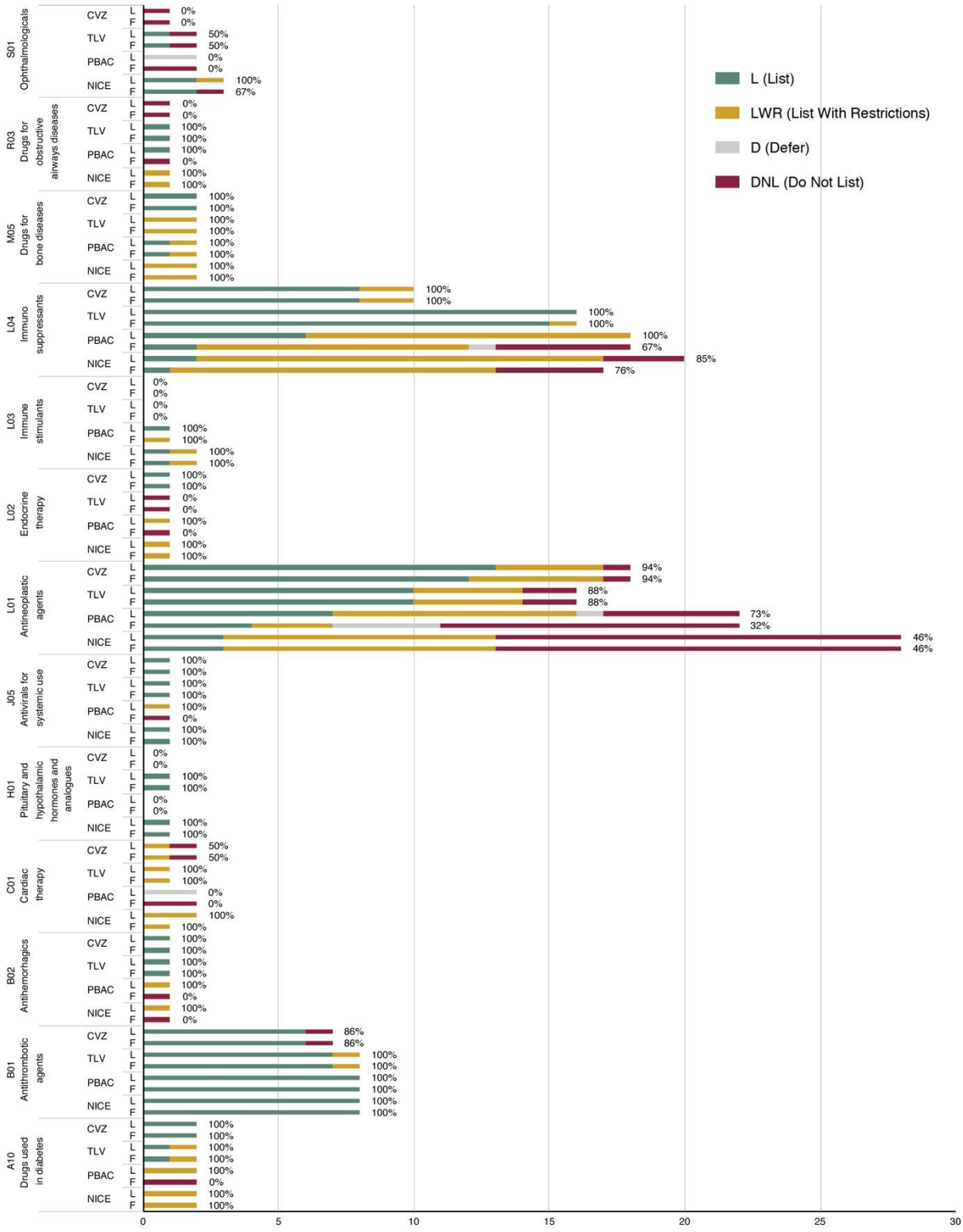
Description of the sample of NICE drug-indication pairs included in the analysis. Number of drug-indication pairs per ATC group. Definitions: A10 = Drugs used in diabetes; B01 = antithrombotic agents; B02 = antihemorhagics; C01 = cardiac therapy; H01 = pituitary and hyathalamic hormones and analogues; J05 = antivirals for systemic use; L01 = antineoplastic agents; L02 = endocrine therapy; L03 = immunostimulants; L04 = immunosuppressants; M05 = drugs for bone diseases; R03 = drugs for obstructive airways diseases; S01 = ophthalmologicals.

eFigure 2. Correspondence analysis biplots representing graphical association between HTA agencies and listing recommendations



(**Left**) First set of listing recommendations for drug-indication pairs: A significant majority of the inertia (77.2%) is explained by dimension 1. (**Right**) Final set of listing recommendations for drug-indication pairs: A majority of the inertia (84.1%) is explained by dimension 1. 'L': List; 'LWR': List with restrictions; 'D': Deferral; 'DNL': Do not list. 'PBAC': Australia HTA agency; 'CVZ': Dutch HTA agency; 'TLV': Swedish HTA agency; 'NICE': UK HTA agency.

eFigure 3. HTA agency listing recommendations, by ATC group

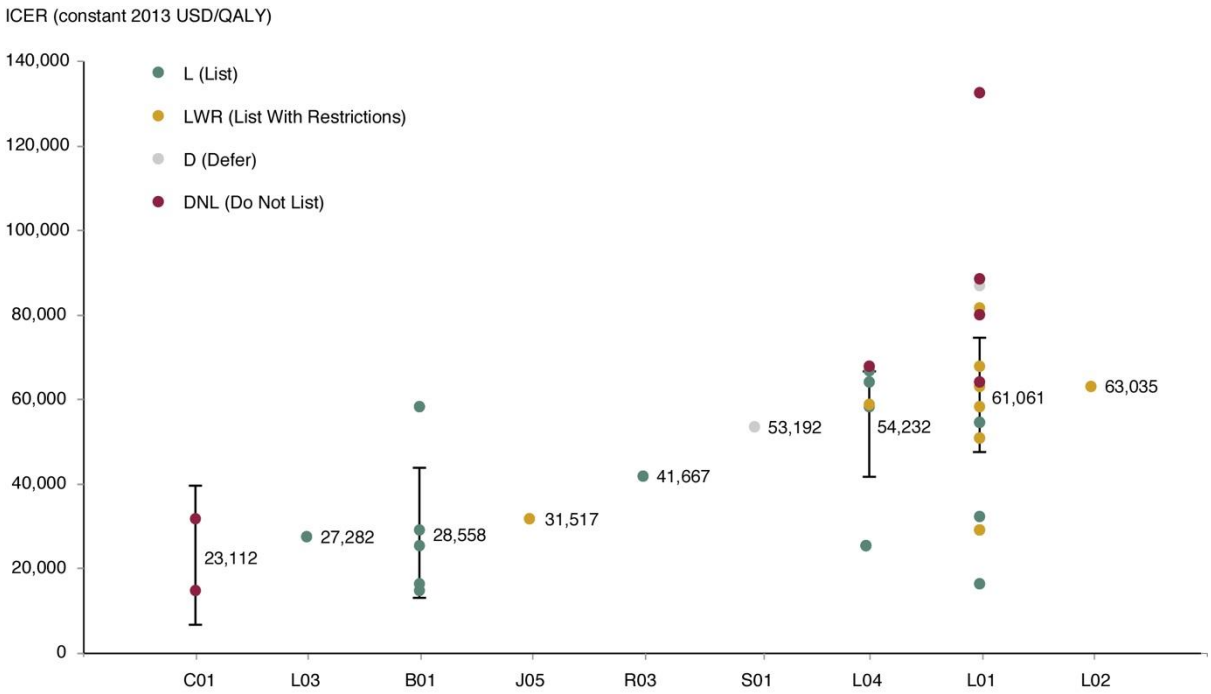


eTable 1. Agreement across HTA agency listing recommendations, without immunosuppressants, antineoplastics, antithrombotic

		First available evaluation			Last available evaluation		
		PBAC	**TLV**	**CVZ**	**PBAC**	**TLV**	**CVZ**
Entire sample, except L01 (immunosuppressants)	NICE	κ = 0.339*** SE = 0.104 n = 35	κ = 0.196** SE = 0.101 n = 33	κ = 0.056 SE = 0.098 n = 27	κ = 0.277** SE = 0.124 n = 39	κ = 0.090 SE = 0.087 n = 36	κ = 0.009 SE = 0.089 n = 28
	PBAC		κ = 0.026 SE = 0.078 n = 34	κ = 0.106 SE = 0.092 n = 28		κ = 0.034 SE = 0.104 n = 34	κ = 0.041 SE = 0.109 n = 28
	TLV			κ = 0.350*** SE = 0.136 n = 26			κ = 0.203* SE = 0.141 n = 26
Entire sample, except L04 (antineoplastics)	NICE	κ = 0.175** SE = 0.087 n = 42	κ = 0.250** SE = 0.113 n = 36	κ = 0.197** SE = 0.096 n = 35	κ = 0.206** SE = 0.1 n = 43	κ = 0.196** SE = 0.115 n = 36	κ = 0.105 SE = 0.092 n = 36
	PBAC		κ = 0.026 SE = 0.076 n = 35	κ = 0.140** SE = 0.08 n = 33		κ = -0.015 SE = 0.112 n = 35	κ = 0.151* SE = 0.105 n = 33
	TLV			κ = 0.009 SE = 0.135 n = 31			κ = 0.050 SE = 0.131 n = 31
Entire sample, except B01 (antithrombotics)	NICE	κ = 0.124* SE = 0.088 n = 49	κ = 0.080 SE = 0.074 n = 41	κ = 0.076 SE = 0.071 n = 38	κ = 0.031 SE = 0.088 n = 53	κ = 0.025 SE = 0.066 n = 44	κ = 0.003 SE = 0.068 n = 39
	PBAC		κ = -0.053 SE = 0.063 n = 42	κ = 0.117** SE = 0.064 n = 36		κ = -0.094 SE = 0.086 n = 42	κ = 0.079 SE = 0.091 n = 36
	TLV			κ = 0.149 SE = 0.136 n = 33			κ = 0.087 SE = 0.134 n = 33

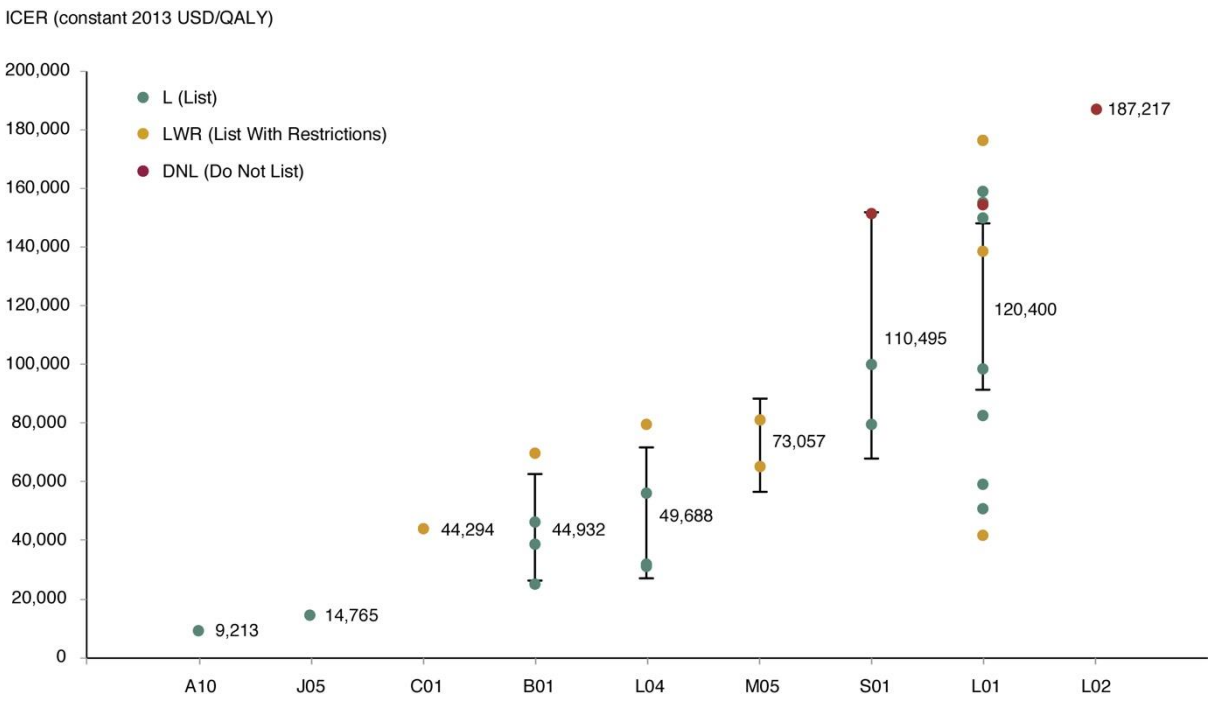
Agreement across agency listing recommendations, standard error, and sample size, after removing L01, L04, and B01 indicated drug products. Levels of agreement measured by kappa (κ) scores, with categorical kappa thresholds defined per Landis & Koch (1977) as poor agreement: $\kappa \leq 0.00$, slight agreement: $\kappa = 0.01–0.20$, fair agreement: $\kappa = 0.21–0.40$, moderate agreement: $\kappa = 0.41–0.60$, substantial agreement: $\kappa = 0.61–0.80$, near perfect agreement: $\kappa = 0.81–1.00$. Statistical testing: *p < 0.10, **p < 0.05, ***p < 0.01.

eFigure 4. Incremental cost-effectiveness ratios for PBAC drug-indication pairs, by ATC group and listing recommendation



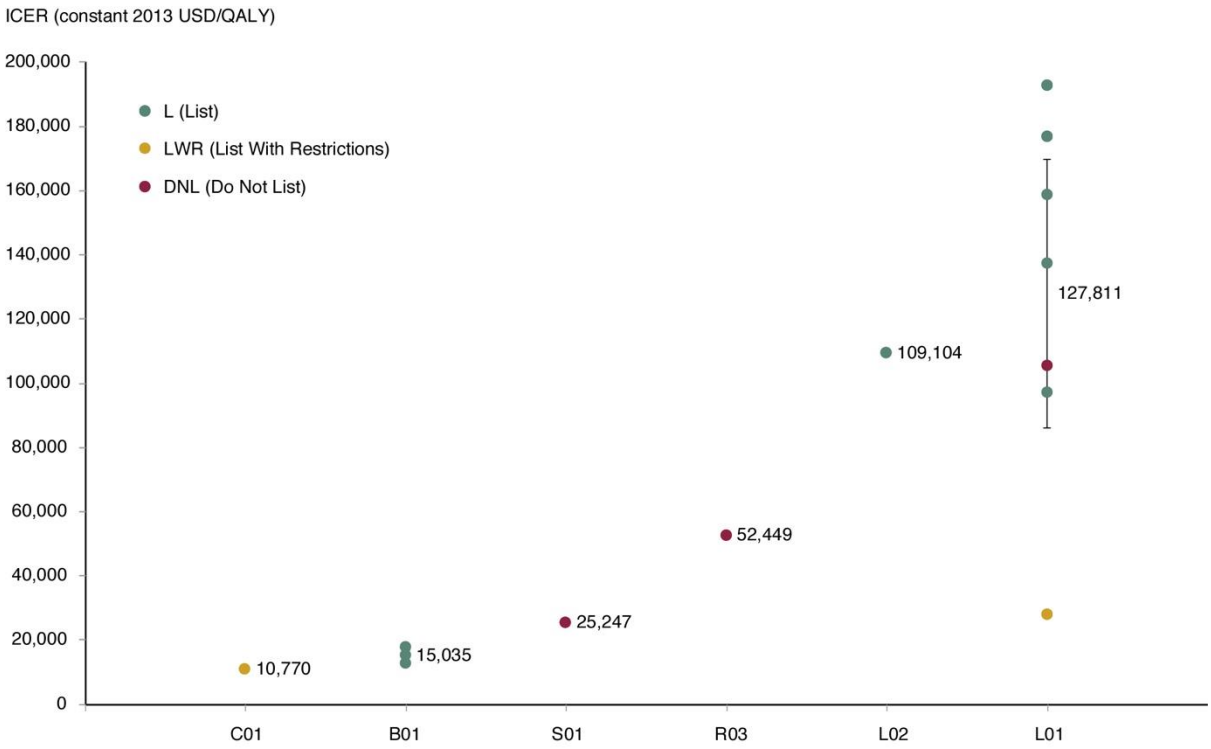
Final available incremental cost effectiveness ratios (ICER) for PBAC drug-indication pairs, by ATC group (x-axis), listing recommendation, and sorted by ATC group average ICER (USD/QALY). Sample includes all drug-indications pairs for which ICERs were available. Where ATC group has >1 observation, 95%CI are provided around group average ICER. All values presented in constant 2013 USD. Definitions: A10 = Drugs used in diabetes; B01 = antithrombotic agents; B02 = antihemorhagics; C01 = cardiac therapy; H01 = pituitary and hyathalamic hormones and analogues; J05 = antivirals for systemic use; L01 = antineoplastic agents; L02 = endocrine therapy; L03 = immunostimulants; L04 = immunosuppressants; M05 = drugs for bone diseases; R03 = drugs for obstructive airways diseases; S01 = ophthalmologicals.

eFigure 5. Incremental cost-effectiveness ratios for TLV drug-indication pairs, by ATC group and listing recommendation



Final available incremental cost effectiveness ratios (ICER) for TLV drug-indication pairs, by ATC group (x-axis), listing recommendation, and sorted by ATC group average ICER (USD/QALY). Sample includes all drug-indications pairs for which ICERs were available. Where ATC group has >1 observation, 95%CI are provided around group average ICER. All values presented in constant 2013 USD. Definitions: A10 = Drugs used in diabetes; B01 = antithrombotic agents; B02 = antihemorhagics; C01 = cardiac therapy; H01 = pituitary and hyathalamic hormones and analogues; J05 = antivirals for systemic use; L01 = antineoplastic agents; L02 = endocrine therapy; L03 = immunostimulants; L04 = immunosuppressants; M05 = drugs for bone diseases; R03 = drugs for obstructive airways diseases; S01 = ophthalmologicals.

eFigure 6. Incremental cost-effectiveness ratios for CVZ drug-indication pairs, by ATC group and listing recommendation



Final available incremental cost effectiveness ratios (ICER) for CVZ drug-indication pairs, by ATC group (x-axis), listing recommendation, and sorted by ATC group average ICER (USD/QALY). Sample includes all drug-indications pairs for which ICERs were available. Where ATC group has >1 observation, 95%CI are provided around group average ICER. All values presented in constant 2013 USD. Definitions: A10 = Drugs used in diabetes; B01 = antithrombotic agents; B02 = antihemorhagics; C01 = cardiac therapy; H01 = pituitary and hyathalamic hormones and analogues; J05 = antivirals for systemic use; L01 = antineoplastic agents; L02 = endocrine therapy; L03 = immunostimulants; L04 = immunosuppressants; M05 = drugs for bone diseases; R03 = drugs for obstructive airways diseases; S01 = ophthalmologicals.