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Do NICE's Decision Outcomes Impact International HTA Decision-making?

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Executive Summary

Health Technology Assessment (HTA) is a crucial component of health care decision-making in many countries with wide-reaching consequences for population health. Within the global HTA landscape, the English National Institute for Health and Care Excellence (NICE) plays a prominent role. However, there is limited evidence on the extent to which this is the case and, if it is, how NICE's decision outcomes on individual interventions affect HTA in other countries.

Using quantitative and qualitative research methods, we explored the impact of NICE's decision outcomes and its potential underlying factors in 12 other countries (Australia, Brazil, Canada, France, Italy, Israel, Japan, South Korea, Poland, Saudi Arabia, Sweden, and the United Arab Emirates).

NICE DECISIONS ARE ISSUED RELATIVELY FAST AND ARE OFTEN POSITIVE

Data on decision outcomes were available for 8 of the 12 countries of interest. Within this sample, NICE was a fast decision-maker compared to other countries and issued positive decisions faster than negative decisions. However, NICE often issued optimised decisions which are recommendations on the use of an intervention in a population that is smaller than stated in its licensed indication but has more favourable cost-effectiveness evidence. These optimised decisions are classified as positive in our sample, although they introduce restrictions on access to medicines. The sample of NICE decisions also includes a set of terminated appraisals which are usually instances where the manufacturer has not provided an evidence submission.

NICE HAS AN IMPACT GLOBALLY, BUT UNDERLYING FACTORS MAY BE MORE IMPORTANT THAN DECISIONS ON INDIVIDUAL TECHNOLOGIES

While the quantitative results do not prove causality and are based on a small sample size, they indicate that terminated appraisals and negative decisions issued by NICE are associated with no HTA being conducted in other countries; positive NICE decisions are associated with positive outcomes in other countries; and NICE's optimised decisions are associated with negative outcomes in other countries. Quantitative analyses suggest that NICE decision outcomes might be particularly influential on HTA outcomes within Poland, South Korea, Italy, and Sweden.

When interpreted with the insights derived from the interviews with manufacturer and academic representatives from 9 of the 12 countries, we can infer some influence of NICE decision outcomes but also from many underlying factors. In fact, interviews highlighted that key assumptions supporting economic models behind the issued decisions as well as the underlying HTA methods developed and implemented by NICE are often more influential than the published decisions themselves. NICE influence often also stems from indirect factors such as the NICE reputation as a methods innovator, NICE's decision speed, the accessibility of NICE's guidance, and the impact of UK educational institutions on international decision-makers.

NICE'S NEGATIVE DECISIONS STAND OUT

The many optimised decisions issued by NICE often relate to negative decisions in other countries. This indicates that other HTA agencies are less willing or able to go beyond binary decision outcomes (i.e., either recommend full access or not) than NICE.

However, this also means that negative decision outcomes issued by NICE stand out. Thus, in such a case, other HTA bodies may be more inclined to scrutinise the evidence underlying economic models submitted or, in price setting, it is used as leverage to demand a lower price.

The following table provides a visual summary of our findings. We decided upon the likelihood of the potential impact of NICE based on our interpretation of both the quantitative and qualitative research conducted.

NICE FUTURE AHEAD?

The future impact of NICE on the global HTA landscape might change. Although it is early to predict the outcome of the increased collaborations between HTA agencies (from those aimed to improve information sharing to those for tackling common method challenges), one can expect that they might strengthen NICE's role on the international stage.

European activities to streamline HTA, such as the Joint Clinical Assessment, are happening without NICE's participation. This and other post-Brexit activities might therefore work in the other direction and weaken the international influence of NICE, particularly in the European region.

SUMMARY TABLE OF THE POTENTIAL INTERNATIONAL IMPACT OF NICE DECISIONS THROUGH QUANTITATIVE AND QUALITATIVE RESEARCH

		Poland	South Korea	Italy	Japan	Sweden	Brazil	UAE	Saudi Arabia	Israel
Overall likelihood of potential impact of NICE		**High**	**High**	**High**	**Moderate**	**Moderate**	**Moderate**	**Low**	**Low**	**Low**
Quantitative findings	Data suggests NICE decisions may impact local HTA decisions	✓	✓	✓	N/A	✓	✗	N/A	N/A	N/A
Qualitative findings	HTA body uses CEA/similar method	✓	✓	✓	✓	✓	✓	✗	✗	✗
	HTA body considers NICE guidance as context/background	✓	✓	✗	✓	✓	✓	✓	✓	✓
	HTA body considers evidence submitted to/assumptions challenged by NICE	✗	✓	✓ (sub-population only)	✓	✗	✓	✓	✗	✗
	NICE decision influences HTA/price negotiation	✓	✗	✓	✗	✓	✗	✓	✗	✗
	Local HTA recommendation is not binding	✓ (Minister of Health decides)	✗	✓ (Regional reimbursement)	✗	✓ (Regional reimbursement)	✗	N/A	N/A	N/A

N/A: No data available

1 Introduction

1.1 Background

Health Technology Assessment (HTA) is a crucial component of health care decision-making in many countries with wide-reaching consequences for population health. HTA is a multidisciplinary process to determine the value of a health technology at different points in its lifecycle and is used to inform decision-making in order to promote an equitable, efficient, and high-quality health system (O'Rourke et al., 2020). According to the International Network of Agencies for Health Technology Assessment (INAHTA), a network of 50 HTA agencies, over 1 billion people in 31 countries around the globe are affected by HTA decisions (The International Network of Agencies for Health Technology Assessment, 2023). However, HTA decision-making, negotiation processes, and coverage or funding decisions can vary significantly from country to country (Fontrier, Visintin and Kanavos, 2021)

Within this global HTA landscape, the English National Institute for Health and Care Excellence (NICE) plays a prominent role. NICE is widely acknowledged for its structured and well-reported processes of decision-making. It was among the first national HTA bodies to be established, in 1999, setting out robust methodology and guidance for the application of cost-effectiveness from the outset. Based on this experience, NICE offers an advisory service (NICE International) for international health organisations seeking support for developing or advancing local HTA and guideline programmes (NICE, 2023).

NICE's international role poses the question of whether its decisions and decision-making processes have an impact on other countries' HTA. The pioneering nature of NICE's work, coupled with its transparent and publicly available methodology and appraisal documents, makes it a key reference point for well-established as well as developing HTA systems. However, empirical evidence on NICE global impact is scarce (Hernández-Villafuerte, Garau and Devlin, 2014). This study attempts to fill this gap and generates new evidence on the direct impact of NICE decisions on individual technologies and indirect channels affecting other HTA systems.

1.2 Objectives

This research investigated the impact of NICE and its decision outcomes on the use of licensed indications of medicines on the decision outcomes of other national HTA bodies. Using a mixed methods approach, we sought to identify direct and indirect factors that may influence an international HTA body's methods or outcomes. Our two primary research questions were:

1. Do NICE recommendations on an individual health technology affect the equivalent recommendation of other HTA agencies?

2. Which are the underlying factors of the NICE decision-making that may impact the decision-making of other HTA agencies?

To the best of our knowledge, this is the first research to combine a quantitative and qualitative approach to understand the impact of NICE on other HTA bodies.

2 Methodology

2.1 Research design

The research design involved a mixed methods approach. We used quantitative methods to explore associations and causal relationships between NICE's decisions and the decisions of other HTA agencies. Qualitative methods based on semi-structured interviews were then used to unearth potential underlying factors of NICE processes that might be considered by other agencies.

The geographic scope of the project included 12 countries, namely Australia, Brazil, Canada, France, Italy, Israel, Japan, South Korea, Poland, Saudi Arabia, Sweden, and the United Arab Emirates. Countries that are usually ahead of the UK in the product launch sequence (e.g., Germany or the USA) were excluded. Figure 1 provides an overview of the countries included within each workstream. The results from both workstreams were combined to reach an overall conclusion related to the two research questions stated in Section Error! Reference source not found..

FIGURE 1: COUNTRY COVERAGE BY WORKSTREAM

2.2 Quantitative methodology

2.2.1 Dataset generation

Firstly, we sought to identify a base set of NICE decisions to compare internationally. Given that some drugs have multiple indications, which are appraised separately by HTA agencies, we defined a set of drug-indication-pairs (DIPs) to ensure appropriate comparisons were made between NICE and the other HTA bodies' decisions. DIPs were searched in the list of published Technology Appraisals (NICE, 2023e) and Highly Specialised Technologies programme (NICE, 2023a). The therapeutic areas of interest were cancer (oncology products) and rare diseases (orphan products). We defined the time period of interest as January 2018 to December 2019; we chose this end date to mitigate any potential impact on HTA from the covid-19 pandemic.

In terms of the selected countries, we sought to include countries from different continents and a mixture of well-established and newer HTA bodies. We collected data from four European countries (France, Italy, Poland, and Sweden), one Asian country (South Korea), one North American country (Canada), one Latin American country (Brazil) and one from the Oceania region (Australia). We explored the feasibility of data collection from two additional Asian countries (China and Japan) and three Middle Eastern countries (Saudi Arabia, United Arab Emirates, and Israel). However, we determined that data availability would be too low to make comparisons.

We sought to maximise the number of comparisons by checking the relevant molecules' launch status in each country using PharmaProjects, a commercial database. We then ranked the DIPs by the number of countries where they were launched and selected them from the top until we reached

a number of DIPs whose retrieval in countries of interest seemed feasible, given the predicted data availability and resource constraints on the data extraction.

As HTA and pricing & reimbursement systems vary across the selected countries, we developed a simple categorisation of country HTA outputs to map to NICE decisions (Table 1), which can be seen in Figure 2 below. This allowed us to conduct comparisons. NICE 'Optimised' decisions were classed as positive decisions as they provided some level of access to the medicine. In addition, evidence of other countries' use of this decision outcome was not explored, as the small size of the sample could not accommodate more than a binary classification.

TABLE 1: OVERVIEW OF NICE OUTCOMES

NICE Outcome	Description
Recommended	The drug or treatment is recommended for routine use in line with the marketing authorisation from the European Medicines Agency (EMA) or Medicines and Healthcare Products Regulatory Agency (MHRA).
Optimised	The technology is recommended for a sub-group/s of patients which is smaller than originally stated by the marketing authorisation.
Not Recommended	NICE does not recommend the use of the medicine within the NHS.
Terminated	The appraisal is terminated before a decision is issued. This is the case if "NICE is not satisfied that the evidence submission is adequate for the appraisal committee to make a decision or if no evidence submission has been received" from the manufacturer (NICE, 2014).
Recommended - CDF	If there is early evidence that a drug has clinical benefits for cancer patients, but still needs more evidence to prove its cost-effectiveness, NICE can recommend it for use within the Cancer Drugs Fund.
Optimised - CDF	An optimised decision issued through the Cancer Drug Fund.

We retrieved information on NICE's HTA process (e.g., the time between approval by the European Medicines Agency (EMA) and a final NICE decision within the different appraisal routes) and outcomes for each DIP and searched equivalent information from HTA bodies in Australia, Brazil, Canada, France, Italy, Poland, South Korea, and Sweden until the end of Q4 2021. To compute timelines between regulatory approval and HTA decision within a country, we also searched for information from the relevant regulatory medicine agency in each region. All decisions were extracted in the first quarter of 2022.

FIGURE 2: NICE DECISION OUTCOMES MAPPED AGAINST OTHER COUNTRIES' OUTCOMES

2.2.2 Statistical analysis

Decision outcomes and decision speeds were analysed using common descriptive statistics. We performed an Analysis of Variance (ANOVA) to test for differences between decision speeds of different countries.

We used categorical independence testing to compare the distribution of NICE decisions against that of other countries, thereby determining if one might influence the other. Testing for categorical independence between outcomes of NICE and other HTA bodies was performed using either Chi-squared or Fisher's exact test, depending on sample size.

We explored causality by framing the question as a treatment effect analysis. To do this, we created dummy variables indicating whether NICE decided before another country's HTA body. We then split the dataset into two groups: a treated group where NICE made the decision prior to other countries and a placebo group where NICE made the decision second. The frequency distribution of these two groups across positive and negative decisions (as coded within Figure 2) was then fed into a contingency table for analysis using the appropriate statistical tests mentioned above.

2.3 Qualitative methodology

We conducted interviews with experts and individuals with direct experience of the local HTA systems. The interviews aimed to elicit the individual's perspective on the extent to which their local HTA body considers or is influenced by NICE based on their knowledge and experience.

In terms of the country representation, we sought to include a mixture of countries included in the quantitative analysis and from countries where data collection wasn't feasible. Countries that are likely to make decisions faster than NICE, as indicated by our quantitative analysis and the wider literature, were excluded from the qualitative workstream.

For potential interview partners, we first targeted individuals who were current or former decision-makers (HTA or Ministry of Health where relevant). If we could not secure an interview with a relevant decision-maker (four cases), we reached out to academics with a strong background in local HTA methodology and processes. We also sought to capture the manfuacterers perspective by interviewing individuals working in the company that commissioned this study who are involved in their country's HTA submission process.

All interviews were conducted via video call by a member of the OHE team. A semi-structured interview format was used; interviewees were sent the interview guide in advance. Interviews were audio recorded, and key themes and results were extracted.

The interview guide consisted of 3 sections:

1. Comparing NICE HTA methods and process with other HTA bodies
2. The impact of specific decisions/outcomes made by NICE
3. Responses on a 5-point Likert scale (agree/disagree) to specific statements[1]

[1] *To allow for comparability across interviews.*

3 Results

3.1 Quantitative analysis

3.1.1 Dataset

From 116 NICE decisions issued between 2018-2019, we identified 87 within the therapeutic areas of interest (cancer & orphan). We then used the ordering exercise described in section 2.1 to maximise the number of matching decisions in other countries. This selection process resulted in 51 DIPs from the therapeutic areas of interest (59% were for cancer, 18% for rare diseases and 23% for rare cancers). Decisions of the selected 51 DIPs within the eight countries of interest created a dataset containing 408 observations, with the NICE decision outcome being an explanatory variable.

3.1.2 Decision Outcomes

Of the 51 DIPs, the NICE outcomes were: terminated appraisal for 7 DIPs (14%), negative recommendation for 4 (8%), and a positive recommendation for 40 (78%). Not all 51 DIPs with a NICE decision were assessed by the other eight countries of interest. Of the 51 DIPs, we found related HTA decisions, from the highest to the lowest, in Italy (n=48, 94%), France (n=45, 88%), Canada (n=36, 71%), Poland (n=35, 69%), Australia (n= 34, 67%), Sweden (n=14, 27%), South Korea (n=11, 22%), and Brazil (n=7, 14%).

Focusing only on completed appraisals (after removing two terminated appraisals in Australia and one terminated appraisal in Poland), Figure 3 shows that most countries have a positive recommendation rate above 75%. This compares to NIC's positive recommendation rate of 90% for all completed (7 terminated appraisals excluded) appraisals.

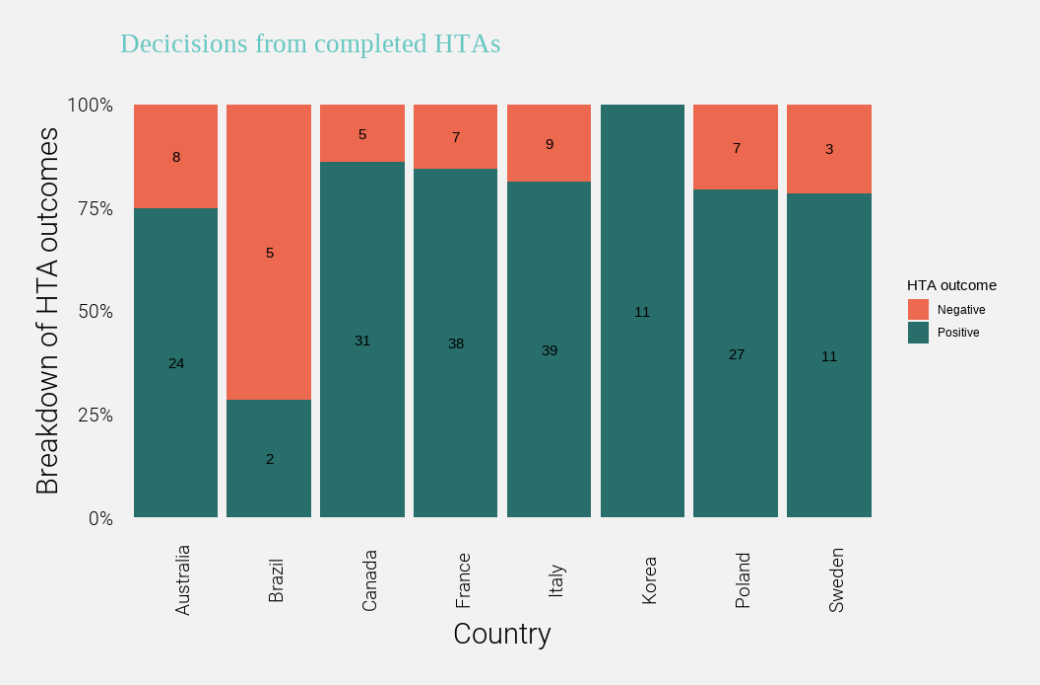

FIGURE 3: DECISION OUTCOMES OF COMPLETED HTA.

3.1.3 Decision Speeds

Within the full dataset (terminated decisions included), the median time between regulatory approval by the European Medicines Agency (EMA) and the issued final NICE decisions is 237 days for cancer drugs (n=30). This time span is twice as long for orphan cancer drugs (459 days, n=12) and 2.5 times for orphan drugs (616 days, n=9).

Terminated decisions are issued fastest, followed by optimised decisions issued through the Cancer Drug Fund (Figure 4). The median time to issue the four negative decisions is 831 days, more than twice as long as the median time for a positive recommendation.

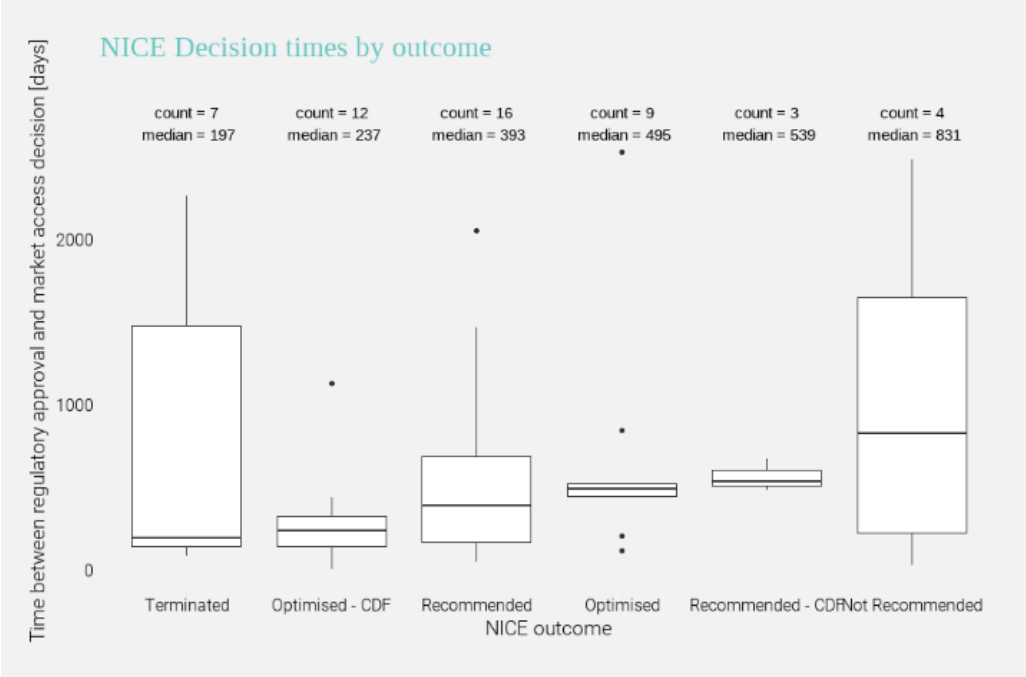

FIGURE 4: NICE'S DECISION SPEEDS BY DETAILED OUTCOME

Compared to the time between the approval from the relevant regulatory agency and the final decision made by the HTA agency in other countries, the median decision time of 347 days (n=51) makes NICE a relatively fast decision-maker compared to other countries within the dataset (Figure 5). Because of the small sample size, however, most differences are not significant at a 0.05 level. ANOVA testing reveals that only the difference between Poland's decision times compared to those of Australia, Canada, France, and Sweden are statistically significant.

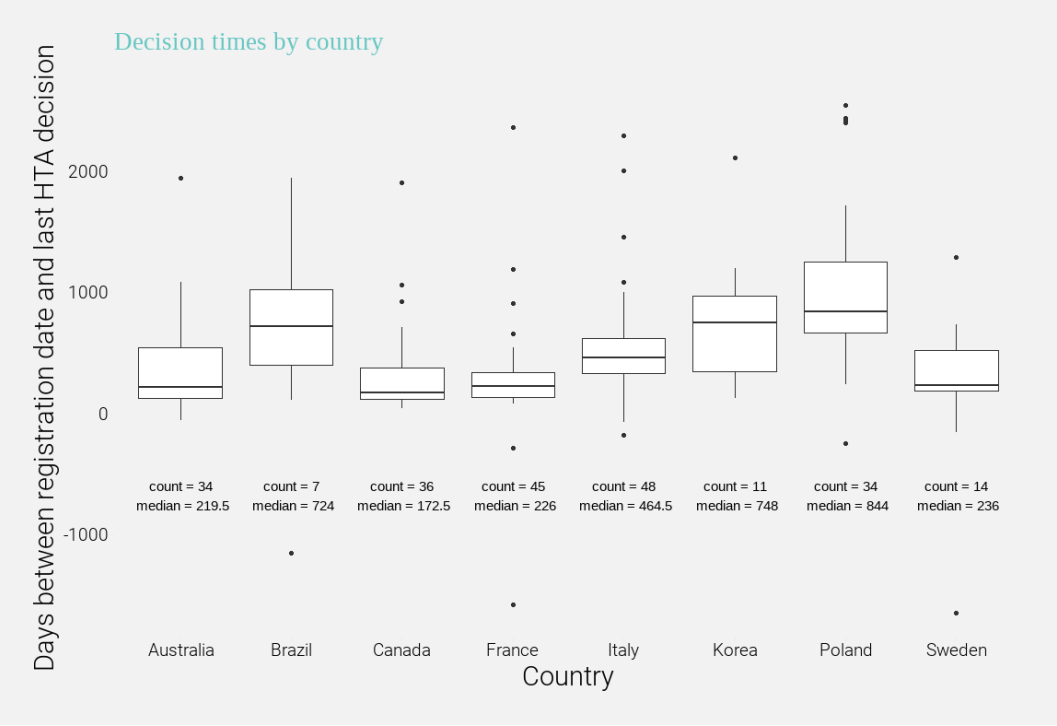

FIGURE 5: TIME PASSED BETWEEN REGULATORY APPROVAL AND FINAL DECISION OUTCOME BY HTA BODY.

3.1.4 Impact of NICE decisions

Within the full sample, we could not detect any correlation between NICE's coded decision outcomes (Positive, Negative, and Other) and the equivalent coded decision outcomes by other HTA agencies (Fisher exact statistic: 0.7).

However, when NICE decisions outcomes were used as originally issued (Recommended, Optimised, Recommended through CDF, Optimised through CDF and Negative), and terminated appraisals were included, categorical NICE outcomes were significantly associated (Chi-squared, p-value: 0.0055) with other countries' decisions.

Inspecting the residuals of the Chi-Square Test indicated that:

- terminated NICE appraisals and negative NICE decisions (i.e., not recommended) are associated with the lack of HTA in other countries[2],
- positive NICE decisions (i.e., recommended) are associated with positive outcomes in other countries,
- Optimised NICE decisions (i.e., positive with restrictions) are associated with negative outcomes in other countries, while the direction of decisions associated with the CDF-related decision was ambiguous.

[2] *It is worth noting that this is a correlation only and this finding could result from an absence of a submission by the manufacturer, either to NICE (captured by the 7 terminated NICE decisions) or to one of the other HTA agencies.*

The exploration of causality using a treatment variable that indicated whether NICE made a decision before or after an individual country showed that a positive recommendation (i.e., recommended and optimised decisions) first issued by NICE had a significant relationship with a negative decision in other countries (Chi-squared, p-value: 0.05), which is counterintuitive. We could not examine the relationship for negative decisions as the sample size was too small even when coded outcomes were used.

Splitting the dataset of decisions by a variable that indicated whether NICE made a decision before or after an individual country, we identified a subset of four countries (Poland, Italy, South Korea, Sweden) where the level of agreement by a decision between NICE and the respective national HTA agency increased when NICE issued their decision first. However, the results were not significant (Fisher exact, p-value: 0.53).

3.1.5 Summary of quantitative results

In summary, we could not detect a significant association between NICE decisions and HTA decisions in another country when using coded outcome categories on an aggregate level.

However, when using uncoded NICE outcomes, our analysis indicated potentially meaningful relationships. An early recommendation of a medicine without any restrictions on its indication by NICE is associated with a positive recommendation on the same drug indication pair by other countries.

On the contrary, when NICE recommends a medicine but restricts its use (optimised decision), follower HTA agencies may seem to be more likely to reach a negative decision on the same drug indication pair. When NICE terminates an appraisal and or issues a negative NICE decision, there is a higher likelihood that no HTA was being carried out in other countries.

3.2 Qualitative analysis

A total of 13 interviews were conducted, with eight manufacturer representatives and five former decision-makers and/or academics, covering a total of nine countries (Sweden, Poland, Italy, Japan, South Korea, Brazil, Israel, Saudi Arabia, and UAE).

3.2.1 Comparing NICE HTA methods and processes with other HTA bodies.

Before comparing the local HTA methods in the countries considered, we provide a brief summary of NICE's HTA guidelines and processes for reference. The primary route for new medicines evaluated by NICE is the Technology Appraisal Programme. NICE committees make their recommendations primarily based on clinical and cost-effectiveness evidence, but there are a number of other considerations that may be taken into account too. NICE's standard cost-effectiveness threshold is between £20,000 and £30,000 per QALY gained. Since 2022, for medicines that treat severe health conditions (as measured by proportional and absolute shortfall), the threshold may be increased to £35,000 or £50,000. This modifier replaced the previous end-of-life modifier. For cancer medicines or innovative medicines where there is considerable uncertainty in the available evidence, they may be included in a coverage with evidence development scheme, the Cancer Drugs Fund or the Innovative Medicines Fund. In 2013, the Highly Specialised Technologies pathway was introduced to evaluate medicines for very rare, and often very severe, diseases; for these medicines, the cost-effectiveness threshold ranges from £100,000 for interventions that provide 10 QALYs gained or less, up to £300,000 for 30 or more QALYs gained. NICE's updated guidance manual can be found here (NICE, 2022a).

In Sweden, the Dental and Pharmaceutical Benefits Agency (Tandvårds- och läkemedelsförmånsverket, TLV) is responsible for conducting HTA. Their methods are centred around cost-effectiveness analysis (CEA), but their guidelines are limited and not prescriptive compared to NICE. As a result, the onus is on the manufacturer to build an appropriately robust economic model to demonstrate the value of the technology. It's worth noting that whilst TLV methods are similar to NICE, reimbursement decisions are made at a regional level in Sweden.

In Poland, the HTA methods and processes of The Agency for Health Technology Assessment and Tariff System (AOTMiT) are similar to NICE, including having an explicit cost-effectiveness threshold. However, the cost-effectiveness of a new technology is one of 13 criteria considered when the Ministry of Health makes decisions on reimbursement. Another notable difference is that optimised/ restricted decisions are only driven by the manufacturer's submission, i.e., the HTA body evaluates the cost-effectiveness based only on the patient population set out in the manufacturer's submitted dossier. Manufacturers may submit their dossier based on a subpopulation if the full authorised indication is unlikely to be cost-effective. In 2011, the Ministry of Health drafted the Act of Reimbursement of Medicines, Foodstuffs Intended for Particular Nutritional Uses and Medical Devices to rationalise the reimbursement policy and improve access to innovative medicines (Kawalec et al., 2016); an interviewee likened this Act to NICE's Innovative Drugs Fund. For a full overview of Polish HTA methods and a comparison to NICE's 2013/2015 guidelines, see Lach et al. (2017).

In May 2020, the first guidelines for economic evaluation were published by the Italian Medicine's Agency, AIFA, indicating the economic analyses (CEA and budget impact) which are expected. For the interviewees, these guidelines are less detailed and structured compared to NICE. The introduction of these guidelines was followed by legislative changes aimed at regulating the negotiation and reimbursement process. For an overview of these guidelines and a comparison to NICE's 2013 guidelines, see Fiorentino and Urbinati (2021). Pharmaceutical companies may also apply for innovativeness status that provides immediate access to regional markets and a dedicated fund. Drugs innovativeness is appraised on the grounds of unmet therapeutic need, therapeutic added value, and quality of the evidence. For an overview of current challenges and next steps for HTA in Italy, including the expected re-organisation of AIFA, see Garau and Jommi (2023).

South Korea was the first Asian country to mandate the submission of pharmacoeconomic data for reimbursement decision-making (Bae, 2019). The Health Insurance Review and Assessment Service (HIRA) conducts HTA using methods relatively similar to those used by NICE. Unlike NICE's new severity modifier or previous End of Life modifier, HIRA does not set out formal modifiers. However, according to our manufacturer representative, if a NICE appraisal includes a modifier, then it is possible for HIRA to also consider it, but it is highly unlikely to be accepted. An interviewee stated that coverage with evidence development is an option in South Korea, but at the time of the interview, there were only two products included; the interviewee expected that the number of products using this type of agreement would increase in the near future. Some drugs used to treat ultra-rare diseases are exempt from economic evaluation. In these cases, to be accepted, their price must be lower than the lowest price among the A7 countries (France, Germany, Italy, Japan, Switzerland, the United Kingdom, and the United States)(Bae, 2019). The National Health Insurance Service (NHIS) negotiates with the pharmaceutical company on pricing based on HIRA's assessment results. For a comprehensive overview of HTA in South Korea, see Bae (2019).

HTA was implemented in Japan by the Ministry of Health, Labour, and Welfare, partly to address the rising costs of healthcare expenditure. Pharmacoeconomic requirements for list-price adjustments were institutionalised in April 2019 following the provisional implementation of a new Health Technology Assessment (HTA) program 2016-2019 (Kamae et al., 2020). Our interviews suggested that the implementation of HTA was partly influenced by NICE. Interviewees stated that given its relatively recent introduction, The Social Insurance Medical Council (Chuikyo) only has the capacity

to review between 5 and 10 products per year. Chuikyo selects the products to be evaluated based on their impact on healthcare insurance expenditure, as measured by a five-tier classification system (with the highest priority being newly listed products with an estimated annual sales above 10 million) (Hasegawa et al., 2020). Similar to NICE and many other HTA agencies, Chuikyo recommends the use of EQ-5D to measure health outcomes and generate QALY estimates. Japan's HTA program mandates incremental cost-effectiveness ratios (ICER) as evidence; this is then used to adjust prices upwards or downwards accordingly. Additionally, the thresholds are shifted 1.5 times higher for medicines for which one of the indications includes rare or paediatric diseases or cancers where the treatment value cannot be fully assessed by ICER only. For a full discussion of HTA in Japan, see Kamae et al. (2020).

In Brazil, the National Committee for Technology Incorporation (Conitec) is responsible for HTA within the public health system. Its methods and processes are similar to those used by NICE, including clinical effectiveness and economic evaluation. According to our interviews, the main difference is that there is no dialogue between HTA and the manufacturer prior to the dossier being submitted. Furthermore, Conitec is set to mandate explicit cost-effectiveness thresholds of R$40,688 (1xGDP), with proposed alternative thresholds for diseases affecting children, severe or rare diseases with significant reductions in quality-adjusted survival and endemic disease in low-income populations (3xGDP)(CONITEC, 2022). Conitec notes the cost-effectiveness thresholds used by NICE in their report but are due to increase their threshold in line with alteration in GDP, a significant departure from NICE's process.

In UAE, the decision is based on clinical effectiveness, with no cost-effectiveness analysis. Decision-makers may consider innovation/unmet need. Our interviewee suggested that there is likely to be an official HTA system introduced in the next three years.

In Saudi Arabia, the Ministry of Health is responsible for reimbursement decisions. They mainly use annual cost comparison across the same therapeutic area in addition to clinical evidence. Our interviewee suggested the Ministry of Health may require a budget impact analysis in some circumstances. According to our interviews, decision-makers may look at NICE documentation for contextual information but would not use it as guidance per se. Saudi Arabia is currently undergoing a number of initiatives aimed at amending drug pricing and reimbursement in the market; in 2020, it was announced that a new Health Technology Assessment (HTA) Unit for Saudi Arabia at a national level would be established (Al-Omar, Attuwaijri and Aljuffali, 2020).

In Israel, the Ministry of Health makes decisions about reimbursement primarily based on efficacy and budget impact, not cost-effectiveness. Our interviewee stated that it is possible to submit an economic evaluation and that the Ministry has economic evaluation guidelines for manufacturers. However, generally, there is no incentive for manufacturers to do so unless the drug is cost-saving or highly cost-effective. Furthermore, they could only recall one submission of an economic evaluation. According to our interviewee, it is common for reimbursement decisions made by the Ministry of Health to restrict the eligible patient population relative to marketing authorisation, similar to NICE's 'Optimised' decisions, but these decisions are made independently of NICE.

3.2.2 The impact of decisions made by NICE

We present the main results by country and in order of what we have categorised as "influence" from NICE to the individual country.

NICE'S DECISION OUTCOMES ARE LIKELY TO HAVE SOME INFLUENCE BUT VARY ACROSS COUNTRIES

In **South Korea**, it was suggested that NICE decisions have a significant impact on HIRA's decisions. However, the position of the two interviewees did not align on all aspects, as one believed that the

final guidance has the most impact, in particular the sections with the recommendation and the most plausible incremental cost-effectiveness ratio (ICER), while the other thought that HIRA considers more NICE's assessment of the clinical and economic evidence (e.g., the validity of clinical evidence or the structure of the model) along with similar summaries from other HTA bodies, They both added that if there has been a positive NICE recommendation, then there is likely to be more pressure from external stakeholder groups (e.g., patient groups) for HIRA to make a positive decision.

In **Brazil,** NICE decisions have a considerable impact on Conitec's decisions. They suggested that both positive and negative decisions have a strong influence, but negative NICE decisions can have more consequences, either for price reasons or quality of evidence assessment.

In **Poland**, positive NICE decisions do not have a significant impact on local reimbursement decisions. But they did suggest that a negative NICE decision or a significant issue with the economic model identified by NICE would require further validation with the submitting manufacturer. It was also suggested that the Polish Minister of the Economic Committee might consider how many other HTA agencies have issued a positive decision. An interviewee pointed out that the recommendation/dossier by the HTA body (AOTMiT) presented to the Minister of Health is likely to include NICE's decision for reference, but they suggested that this would not influence the decision directly.

In **Sweden**, TLV may look at the NICE guidance but would make their own independent decision. It's worth noting that NICE decisions may have less relevance in Sweden due to TLV's much wider cost-effectiveness threshold range than NICE. An interviewee said that TLV might refer to areas of the manufacturer submission which received particular scrutiny from the NICE committee (according to the published NICE documentation). They also suggested that in the past, if TLV has made a negative, but NICE has issued a positive decision, this may trigger a re-evaluation so the TLV and the manufacturer can come to an agreement on price.

In **Japan**, decisions from other HTA bodies, including NICE are requested by Chuikyo, but it is unclear how they are used and to what extent they influence their final decision, if at all. In addition, Chuikyo may look at NICE committee documents to gain an understanding of NICE's evidence review (e.g., checking the validity of clinical evidence or model structure, choice of comparators etc.), but with the caveat that NICE's recommendations may not necessarily be transferable to the Japanese setting.

In **Italy**, AIFA does not tend to look at the NICE decision itself but may look at the specific patient population the treatment has been recommended for in the case of optimised decisions. It was suggested that AIFA committee members might look at NICE documents and outcomes but mainly for complex appraisals such as innovative therapies or high-cost products. Since the introduction of economic evaluation, AIFA may refer to technical points raised during the NICE appraisal.

In **Saudi Arabia**, it was suggested that the Ministry of Health might look at the NICE decision for context and to understand to what extent the product was recommended or not recommended.

In **UAE**, decision-makers look at the eligibility criteria of the population recommended, restrictions, and commercial agreements. If a medicine has been rejected by NICE, price negotiations are more difficult.

In **Israel**, the HTA/academic representative stated that the Ministry of Health might consider NICE's decision and the most plausible ICER for reference if available, but in many cases, the Ministry is likely to make its decision before NICE's final decision is published. The interviewee also added that committee members are unlikely to be familiar with the methods of economic evaluation and, therefore, are not well situated to review or consider NICE guidance.

MOST LOCAL DECISION-MAKERS WOULD ONLY TAKE FINAL DECISIONS INTO CONSIDERATION

Most interviewees said that, in most circumstances, their HTA body would not look at intermediate NICE documentation, given that the decision could change. Most interviewees said their HTA body would not wait for NICE's final decision. Except in South Korea, if the final decision was expected to be published soon. All interviewees said that decisions involving extensions of indication had less impact than newly authorised medicines in their first indication.

MANY HTA BODIES CONSIDER OR REFERENCE OTHER INTERNATIONAL HTA BODIES AS WELL

When asked about other influential HTA bodies, the most mentioned was Canadian Agency for Drugs and Technologies in Health (CADTH). The Scottish Medicines Consortium (SMC), France's Haute Autorité de santé (HAS), Germany's Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) and Australia's Pharmaceutical Benefits Advisory Committee (PBAC) were also mentioned.

NEGATIVE NICE DECISIONS HAVE MORE IMPACT THAN POSITIVE DECISIONS.

Interviewees from Italy, Sweden, and Brazil said that a negative decision could impact price negotiations. Interviewees from Italy, Sweden, Poland, and Brazil said that technical issues in the economic evaluations flagged by NICE might lead to further scrutiny from other HTA bodies. In South Korea, a not recommended decision was perceived to have a negative impact on HIRA even when the treatment ICER was under the South Korean cost-effectiveness threshold. The South Korean and Polish interviewees said that a positive decision had a smaller impact than a negative decision during the Likert questions.

3.2.3 Likert scale questions

On average, our interviewees tended to **agree** with the following statements:

- My country's HTA body considers the decisions of other HTA bodies in their decision-making process.
- NICE is an HTA methods and processes innovator.
- The development of my country's HTA body's methods and processes were/are influenced by NICE.
- Individual NICE decisions have an impact on my country's appraisal of the same drug-indication pair.
- A positive NICE decision increases the probability of a positive decision of my country's HTA body for the same drug-indication pair.
- A negative NICE decision increases the probability of a negative decision of my country's HTA body for the same drug-indication pair.
- A NICE decision is made – on average – faster than a decision by my country's HTA body.

On average, our interviewees were **neutral** about the following statements:

- Recent updates to NICE's methods and processes have had an impact on my country's HTA body.

- A managed access decision (i.e., Cancer Drugs Fund or a discount to list price, which may or may not include outcomes collection) increases the probability of my country's HTA body issuing a positive decision for the same drug indication.

On average, our interviewees tended to **disagree** with the following statement:

- Terminated NICE decisions (i.e., no submission made) increases the probability of a negative decision of my country's HTA body for the same drug indication.

3.2.4 Summary of qualitative results

Most interviewees indicated that their local HTA body would consider NICE's decisions when evaluating a medicine. However, the way and extent to which NICE influences HTA outcomes varied across countries, as seen in Table 2. Negative NICE decisions were perceived to have the biggest impact, sometimes making price negotiations more difficult. Some HTA bodies are not likely to wait for NICE's decisions, nor will they look at intermediate NICE documentation, except for HIRA in South Korea. For the most part, interviewees from the same country had similar views. However, external interviewees tended to think NICE had less influence on HTA decisions.

TABLE 2: OVERVIEW OF INSIGHTS EXTRACTED FROM INTERVIEWS

	Poland	South Korea	Italy	Japan	Sweden	Brazil	UAE	Saudi Arabia	Israel
Uses CEA/similar methodology	✓	✓	✓	✓	✓	✓	✗	✗	✗
Considers NICE as context/background	✓	✓	✗	✓	✓	✓	✓	✓	✓
Considers evidence submitted to or assumptions challenged by NICE	✗	✓	✓ (sub-population only)	✓	✗	✓	✓	✗	✗
NICE decision influences HTA/ price negotiation	✓	✗	✓	✗	✓	✗	✓	✗	✗
Local HTA recommendation is not binding	✓ (Minister of Health decides)	✗	✓ (Regional reimbursement)	✗	✓ (Regional reimbursement)	✗	N/A	N/A	N/A

4 Discussion

Using a combination of quantitative and qualitative research methods, this work confirms the position of NICE in the international HTA field. However, the way and extent to which NICE influences HTA outcomes in other countries vary and might be driven by a range of factors.

4.1 Implications of NICE optimised decisions

NICE optimised recommendations support the use of a medicine for a smaller group of patients than stated by the marketing authorisation, based on the findings of the appraisal relating to clinical and cost-effectiveness in different patient groups. The option for NICE to 'optimise' recommendations offers a route to treatment access for sub-groups of patients for whom a medicine offers a clinically- and cost-effective alternative to current practice in cases where this is not the case for the full patient population (determined by the licensed use and the scope of NICE's appraisal). NICE includes optimised recommendations in their reporting of positive recommendations, stating that 84% of their recommendations are positive (NICE, 2023d). However, the level of patient access associated with optimised recommendations is unclear. Previous OHE research has shown that between 2015 and 2019, on average, only 39% of the patient population potentially eligible for treatment was recommended via optimised decisions (Bulut, O'Neill and Cole, 2020).

While optimised decisions offer a valuable route for patient access in cases where treatment for the full population may not be cost-effective, given that optimised decisions were coded as positive in our quantitative analysis, the relatively low proportion of patients recommended for treatment via optimised decisions may explain some of our more counterintuitive results. For example, we found that optimised NICE decisions were associated with negative decisions in other countries and that positive (recommended and optimised) decisions first issued by NICE were significantly correlated with negative decisions in other countries. These findings may be partly explained by the average level of patient access recommended by NICE and the lack of a similar 'recommendation for a patient subgroup' decision outcome in other countries. Binary decision outcomes may not be nuanced enough to capture cost-effective subpopulations, thereby denying therapy to some individuals for whom there may be an economic case for offering treatment.

4.2 Possible mechanisms for NICE's influence

NICE was one of the first HTA bodies established, adopting cost-effectiveness evaluations to inform their decision-making and setting an explicit cost-effectiveness threshold range. Many regard NICE as setting the scene for the use of cost-effectiveness in Europe and further afield.

Since its establishment, NICE has highlighted the importance of transparency and accountability in its decision-making processes. Its guide to methods and recommendations for health technologies have been publicly available on its website, allowing for all stakeholders to observe, assimilate and potentially draw on their processes.

Within our sample, NICE is a relatively fast decision maker and issues their decision on average 347 days after EMA issued regulatory approval. This result is in line with findings by others that found a median time of 329 days across all products between 2018 and 2021 (Newton et al., 2023) and 288 – 386 days between 2017 and 2021 (CIRS, 2022), respectively.

From the qualitative interviews, we heard that some HTA bodies with fewer resources or less experience compared to NICE might look to at NICE's interpretation and review of company evidence to help critique the evidence submitted to the local HTA body.

With various tools at their disposal (modifiers, patient access schemes, CDF, etc.), NICE committees often reach a positive decision. Thus, in circumstances where a negative decision is made, other HTA bodies may be more inclined to scrutinise evidence or use this as leverage to demand a lower price.

UK universities, predominantly York and Sheffield, are widely thought of as the birthplace of health economics as a discipline. Over the past 50 years or so, people from all over the world have trained as health economists in the UK, meaning they are familiar with NICE's methods and processes. Many of these people have been part of establishing and refining HTA bodies globally, perhaps implicitly being influenced by NICE.

Another potential mechanism for NICE's impact that was not explored in this study is its advisory service through NICE International for health organisations outside the UK seeking support for developing or advancing local HTA and guideline programmes. This service has mostly been made available in low and middle-income countries, and to the best of our knowledge, Brazil is the only country considered in this report to have utilised NICE International's services. So, whilst its impact may not have been detected specifically in this report, there are likely to be many countries with less developed HTA bodies for which there is considerable impact. Indeed, NICE has recently served as a strategic technical partner to Cyprus' Health Insurance Organisation to facilitate the contextualisation and adaption of NICE guidelines for use in the country as an alternative to developing their own (NICE, 2021). They have also recently supported the establishment of HTA processes in Egypt and further developed HTA in Denmark.

In addition to the work of NICE International, we are also seeing an appetite for HTA collaborations in various capacities across the world that might strengthen NICE's prominent role. For example, NICE, CADTH and the Institute for Clinical and Economic Review (ICER) in the USA recently announced that they are changing the way confidential information about health technologies is handled to streamline processes and increase transparency (NICE, 2023c). Another example is the collaboration by agencies from three continents announced in 2022 to collaborate to identify solutions to common challenges (NICE, 2022b). More recently, NICE has announced that it is engaging with another group of HTA agencies to develop guidance on the use of surrogate outcomes and explores offering related to joint scientific advice (NICE, 2023b). Overall, these collaborations offer opportunities where NICE can play an important role and impact other countries' HTA, particularly those that work within the quality-adjusted life year (QALY) paradigm.

However, other collaboration efforts might take the influence of NICE in the opposite direction. The new EU HTA regulation could decrease the role that NICE may play in the future in the European area. The Joint Clinical Assessment (JCA) and the EUnetHTA-21 do not include the UK, and they will shape HTA methods and processes in European countries after its implementation, expected to be in 2025 (European Commission, 2023; EUnetHTA, 2021).

More research on how to increase the efficiency of current HTA processes is needed, assessing whether it should come from collaborative efforts, joint assessments, and/or adaptation of evidence generated in or for other geographical contexts. With respect to quantitative analyses of the impact of one set of HTA decisions in different jurisdictions, further research can be done to build a large dataset capturing multiple countries and allowing for robust statistical analyses.

4.3 Limitations

The limitations of the quantitative work are related to the small sample size of DIPs and the fact that many countries only appraised a subset of these. The dataset of NICE decisions was also heavily biased towards positive decisions and positive decisions with restrictions, which did not fully allow us to explore the international impact of a negative NICE decision. Finally, selection bias may arise due to the focus on oncology and orphan medicines and the exclusion of those countries that issued their decisions on average before NICE.

There is a high risk of confounding stemming from a relatively large number of DIPs without an HTA decision in many of the analysed countries. For example, a negative NICE decision outcome was associated with no HTA being performed in other countries. Reasons for such an outcome could include that HTA agencies may not see it as worthwhile to conduct an HTA on a DIP that was rejected by NICE. However, this may also reflect companies' internal launch strategies and timings.

The number of interviews was also limited; hence, insights presented in the qualitative analysis may not wholly represent the reality of each country's HTA body or reimbursement system. In countries where we conducted both a manufacturer and decision-maker/academic interview, there was good agreement in terms of comparability of the local HTA body and NICE, and only in a couple of cases, were interviewees not fully aligned.

Given the wide variety of countries considered in this research, there are significant differences in regulatory, HTA, and reimbursement processes across countries and regions. As such, our mapping in the quantitative work may not be fully representative of these differences. Our qualitative work attempted to explore the differences in local HTA methods and processes compared to NICE, but these were not exhaustive and probably are not fully reflective of appraisal processes in practice.

On a similar note, the transferability of HTA decisions across jurisdictions is likely to be limited. HTA decisions, along with the supporting cost-effectiveness evidence, should not be used without due consideration of the different parameters, such as costs and contextual factors. Fontrier, Visintin, and Kanavos consider the difference between the *assessment* of clinical and economic evidence and the *appraisal* of this evidence in the context of the health system and consider the HTA bodies' social value judgement (2021). The assessment part includes the development of the economic model, which needs to reflect the characteristics of the local health systems and the way the condition is treated; therefore, the incremental cost-effectiveness ratio developed for one country is not necessarily relevant in a different context. Countries might also have a different ability or willingness to pay for health which can inform the cost-effectiveness benchmark used to reach decisions. The appraisal stage leads to decisions that reflect the national needs and values, and therefore, decisions are likely to vary somewhat. However, in countries that have newly developed or developing HTA bodies, capacity and capability constraints may lead to more guidance from or reliance on more advanced HTA systems. For a more detailed review of the transferability of HTA, see Heupink et al. (2022).

5 Conclusions

NICE historically has been seen as a leading HTA agency and as a methods innovator. Most countries consider a NICE decision when evaluating a medicine. However, the extent to which this influences a country's own decision varies. Negative NICE decisions have a bigger impact than positive ones, as they can increase the scrutiny applied to other HTA agencies' submissions and lead to downward pressures on price during negotiations rather than influence the HTA decision outcome as such. Within Brazil, Poland, and South Korea, NICE decisions and related outputs seem to have more impact. However, specific aspects of the appraisal (e.g., population considered, model structure) matter more than the decision outcome itself.

While the quantitative results do not prove causality and are based on a small sample size, they indicate that terminated appraisals and negative decisions issued by NICE are associated with no HTA being conducted in other countries; positive NICE decisions are associated with positive outcomes in other countries; and NICE's optimised decisions are associated with negative outcomes in other countries. Quantitative analyses suggest that NICE decision outcomes might be particularly influential on HTA outcomes within Poland, South Korea, Italy, and Sweden.

We conclude that getting a positive recommendation from NICE is important as it has spill-over effects on HTA processes and, ultimately, access to new medicines in other countries. However, these effects vary by country and are less driven by individual decision outcomes. For some countries, influence stems rather from underlying factors, such as the perception of NICE as a methods innovator, NICE's decision speed, the accessibility of NICE's outputs, and the impact of UK educational institutions on international decision-makers.

In the future, the impact of NICE in the international HTA policy field might change. On the one hand, its impact might increase in methods development within the agencies which rely on cost-effectiveness analysis outside the European Union (such as Canada and Australia) because of the increased appetite for international collaborations. On the other hand, it might decrease the processes and methods applied in European countries following the implementation of JCA. More research on how to increase the efficiency of HTA processes across borders (particularly in terms of their sequence and transferability) and capacity building might be beneficial.

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