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NAVIGATING CHANGE

How Have HTA Agencies Evolved Their Methods Over Time?

CONTRACT RESEARCH REPORT
APRIL 2024

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CONTRACT RESEARCH

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Executive Summary

Health Technology Assessment (HTA) plays an important role in informing the use and reimbursement of health technologies in several countries. Navigating and staying up to date with the changes in methods and processes in HTA, within and between jurisdictions, can be a challenge. Nevertheless, geographical variations in HTA policy have a significant impact on patient access to new interventions.

This report explores the breadth of variation in past and current positioning of HTA agencies on five key methodological topics: discount rates, modifiers, patient involvement, real-world evidence, and surrogate endpoints.

We investigated 14 HTA agencies across four continents, including ACE (Singapore), AIFA (Italy), AEMPS (Spain), CADTH (Canada), CDE (Taiwan), DMC (Denmark), HAS (France), INFARMED (Portugal), IQWiG (Germany), KCE (Belgium), NICE (England), PBAC (Australia), TLV (Sweden), and ZIN (The Netherlands).

We pinpointed the factors propelling reforms in methods and processes (M&P) as "drivers" and classified them into three overarching themes: stakeholders, country-specific context, and cross-border context. The drivers framework, based on the results from the literature review and validated through expert interviews, aims to cover all the enablers that may trigger a review of the M&P or lead to the implementation of changes.

KEY INSIGHTS

- **Geographical variation** in Health Technology Assessment (HTA) policy can have a significant impact on patient access to new interventions. This report focuses on **five key topics** (discount rates, modifiers, patient involvement, real world evidence, and surrogate endpoints) in a set of HTA agencies in Europe, Asia-Pacific, and North America.
- HTA agencies' approach with regards to the topics investigated have **become more explicit** over time, since their establishment or since 2010 (which was the cut-off point of our literature review). However, some HTA agencies have not yet introduced explicit guidelines on all the considered topics.
- The **shifts in the position** of the HTA agencies vis-à-vis the five key topics show an increasing **adaptability** and **pragmatism** in evaluating new treatments, with variation among agencies.
- However, methods guidelines remain **heterogenous**, highlighting a lack of harmonisation among HTA agencies leading to variations in evidence requirements from different stakeholders.
- **International collaboration** represents a useful route to accelerate HTA reforms through consideration of methodological challenges at an **early stage** and development of consistent approaches to address them. These alliances could facilitate timely changes and **consistency** of HTA methods, which could benefit all stakeholders and improve outcomes for patients.

DISCOUNT RATES

Discount rates

- HTA typically involves economic evaluation analysing costs and health outcomes which occur at different points in time after treatment.
- Costs and health outcomes are usually valued differently when predicted to occur in the future, because there is a desire to enjoy benefits now rather than in the future.
- This is reflected in the discount rate that is used to calculate the stream of costs and benefits accruing over the time horizon of the analysis.

We found that discount rates for the HTA agencies included in this study are spread over a range from 1.5% to 5%, with the majority of HTA agencies using a rate between 2.5% and 3.5%. Most HTA agencies have the same discount rate across costs, outcomes, and time horizons. However, some of them have different discount rates for costs and benefits, and for others, the discount rates decline with a longer time horizon (DMC, 2021; HAS, 2020a, p.20). The general trend over time across all HTA agencies leans towards using lower discount rates, which reflects a greater value placed on future outcomes compared to situations with high discount rates.

MODIFIERS

Modifiers

- Health gains can be valued differently depending on the characteristics of the disease or the patients accruing them.
- Modifiers can be used to capture this and, in effect, change the benchmark used to judge the value for money of new treatments.
- Countries have introduced quantitative and qualitative modifiers for treatments that they value highly, for example treatments for severe diseases and highly innovative treatments.

All HTA agencies included in this report appear to use some forms of modifiers in their decision-making to some extent, whether through an explicit framework or implicitly with an element of discretion. Formal frameworks utilised by HTA agencies have considered either qualitatively or quantitatively severity of the disease, unmet need, rarity, and end-of-life treatment. The general trend over time across most HTA agencies leans towards the consideration of more modifiers. This signifies a greater degree of flexibility in taking into account factors that are not included in the standard cost-effectiveness paradigm and an aim to address equity in resource allocation decisions.

PATIENT INVOLVEMENT

Patient involvement

- Patient involvement can ensure that perspectives and evidence not captured in clinical or economic analyses are considered in decision-making.
- Including patients can promote legitimacy, improving the HTA process.
- Patients may be included in the HTA process in different ways, from submitting evidence to participating in committee meetings.

In recent years, there has been an increasing trend for patient engagement in HTA as more agencies provide explicit guidance on processes for involvement and input into recommendations. While the majority of HTA agencies included in this report have an explicit stated position on patient

involvement, a few do not mention it at all in their guidelines. The general trend of increased patient involvement suggests that HTA agencies are gradually opening up to a more systematic consideration of the patient voice in decision-making.

REAL WORLD EVIDENCE

Real World Evidence

- RWE is evidence derived from real world data (RWD). RWD refers to the collection of data about patients' clinical outcomes in routine healthcare delivery.
- RWD is therefore collected outside of a controlled environment and may arise from observational studies, amongst other elicitation methods.
- RWD is useful for monitoring long-term health effects of interventions and measuring effectiveness amongst representative populations.

Most of the HTA agencies included in the study generally consider RWE within their guidelines, but the degree of acceptance differs. While some agencies encourage the use of RWE with the preference of local sources, others focus on RWE use in specific disease areas, such as oncology, and others only consider its use as a complement of randomised control trial (RCT) data (which remains the preferred source of evidence in HTA). The general trend over time across most HTA agencies, leans towards an increased consideration and level of detail given to existing considerations of RWE as evidence for HTA processes. Nevertheless, HTA agencies generally still lack clarity about which type of evidence can be used and when.

SURROGATE ENDPOINTS

Surrogate endpoints

- Surrogate endpoints, such as biomarkers, are considered intermediate endpoints intended to predict clinically meaningful endpoints such as mortality and quality of life.
- The use of surrogate endpoints by HTA agencies enable faster patients access to treatments; however, their use is controversial due to uncertainties associated with the link between the surrogate endpoint and the associated clinically meaningful endpoint.
- Validation of surrogate endpoints is key, but HTA agencies vary in their approach to using surrogate endpoints in HTA.

Nearly all HTA agencies included in this report accept, to some extent and under certain conditions, surrogate endpoints, with the caveat that final outcomes are preferred. The level of acceptance is heterogeneous across agencies, with various degrees of detail and clarity in their methodological guidance on the translation of surrogate endpoints to final outcomes and evidence requirement levels. The general trend over time across most HTA agencies, leans towards clearer guidelines for the consideration and acceptance of surrogate endpoints. This shift has major implications for patient access, providing alternative routes for evidence generation and enabling faster access to treatment.

Introduction

Background

Health Technology Assessment (HTA) plays an important role in informing the use and reimbursement of health technologies in several countries. '*HTA methods*' refers to how HTA should be conducted, and '*HTA process*' relates to the steps taken to complete the HTA of a new medicine. HTA methods and processes (M&P) are typically captured in guidelines documents produced by HTA agencies. M&P guidelines usually specify HTA agencies' recommendations or requirements around a number of diverse methodological topics, for example, which economic evaluation method is preferred, if and how future costs and outcomes are discounted to estimate their present value, which instrument is preferred to measure outcomes, and what is the degree of patient involvement into the HTA process.

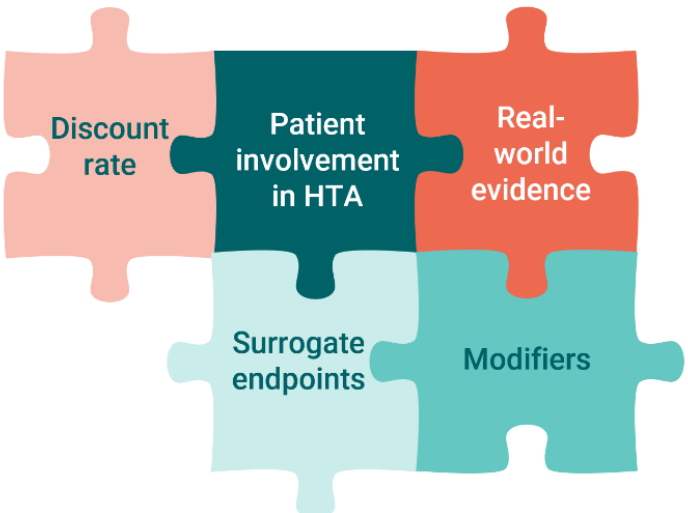
The *M&P guidelines employed* in each HTA, as well as *changes to them*, can wield considerable influence on recommendations on the use of new treatments and other health technologies made by HTA agencies, thus impacting patients, healthcare providers, the industry, and society at large. In particular, the *heterogeneity* in *topic-specific positioning* across countries has important implications for patients – with respect to different degrees of access to new medicines – and manufacturers – in terms of incentives in relation to R&D investments and evidence requirements. Finally, understanding the *drivers of M&P reforms* could provide additional nuance and reasoning for explaining agencies' positioning, as well as revealing opportunities for stakeholder involvement in shaping the evolution of the HTA landscape.

Despite the significance of all these factors, the evolution of M&P in HTA, both between and within jurisdictions over time, is a challenge to navigate – let alone stay up to date on.

Objectives

This report aims to understand the breadth of variation in past and current positioning between and within HTA agencies on the following key topics: discount rates, modifiers, patient involvement in HTA, real-world evidence (RWE), and surrogate endpoints (see Figure 1). These topics were selected by the authors as deemed dominant in recent HTA debates and expected to drive reforms in the future. We also explore the factors that may drive changes in HTA M&P and link them to topic-specific changes to guidelines across HTA agencies when relevant.

FIGURE 1 KEY TOPICS FOR CONSIDERATION



Methods

We combined information extracted from a targeted literature review with semi-structured interviews with HTA experts and used several analytical tools to structure and examine our findings. This section describes the main elements of information retrieval and analysis. Further information on the search protocol and methods can be found in Appendix 1: Methods.

Our research focused on the main HTA for pharmaceutical products, including medicines and vaccines[1], which starts when a product is selected for assessment and concludes with a recommendation on funding within the healthcare system. Other activities which may sometimes be carried out by HTA agencies, such as horizon scanning, were not included in the scope. We investigated 14 HTA agencies, listed in Box 1, and selected to include different geographies and a wide range of approaches.

BOX 1 FULL AND ABBREVIATED NAME AND LOGO OF HEALTH TECHNOLOGY AGENCIES OF COUNTRIES INCLUDED IN THE STUDY.

Logo	Acronym	HTA agency – full name	Country
	PBAC	Pharmaceutical Benefits Advisory Committee	Australia
	KCE	Belgian Health Care Knowledge	Belgium
	CADTH	Canadian Agency for Drugs and Technologies in Health	Canada
	DMC	Danish Medicines Council	Denmark
	NICE	National Institute for Health and Care Excellence	England
	HAS	Haute Autorité de Santé	France
	IQWiG	Institut fur Qualitat und Wirtschaftlichkeit im Gesundheitswesen	Germany
	AIFA	Agenzia Italiana del Farmaco	Italy
	INFARMED	National Authority of Medicines and Health Products	Portugal
	ACE	Agency for Care Effectiveness	Singapore
	AEMPS	Agencia Española de Medicamentos y Productos Sanitarios	Spain
	TLV	Dental and Pharmaceutical Benefits Agency	Sweden
	CDE	Centre for Drug Evaluation	Taiwan
	ZIN	National Health Care Institute	The Netherlands

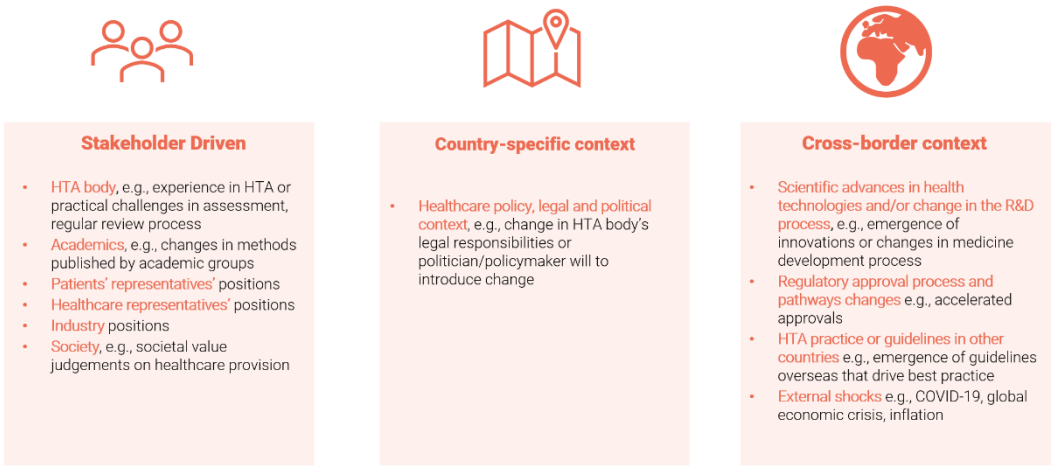
[1] *In some countries vaccines are considered by a separate organisation, such as the Joint Committee on Vaccination and Immunisation (JCVI) in the UK*

We first conducted a targeted literature review to identify relevant documents published by the HTA agencies of interest and secondary literature (i.e., relevant documents not published by HTA agencies). HTA bodies can have one set of guidelines discussing M&P together, separate documents for each, or additional documents pertaining to specific topics. The core literature review ran from January 2010 to April 2022 (for Australia, Canada, England, France, Germany, Italy and Spain) and to April 2023 (for Belgium, Denmark, Portugal, Singapore, Sweden, Taiwan and the Netherlands). Additional updates published between the end dates of the searches and September 2023 were identified on an ad hoc basis. The review was conducted in two stages. The first stage identified relevant documents relating to major changes in HTA M&P in general. In the second stage, we first identified information specific to changes in the five topics of interest in the documents retrieved and then carried out additional topic-specific searches.

We supplemented our literature review by interviewing HTA experts with direct experience with the HTA agencies of interest. We performed a total of 29 semi-structured expert interviews (two experts per agency and an additional expert from the EUnetHTA collaboration). These interviews served to validate our initial findings from the literature review and provided additional insights, both on historical and prospective motivations for these changes.

We analysed the data obtained from the literature search and interviews to pinpoint the factors propelling reforms in M&P. These *drivers* were then classified into three overarching themes: stakeholders, country-specific context, and cross-border context (see Figure 2). The stakeholders group includes HTA agencies, academics, patient representatives, healthcare professionals, industry, and society. The country-specific context refers to healthcare policy and the legal and political context. For the cross-border context, we highlighted the following drivers: scientific advances in health technologies and/or changes in the R&D process; regulatory approval process and pathways changes; HTA practices or guidelines in other countries; and external shocks.

FIGURE 2 DRIVERS FRAMEWORK



Findings from the literature review and interviews were analysed using the following techniques:

- *static graphics* representing the current positioning of each agency relative to each other (at the time that the study was conducted) with regard to each topic;
- HTA M&P *dynamic heatmaps* showing the evolution in positioning and drivers to change;
- topic-specific *timelines* summarising the positioning of the HTA agencies at the time when changes took place.

The dynamic heatmaps are hosted on a separate, interactive platform, which can be accessed through individual links found in the relevant sections, that only include snapshots of the maps. The topic-related timelines are shown in Appendix 2: Timelines.

HTA agencies' topic-specific positions and evolution

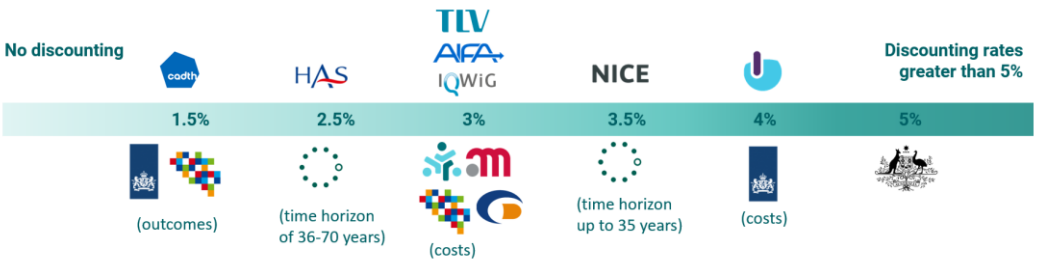
Discount rates

HTA typically involves economic evaluation that analyses costs and health outcomes that occur at different points in time after treatment. However, costs and health outcomes that are predicted to occur in the future are usually valued less than present costs because there is an opportunity cost to spending money now and a desire to enjoy benefits now rather than in the future. It is, therefore, widely acknowledged that cost-effectiveness results should be reflective of the present value associated with the stream of costs and benefits accruing over the time horizon of the analysis to account for this time preference.

Whilst the need to discount to present value is generally accepted in economic evaluation, there isn't a consensus on the rate to use and how to set it. Specific rates may vary between HTA agencies and within each agency over time. The higher the discount rate chosen, the less value is attached to costs and health outcomes in the future. As such, choices on discount rates significantly impact the outcomes of economic evaluations of interventions, particularly those where costs are expected to occur in the present and benefits to occur over a long period of time, such as in the case of gene therapy.

The discount rates indicated in guidelines published up to 2022 by each HTA agency are presented in Figure 3.

FIGURE 3 HTA AGENCY POSITIONS - DISCOUNT RATES

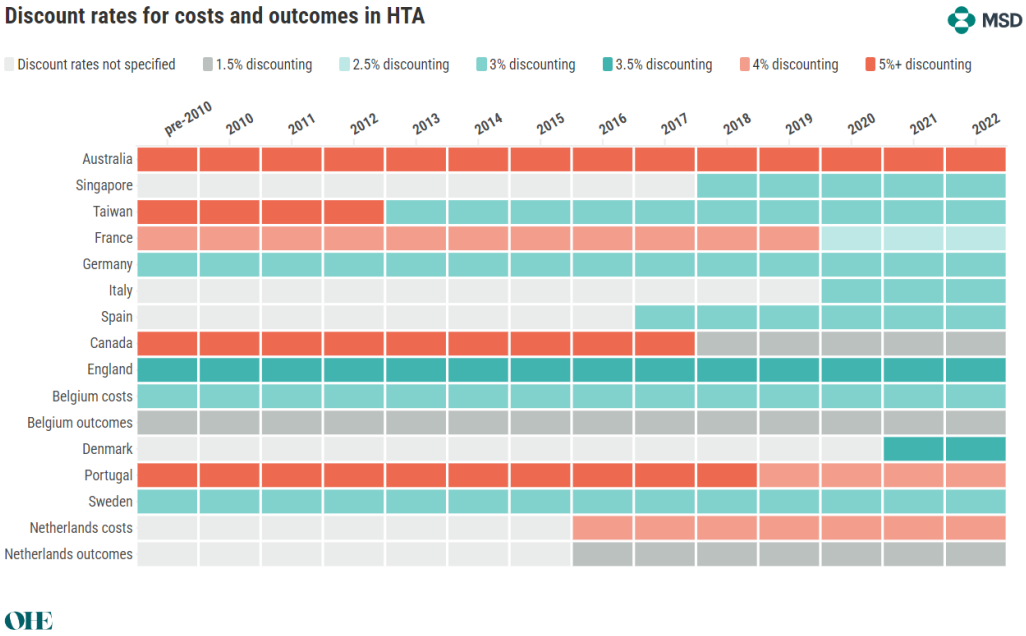


Discount rates for the HTA agencies are spread over a range from 1.5% (CADTH for both costs and outcomes; KCE and ZIN for outcomes only) to 5% (PBAC for both costs and outcomes), with a cluster of HTA agencies in-between (CADTH, 2022a; Cleemput and Neyt, 2012; National Health Care Institute, 2016). The majority of HTA agencies have discount rates falling within the range of 2.5% and 3.5%.

Most HTA agencies have the same discount rate across costs, outcomes, and time horizons. The exceptions are KCE and ZIN, with different discount rates for costs and benefits, and DMC and HAS, with a discount rate that declines with a longer time horizon (DMC, 2021; HAS, 2020a, p.20). For DMC, the choice of discount rates over time aligns with the prevailing rates applied to public sector investments in the country.

Figure 4 presents a snapshot of the dynamic heatmap created to showcase the evolution of the positioning for each agency over time. HTA agencies in five of the 14 countries (ACE, AIFA, AEMPS, DMC and ZIN) have explicitly adopted a discount rate since 2010, and four of the nine HTA agencies which had already specified their base-case discount rate by 2010 (CADTH, CDE, HAS, and INFARMED) have changed it since 2010. The general trend over time is to specify a discount rate in the HTA M&P guidelines and to set up the discount rate between 1.5% and 3.5%. This suggests that agencies have moved towards a greater degree of value placed on future outcomes. (ACE, 2021; AIFA, 2020a; AEMPS, 2013; CDE, 2013; IQWiG, 2020; TLV, 2017).

FIGURE 4 SNAPSHOT OF DYNAMIC HEATMAP – DISCOUNT RATES



The HTA agencies maintaining a discounting rate above 3.5% at the time of our analysis were PBAC (which is the only agency that maintained its rate at 5% since the period pre-2010), INFARMED and ZIN (cost). In the case of PBAC, potential changes to the discount rate are under discussion in the ongoing methods review. In Portugal, as an official discount rate for investment decisions with public funding is not in place, INFARMED's choice of a 4% discount rate followed "the practice of several European countries", also seeking to use the lowest public investment discount rate (INFARMED, 2019).

Reasons for reform to the discount rate were generally motivated by two main drivers: HTA practice in other countries (e.g., CADTH's choice of 1.5% in 2018) and the country-specific healthcare policy, political and legal context (e.g., DMC and HAS adjusting discount rates in line with other public sector investments). Additionally, the lowering of the discount rate to 4% in Portugal was influenced by stakeholders in industry and academia. Further details about drivers can be accessed in the dynamic heatmap at the following link: dynamic heatmap – discount rates.

Modifiers

Health gains can be valued differently depending on the characteristics of the disease or of the patients accruing them. Modifiers can be used to capture this and, in effect, change the benchmark used to judge the value for money of new treatments. Quantitative modifiers change the explicit cost-effectiveness threshold below which the incremental cost-effectiveness ratio (ICER) must fall and thus imply a direct change to the decision-making rule for reimbursement.

Agencies have introduced quantitative modifiers to increase cost-effectiveness thresholds for treatments that they value highly, such as treatments for severe diseases and innovative treatments. Qualitative modifiers, which may be considered during – and potentially change the outcome of – decision-making, have also been used for the same purpose. It is worth noting that while it is easy for HTA agencies to state that they consider a certain qualitative modifier, it is relatively difficult to determine whether it is applied in practice.

In this section, we consider modifiers which have been used to reflect the valuation of treatments for severe diseases (including treatments at the end-of-life), for rare diseases, for unmet need, and for innovative treatments. The current positioning of HTA agencies with respect to how much guidance they provide in relation to modifiers is presented in Figure 5.

FIGURE 5 HTA AGENCY POSITIONS - MODIFIERS

All HTA agencies appear to use modifiers in their decision-making, whether through an explicit framework or, as interviews revealed for CADTH, DMC, INFARMED, and TLV, implicitly with an element of discretion. Formal frameworks utilised by HTA agencies have considered either qualitatively or quantitatively severity, unmet need, rarity, innovative treatments and end-of-life.

Three agencies provide explicit guidance on more than three modifiers. PBAC's "rule of rescue" states that there are three factors which apply in exceptional circumstances that are particularly influential in favour of listing: lack of alternative treatment for the condition; if the condition is severe, progressive and expected to lead to premature death; and if the condition applies to only a very small number of patients (PBAC, 2006). In Spain, a Royal Decree in 2015 stated that the P&R decision should take into account criteria such as the severity of the disease, unmet needs, therapeutic and social value of the medicine, and degree of innovation of the medicine, among others (Ministerio de Sanidad, Servicios Sociales e Igualdad, 2015). NICE considers quantitative modifiers for severity (which replaced the previous end-of-life modifier) and can consider innovation in a qualitative fashion. Rarity[2] is also differentiated through NICE's highly specialised technology (HST) programme (NICE, 2022a).

[2] *Note that 'rarity' is not considered as a modifier in and of itself by NICE. There are several qualifying criteria for HST which do not directly relate to rarity, and only about half of rare disease treatments go thought HST.*

The agencies with guidance on two modifiers include ACE, AIFA, HAS and IQWiG. ACE established a rare-disease fund (RDF) in 2019 to support patients with rare diseases who require costly treatments. This was incorporated in the guidelines with a note including the consideration of severity as a modifier (ACE, 2021). AIFA's model for ranking the level of "therapeutic innovation" offered by a new drug states that lower quality evidence may be accepted for treatments for rare diseases (AIFA, 2018). For HAS, severity operates as a qualitative driver in the assessment of clinical benefit (Angelis A. et al., 2017). Regarding rarity, HAS and IQWiG operate a qualitative modifier – if a treatment for a rare disease has received marketing authorisation through the European Union's orphan designation, then HTA is not required if the budget impact is less than 50 million Euros annually (Heyes et al., 2018). Additionally, IQWiG incorporates additional provisions for rarity as a modifier within its guidelines (IQWiG, 2008).

The agencies considering only one modifier include CDE, DMC and ZIN. CDE highlights that the severity of the disease should be described in any submissions and that the lives of patients who meet "end-of-life considerations" can be given a higher weight (CDE, 2013). For DMC, the interviews revealed that disease severity and age-adjustments (especially in some paediatric or neurological indications) have been considered in previous submissions, although not explicitly included in the guidelines. A recent publication indicated that the Board of the Danish Regions gave the Council a mandate to take severity into account in a deliberative process rather than as a modifier (DMC, 2020). ZIN is one of few agencies that explicitly gives more weight to indications which treat patients who are more severely affected by conditions (Schurer et al., 2022). The severity of illness is captured through an individual's proportional shortfall in expected lifetime health, which is then used to adjust the acceptable cost of a QALY gain (Ministerie van Volksgezondheid, 2015).

FIGURE 6 SNAPSHOT OF DYNAMIC HEATMAP – MODIFIERS

For KCE, despite a lack of clear guidance, the interviews revealed that there have been specific dossiers where the commission's feedback to the company indicated that, for certain conditions

such as cancer, they might be willing to consider a higher cost-effectiveness threshold. In the case of TLV, interviewees highlighted that HTA is guided by the ethical platform, which includes a "need and solidarity" principle. This suggests that Swedish healthcare legislation allows priority to be given to those in highest need, suggesting an implicitly higher ICER for severity (TLV, 2022). Lastly, the Canadian government has committed to developing a national strategy for drugs for rare diseases starting in 2022, which may have implications for HTA (CADTH, 2022a).

Figure 6 presents a snapshot of the dynamic heatmap created to showcase the evolution of the positioning for each agency over time. Eight of the 14 HTA agencies (ACE, CDE, HAS, IQWiG, AEMPS, NICE, DMC and ZIN) have changed their position on modifiers since 2010. Each of these changes resulted in (additional) modifiers being explicitly considered in their guidelines.

The general trend over time across most HTA agencies is to move towards consideration of more modifiers. Our analysis did not identify any agencies which did not consider modifiers at all in 2022. Those that do not have clear guidance were found to have implicit considerations for severity (CADTH and KCE), rarity (INFARMED) and both severity and rarity (TLV). The trend of allowing for more flexibility for exceptional cases implies a positive outlook on reducing inequity in access to medicines for patients with certain diseases (severity, rarity, unmet needs).

We identified the following predominant drivers of changes to modifiers: the healthcare, political and legal context; HTA practice in other countries; the HTA agency itself; and society. NICE has influenced CDE through the latter's consideration of end-of-life, and in turn, has been influenced by ZIN's severity modifier approach (NICE, 2020). The agencies moving from no consideration to some consideration since 2010 include ACE, HAS and AEMPS. The degree of acceptance varies from providing guidance on one modifier (HAS), to two modifiers (ACE), to three+ modifiers (AEMPS). Other agencies are changing their position from a starting point of no formal guidance to including one modifier, such as CDE, DMC and ZIN. Some agencies maintain their position of considering modifiers in an implicit manner (CADTH, KCE, INFARMED, TLV), while PBAC and AIFA maintain their position of considering three+ and two modifiers, respectively. Lastly, NICE changed its position to consider three+ modifiers, compared to previously only considering two.

Patient involvement

Incorporating the patient voice into HTA can ensure that perspectives and evidence that may not be captured by clinical or economic analyses are considered in decision-making. In this sense, including patients can promote the legitimacy and credibility of the HTA process. Patients may be included in the HTA process in different ways, with the level of commitment for inclusion from HTA agencies varying, from submitting evidence relevant to treatments to participation in HTA decision-making meetings. For example, including patient organisations in the list of relevant stakeholders, inviting comments at various stages in the assessment process, including a patient representative on the decision-making committee, and including evidence from patients with the specific condition at committee meetings.

In our research, we identified changes in the existence and degrees of patient involvement as described in HTA M&P. The current positions of HTA agencies are presented in Figure 7.

FIGURE 7 HTA AGENCY POSITIONS - PATIENT INVOLVEMENT

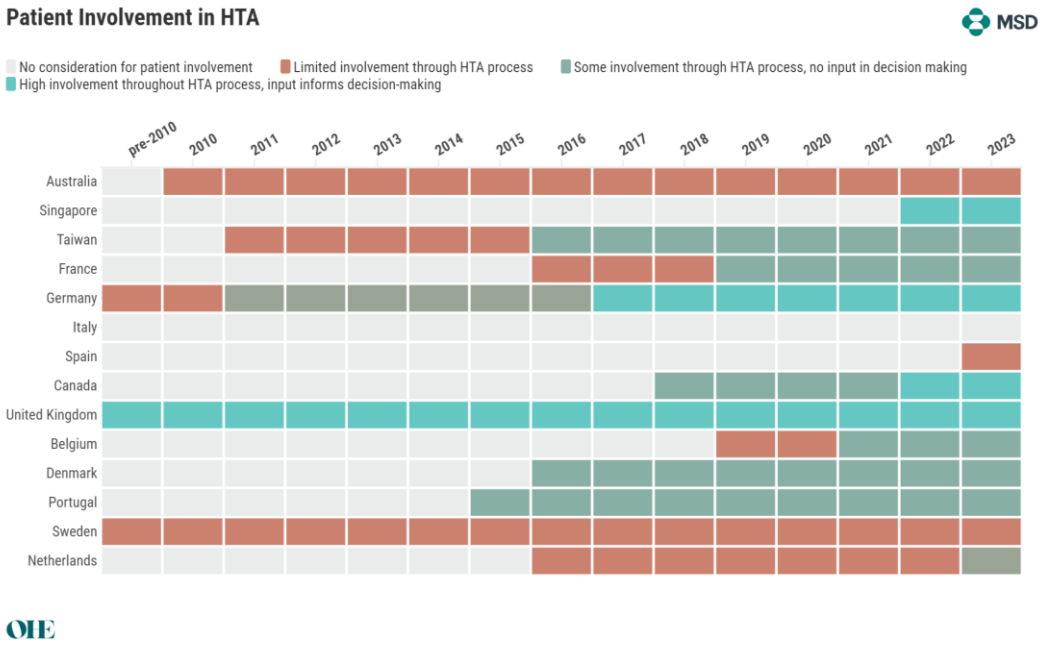
Recent years have seen an increasing trend for patient involvement in HTA and clarification of opportunities for engagement with ACE, CADTH, IQWiG and NICE. ACE has launched a consumer engagement and education (CEE) team to enhance patient, carer and public engagement in its work (ACE, 2022). CADTH, IQWiG and NICE provide multiple opportunities for patient engagement throughout the HTA process, with the possibility for patient input in decision-making (CADTH, 2020, 2022a; IQWiG, 2017; NICE, 2022a).

There are agencies with some involvement of patients, but that do not actively involve patients in the decision-making process. ZIN, KCE and CDE (National Health care Institute, 2023; KCE, 2019; Chen, Chang and Chang, 2018) have separate reports or position statements on opportunities for patient involvement at certain points in time but to a lesser extent of involvement than ACE, CADTH, IQWiG and NICE. INFARMED enables patient participation through a survey launched as part of an increasing inclusion project, and DMC includes patients as part of its expert committee (INFARMED, 2015). HAS collects contributions from patient associations via an online system and has made the involvement of patient advocates mandatory since 2017, in addition to declaring patient engagement as a priority in its 2019-24 Strategic Plan (Gesbert et al., 2021; HAS, 2020b).

While the majority of HTA agencies have an explicit stated position on patient involvement, AIFA, AEMPS, HAS, PBAC, and TLV do not mention patient involvement in their guidelines. Nonetheless, interviews revealed that PBAC and TLV are willing to take patient input into account. For AEMPS, a recent public consultation engendered the approval of a Royal Decree recommending that patients should be involved in the HTA process (Ministerio de Sanidad, 2023). AIFA provides no consideration for patient involvement within their guidelines.

Figure 8 presents a snapshot of the dynamic heatmap created to showcase the evolution of the positioning for each agency over time. Six of the 14 HTA agencies (CDE, HAS, IQWiG, CADTH, KCE and ZIN) have evolved their position on patient involvement since 2010, and nine agencies (ACE, AEMPS, CADTH, CDE, DMC, HAS, INFARMED, KCE, PBAC, ZIN) have moved from no consideration of patient involvement in guidelines to clarification of their position or implementing informal opportunities that were revealed through the interviews. Each of these changes resulted in additional guidance on patient involvement.

FIGURE 8 SNAPSHOT OF DYNAMIC HEATMAP – PATIENT INVOLVEMENT



The general trend over time across most HTA agencies leans towards more acceptance and inclusion of patient involvement either explicitly within guidelines or implicitly in less formal processes. In 2016 and 2019, respectively, CDE and KCE published new patient involvement guidelines, and in 2023, ZIN clarified that patients are consulted at the start of the HTA process to identify the outcomes that are most important to them and following the assessment to develop additional documents (Yang, 2017; KCE, 2019). This suggests that HTA agencies are opening up to the idea of involving patients in the process, and some of them even consider giving patients a voice in decision-making. AIFA is an exception to this in the sense that it has no explicitly stated position in its guidelines on patient involvement and the interviews did not uncover any implicit or historic consideration either.

In relation to drivers, our research found that HTA guidelines and practices in other countries have been key drivers of changes to patient involvement in HTA. As such, it is not surprising to see that more established HTA agencies such as NICE, CADTH and IQWiG have detailed guidance around patient involvement. This trend suggests a positive move towards increased inclusion of patients in HTA, which benefits patients and has the potential to improve relevant outcomes for them.

Real-world evidence

Real-world evidence (RWE) is evidence derived from real-world data (RWD). RWD refers to the collection of data about patients' clinical outcomes in the course of routine healthcare delivery. RWD is therefore collected outside of a controlled environment such as a clinical trial and may arise from observational studies, amongst other elicitation methods.

RWD is useful for monitoring the long-term health effects of interventions and measuring effectiveness amongst representative populations and given real-world practice. However, there are also challenges associated with RWE, including biases arising from data quality and lack of randomisation. RWE may supplement the evidence supplied by clinical trials or used instead of clinical trial data, depending on the HTA agency and intervention assessed.

RWE is considered by most HTA agencies (see Figure 9). Although not described in the literature, the interviews revealed that PBAC generally accepts RWE while emphasising the need to reflect the uncertainty associated with it in the price of the intervention. Similarly, KCE guidelines state that the results of the model should be logically consistent with real-life observations and data, and allow for the inclusion of real-world costs if secondary cost data are used (Cleemput and Neyt, 2012).

FIGURE 9 HTA AGENCY POSITIONS - RWE

While the rest of the HTA agencies generally consider RWE within their guidelines, the degree of acceptance differs. IQWiG notes a preference for randomised control trials (RCTs) and consideration of RWE only when RCT data is not available (IQWiG, 2008). In the case of CDE, while not explicitly referred to in the guidelines, RWE has previously informed the re-assessment of funding decisions and price adjustments (Besley et al., 2023).

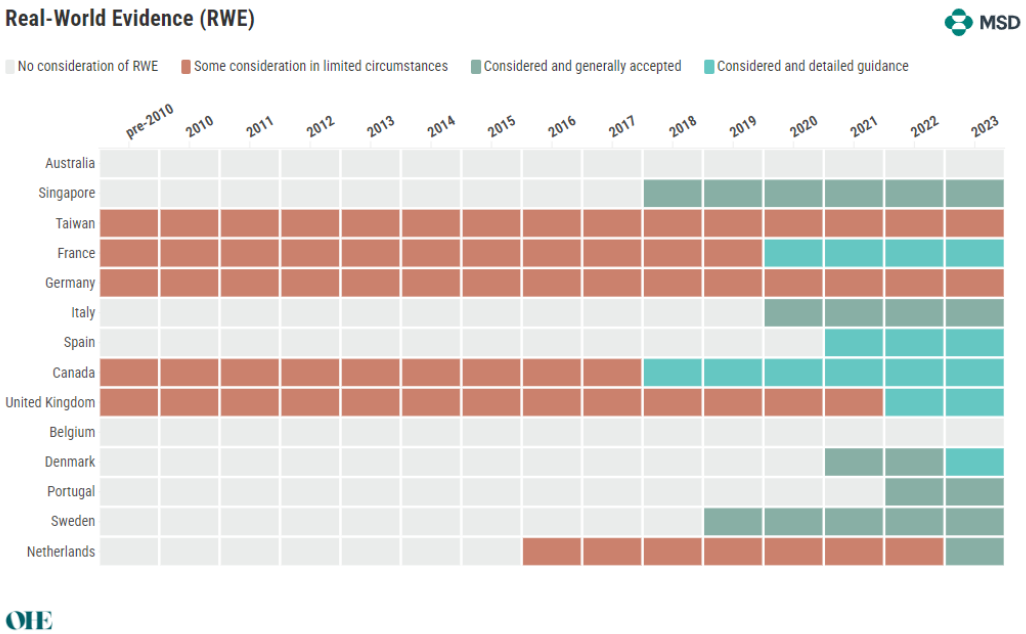
Several HTA agencies consider and generally welcome the use of RWE, but their guidelines provide limited detail or guidance. AIFA encourages the use of RWE with a preference for local sources (AIFA, 2018), and TLV focuses on RWE use in oncology (TLV, 2019, 2021). INFARMED and ZIN encourage the use of RWE as a complement of randomised control trial (RCT) data (which is the preferred source of evidence in HTA), and ACE recommends a careful study design to mitigate bias (National Health Care Institute, 2016; ACE, 2021).

Since 2022, explicit guidance on RWE in HTA has been published by DMC, NICE, and CADTH, outlining the methodology for reporting and including it in submissions (DMC, 2023; NICE, 2022b; CADTH, 2023). Furthermore, CADTH and AEMPS have post-marketing surveillance study programmes to collect data on real-world safety and effectiveness (CADTH, 2022b; Serrano-Aguilar et al., 2019). In the case of HAS, its guidelines state that RWD can be utilised, particularly in cases where there is a request to re-register or extend the indication within the same therapeutic area, with

a preference for the use of French sources in the measurement of resources consumed to produce or acquire the intervention being assessed (HAS, 2020a).

Figure 10 presents a snapshot of the dynamic heatmap created to showcase the evolution of the positioning for each agency over time. Five of the 14 HTA agencies (HAS, CADTH, NICE, DMC and ZIN) have changed their position on RWE since 2010, with an additional five agencies clarifying their stance on RWE after previously not having considered it in their guidelines (ACE, AIFA, AEMPS, INFARMED and TLV). Each of these changes resulted in the introduction of more detailed guidelines on RWE. Only PBAC and KCE do not mention RWE in relation to clinical evidence in their guidelines.

FIGURE 10 SNAPSHOT OF DYNAMIC HEATMAP – RWE



The general trend over time across most HTA agencies leans towards an increased consideration and level of detail given to acceptance of RWE as evidence for HTA evaluations. From 2018 onwards, every agency that published initial positions on RWE has been more open to considering and generally accepting RWE (ACE, AIFA, DMC, INFARMED and TLV). Nevertheless, HTA agencies generally still lack clarity about which type of evidence can be used and when.

The drivers of changes to RWE M&P have been identified as the HTA agency itself, HTA practice in other countries, legal and political context, and industry. The breadth of driving forces across stakeholders, borders and country-specific factors is unsurprising, given that RWE is a topic of concern for all stakeholders and as the digital infrastructure for RWD collection continues to develop. Furthermore, international organisations, including ISPOR and EUnetHTA, have recently provided guidance on RWE use (EUnetHTA, 2022; ISPOR, 2023), which could influence the positioning of the countries involved. EUnetHTA highlights the need for the control of confounding biases when estimating treatment effectiveness, while ISPOR focuses on transparency of research design and process and ensuring quality of characteristics and data relevancy when using RWE in research. There is overlap in these organisations' favourable outlook on RWE use in research, providing full transparency and accountability from researchers.

Surrogate endpoints

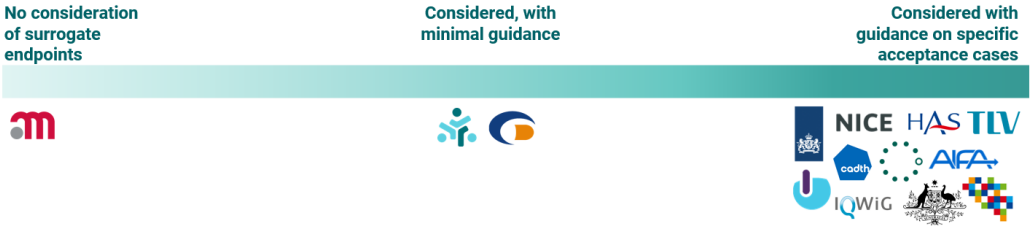
Surrogate endpoints, such as biomarkers, are considered intermediate endpoints intended to predict clinically meaningful outcomes such as mortality and quality of life. Disease areas with a strong tradition of surrogate endpoints include oncology (e.g., tumour response for overall survival) and cardiovascular disease (e.g., blood pressure for cardiovascular mortality or morbidity). When used as primary outcomes, surrogate endpoints enable clinical trials to have a smaller sample size, shorter duration, and lower cost than trials with a final primary endpoint.

The acceptance of surrogate endpoints by HTA agencies can result in faster patient access to treatments; however, their use is controversial due to uncertainties associated with the link between the surrogate endpoint and the clinically meaningful final outcome. As such, validation of surrogate endpoints is key. HTA agencies vary in their approach to consider and accept surrogate endpoints in their processes.

As of 2023, all HTA agencies, except for AEMPS, accept to some extent and under certain conditions surrogate endpoints with the caveat that final outcomes are preferred (See Figure 11). Note that the GENESIS guideline used by AEMPS includes examples of scenarios where surrogate endpoints are used, but it does not provide any guidance or specification (Grigore B. et al., 2020).

The level of acceptance in the use of surrogate endpoints varies across agencies, with some agencies providing only minimal methodological guidance on the translation of surrogate endpoints to final outcomes and evidence requirement levels (ACE and CDE). ACE stipulates that evaluations should ideally be based on studies that "report clinically important, patient-relevant outcome measures" (ACE, 2021), while CDE guidelines highlight that surrogate endpoints of clinical trials should be linked to end results in the development of the economic model (CDE, 2013).

FIGURE 11 HTA AGENCY POSITIONS - SURROGATE ENDPOINTS



The majority of HTA agencies consider surrogate endpoints only in specific instances, providing reasonable levels of guidance for these cases. It is generally accepted that final outcomes are the preferred measure for all HTA agencies; however, it is also commonly understood that these may not always be available. In these cases, HTA agencies require clear justification for the validity of the surrogate endpoints and their association with the final outcomes. Most HTA agencies also require that any uncertainty generated by using a surrogate endpoint should be explored in sensitivity analyses. Furthermore, some agencies specify that in cases where surrogate endpoints have been used, a scenario analysis should be conducted to evaluate the uncertainty surrounding final outcomes (AIFA, 2020b; CADTH, 2018; Grigore B. et al., 2020).

Figure 12 presents a snapshot of the dynamic heatmap created to showcase the evolution of the positioning for each agency over time. Six of the 14 HTA agencies (PBAC, IQWG, CADTH, NICE, INFARMED and ZIN) have changed their position on the acceptance of surrogate endpoints since 2010, and six agencies have introduced guidance on their consideration for surrogate endpoints (ACE, HAS, AIFA, DMC, INFARMED and ZIN). Each of these changes resulted in more detailed guidelines on the acceptance of surrogate endpoints.

FIGURE 12 SNAPSHOT OF DYNAMIC HEATMAP – SURROGATE ENDPOINTS

The general trend over time across most HTA agencies, leans towards clearer guidelines for the acceptance of surrogate endpoints. This shift has major implications for patient access, providing alternative or additional routes for evidence generation with potential faster access to treatments.

PBAC has undergone major changes relating to its consideration of surrogate endpoints. The expert interviews suggested that the reason for this was that PBAC was striving to provide greater clarity in their guidelines to encourage standardisation in reporting surrogate endpoints. This was due to increased variation in the quality of methods used by companies in relation to extrapolation regarding surrogate endpoints. IQWiG's update in guidelines has been to soften its language by stating that valid surrogate endpoints may be considered in the evaluation of the benefits and harms of interventions (IQWIG, 2006). For INFARMED, the interviews suggested that the agency has changed its position on surrogate endpoints to give more weight to final outcomes, likely as part of a movement towards patient-centred care that prioritises outcomes with a tangible impact on patient's quality of life rather than intermediate laboratory-measured outcomes.

The main drivers of reform relating to surrogate endpoints are the HTA agency itself and HTA practices in other countries. The use of surrogate endpoints has become more relevant in recent years. Therefore, an inward drive to change, influenced by the external HTA environment, can explain the motivation behind changes in perspective for accepting surrogate endpoints.

Discussion and Conclusion

This report highlights similarities and discrepancies between the positioning of several HTA agencies on the following key topics: discount rate, modifiers, patient involvement in HTA, real-world evidence and surrogate endpoints.

General trends showed that HTA agencies' positions with regard to the topics investigated have become clearer over time. This was generally achieved by introducing new guidelines on specific topics, clarifying existing ones, or publishing additional separate documents pertaining to the agency's positioning on the topic. Furthermore, the direction of change is generally oriented towards more flexibility in evidence acceptance. The latest reforms have involved an increased number of modifiers included in decision-making and clearer guidance for the consideration of RWE and surrogate endpoints.

In the case of discount rates, there is a general downward trend for agencies starting with a higher rate and consistency across those agencies with a rate between 2.5% and 3.5%. This signifies a move towards placing greater value on future outcomes. However, some HTA agencies have not yet introduced explicit guidelines on topics such as patient involvement, RWE and surrogate endpoints. This has the potential to increase the difficulty of navigating evidence requirements for manufacturers and prolong submission times.

Although observed over a relatively long period of time, these shifts in attitude from HTA agencies vis-à-vis the five key topics show an increased adaptability and pragmatism. As a result, increased acceptance within topics such as RWE and surrogate endpoints can enable faster patient access.

Nevertheless, the current heterogeneity between countries' guidelines highlights the lack of international harmonisation of HTA guidelines and the presence of national barriers to the introduction of new reforms and methodological changes. This could create challenges and delays in access. In addition, our report did not investigate how and to what extent existing methods guidelines are applied in decision-making in practice, i.e. how committees use them to reach a recommendation on use or reimbursement status for new interventions. Further research should explore the level of consistency in applying published guidelines by HTA agencies and their committees, and measure the impact of key method reforms on patient access and other metrics.

Our research has a number of limitations. First, some HTA M&P changes may not be published or referred to in academic, peer-reviewed journals. We attempted to fill these informational gaps through the interviews. Second, only English-language publications were included in the first review. To overcome this limitation, a number of documents written in non-English that were identified as relevant were professionally translated into English. Additionally, as we exclusively focused on published methods guidelines, our analysis could not capture agencies' practice in interpreting clinical data (such as their attitude to surrogate endpoints and RWE). Finally, our sample of countries covers four continents, but it does not explore other relevant geographies such as the United States or Latin America. Further research is encouraged to broaden our comparison and explore changes in M&P and drivers to those changes in a wider setting.

International collaborations (such as the recent one between HTA agencies in Australia, Canada, and the UK (NICE, 2023), the Nordic collaboration, FINOSE (FINOSE, 2023) and the European Network for HTA (EUnetHTA)) represent a useful route to accelerate changes and ensure wide stakeholder engagement. These alliances could create cohesion and consistency between HTA guidelines and provide international leadership in methods change. This could be beneficial for those agencies with limited or no guidance in certain topics; however, to what extent potential reforms can be implemented depends on the interaction with existing legislative and political factors in each country.

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Appendix

Appendix 1: Methods

Research methodology

We employed two separate methodologies to achieve our objective: a targeted literature review and semi-structured expert interviews. These techniques were combined to analyse the results using several tools described in the next section.

Our research focused on the core HTA for pharmaceutical products, including medicines and vaccines, which starts when a product is selected for assessment and concludes with a recommendation on funding within the healthcare system. Other activities that may sometimes be carried out by HTA agencies, including horizon scanning and pricing, were not included in the scope.

Besides HTA M&P changes, we focused our analysis on five topics: discount rates, modifiers, patient involvement in HTA, real-world evidence (RWE), and surrogate endpoints. We considered these HTA topics particularly important in the recent HTA debate and deemed them as representative of documenting a comprehensive set of changes over time.

We conducted a targeted literature review to identify relevant documents published by the HTA agencies of interest and secondary literature (relevant documents not published by HTA agencies). This part aimed to understand how HTA M&P has changed over time, the process for these changes, and their drivers. The pragmatic search of HTA agency websites and bibliographic databases was conducted in two stages. The first stage identified relevant documents published by the HTA agencies of interest and secondary literature relating to major changes in HTA M&P in general. In the second stage, we identified information specific to changes in the five topics of interest. Data was extracted on the timing of key M&P changes, qualitative descriptions of the policy changes and the agency's positions on topics, drivers of reform, and references to other HTA agencies in the guidelines.

We supplemented our literature review with interviews of HTA experts with direct experience with the HTA agencies of interest. We performed a total of 29 semi-structured expert interviews (two experts per agency and an additional expert from the EUnetHTA collaboration). These interviews served to validate the results of our literature review. They also sought to provide additional insights, both prospectively and historically, into motivations for and constraints to M&P reforms within HTA agencies; HTA agencies' appetite for change in relation to M&P introduced by other HTA agencies; and the challenges to HTA M&P raised and debated in the research and policy community.

Analysis techniques

The literature review and the interviews were combined to analyse the results employing the following techniques: (i) production of static graphic representing the current positioning of each agency with regards to the specific topics; (ii) production of static timelines of position changes of each agency with regards to the specific topics; (iii) production of HTA M&P dynamic heatmaps that show the frequency, chronology, and intensity of the changes implemented for each agency with regards to the specific topics.

Relative positioning of HTA agencies

For each topic, we provide a static graphical representation of the breadth of positions currently held by each agency based on their most recent M&P guidelines. It is important to note that the scales presented do not classify the positions in order of desirability or innovativeness, as the definition of these terms can vary depending on the perspective taken. The relative positioning of HTA agencies on the topics is not intended to be comparative or to express a value judgement about the different agencies and/or markets.

Static timelines

The static positions described in the preceding section represent HTA agencies' positions at one snapshot in time at the point of developing this report. We developed a series of static timelines based on the findings from the literature search and interview responses depicting key timepoints at which HTA M&P reforms were implemented on a particular topic or where the position of the topic was made explicit in M&P documents. Where interviews suggest that the HTA body holds an implicit stance on a topic, this is marked on the timeline, not anchored to a specific date.

Several countries have revisited their stance on a topic. Therefore, the entry on the timeline represents a step-change in the HTA M&P approach. For other instances, entries may simply reflect a clarification or confirmation of the HTA body's stance on the topic from a previously implicit stance or continuation of a stance outlined in a previous guideline iteration. Please note that distances between entries on the timeline are not to scale.

Dynamic heatmaps

The dynamic heatmaps represent the evolution of HTA agencies' positions over time from 2010 to the point of developing this report. The heatmaps depict squares relating to the position of the HTA body in a given year, shaded in a colour that broadly reflects the openness or flexibility of the topic of interest. The exception is the heatmap for discount rates, in which the entry colour reflects numerical values.

Several countries have revisited their stance on a topic. Therefore, a change in colour represents a step-change in the HTA M&P approach. For other instances, the colour may not change, but the entry may simply reflect a clarification or confirmation of the HTA body's stance on the topic from a previously implicit stance or continuation of a stance outlined in a previous guideline iteration.

Literature review and interview protocol

Two methodologies were employed to achieve the objectives listed in the main text.

First, we conducted a targeted literature review to identify relevant documents published by the HTA agencies of interest and secondary literature (relevant documents not published by HTA agencies). This part aimed to understand how HTA M&P has changed over time, the process for these changes, and their drivers.

Second, we supplemented our literature review with interviews of HTA experts with direct experience with the HTA agencies of interest. These interviews served to validate the results of our literature review. They also sought to provide additional insights into motivations for and constraints to M&P reforms within HTA agencies (both prospectively and historically); HTA agencies' appetite for change in relation to M&P introduced by other HTA agencies; and the challenges to HTA M&P raised and debated in the research and policy community (both prospectively and historically).

The literature review and the interviews were combined to analyse the results.

As well as general HTA M&P changes, we explored changes around specific topics in HTA M&P over time. The following topics were prioritised:
- Discount rates
- Modifiers
- Patient involvement in HTA
- Real World Evidence (RWE)
- Surrogate endpoints

We tailored the pragmatic conceptual break-down in PICOTS/PEO/PICAR structures to accommodate our specific research objectives. Our framework is shown in phase 1 Table 1. Note that different searches were performed, excluding some of the items listed in 'Key Content'.

Search strategies and main results

The countries in scope were searched at two different timepoints, referred to as Phase 1 (relating to Australia, Canada, England, France, Germany, Italy and Spain) and Phase 2 (Belgium, Denmark, Portugal, Singapore, Sweden, Taiwan, and the Netherlands).

For each phase, two different pragmatic searches were performed. A first literature search identified the major changes in general HTA M&P over time. We defined major changes as changes that result in new processes or decision frameworks that would impact the decision outcomes or timelines (whereas minor changes were defined as the incremental tweaks to M&P that are unlikely to impact the outcome). A second literature search targeted changes around specific topics of interest (see 'Key Content' in Table 1). This second search also aimed to retrieve literature on the main drivers of HTA-related M&P changes. The identification of the main drivers was completed with a posterior analysis of the relevant documents.

First search: major changes in HTA M&P over time

The first search was based on the following search techniques: web searching, hand searching, and a tailored list of databases. We identified the websites relevant to each country's HTA agency (see Table 3) and directly browsed the websites of useful organisations. We used direct search, with input from the ISPOR website section 'Pharmacoeconomic Guidelines Around the World'.

A pragmatic search was conducted using Embase and Econlit through the OVID platform. Search terms were defined using a combination of Medical Subject Heading (MeSH) terms and single keywords associated with the area ('Intervention') and topics of interest ('Key Content'), and countries of interest ('Population'), following the structure in Table 1. When applicable, wildcards (i.e., characters such as * or $ used in a search term to represent one or more other characters) were used to increase the sensitivity to various forms or spellings of search terms.

Screening protocol

After the removal of duplicate citations, titles and abstracts of publications identified were screened by a single researcher for inclusion against agreed criteria with a random sample being screened by two researchers to ensure consistency with the inclusion/exclusion criteria. Any discrepancies were discussed. Full papers of potentially relevant studies identified in the first pass were obtained and screened by two researchers, again using the inclusion criteria as a reference. Reasons for exclusion were recorded during full-text review.

Since changes in HTA M&P dated after April 2022 (for Australia, Canada, England, France, Germany, Italy, Spain) or after April 2023 (for Belgium, Denmark, Portugal, Singapore, Sweden, Taiwan, and the Netherlands) were not retrieved as part of a systematic review, some currently available information may not be reflected in the report.

PHASE 1

TABLE 1 SEARCH STRATEGY (FIRST SEARCH)

Dimension/Item	Search command	Search [#]
Population	(Europ* OR Canada OR Canadian OR Australia OR Australian OR England OR English OR British OR United Kingdom OR France OR French OR Germany or German OR Spain OR Spanish OR Italy OR Italian) .ti,ab.	75
Intervention	AND (((health technology assessment) OR pharmacoeconomic) adj2 (guideline* OR manual* OR guidebook)).ti,ab.	
Key content	n/a *	

*#: number of documents retrieved, removing duplicates; *: no search command has been added*

FIGURE 13 PRISMA DIAGRAM OF RESULTS FROM FIRST SEARCH

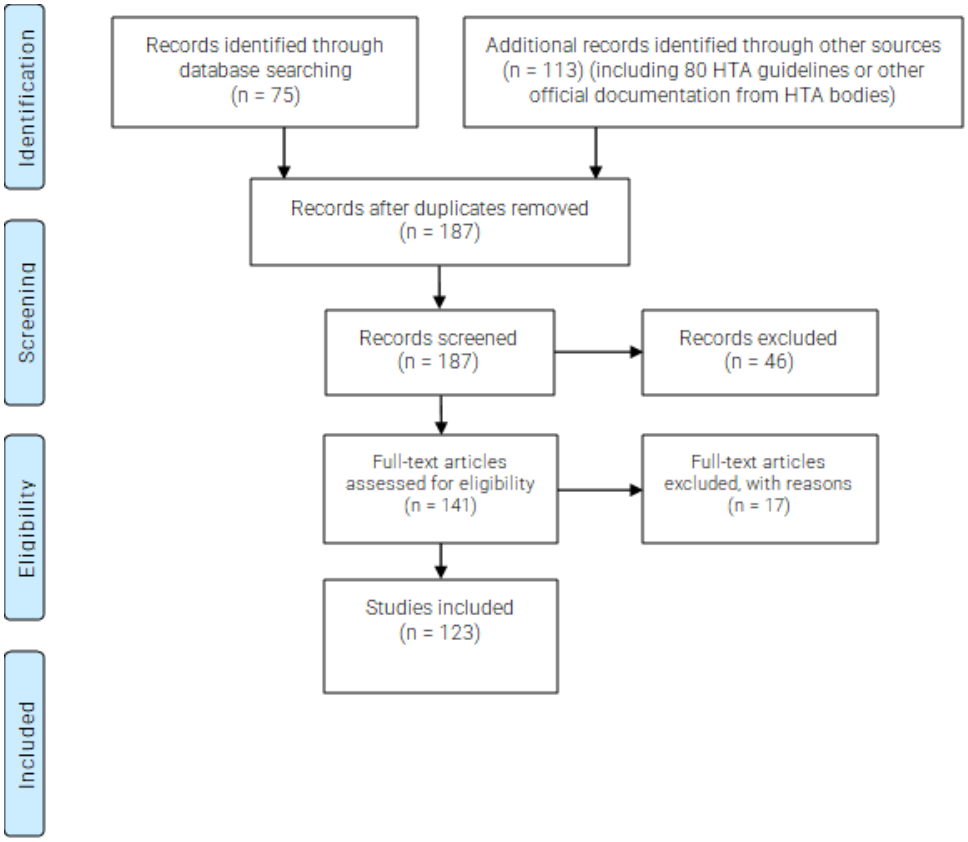


TABLE 2 SEARCH STRATEGY (SECOND SEARCH)

Dimension/Item	Search command	Search [#]
Population	(Europ* OR Canada OR Canadian OR Australia OR Australian OR England OR English OR British OR United Kingdom OR France OR French OR Germany or German OR Spain OR Spanish OR Italy OR Italian) .ti,ab	559
Intervention	AND ((health technology OR pharmacoeconomic) adj2 (assessment OR institution* OR agenc* OR agency OR agencies OR expert* OR organi*ation* OR institute* OR guideline OR manual OR decree* OR policy OR regulation* OR rule*)) .ti,ab AND ((evolution OR changes OR new OR update* OR novel OR innovat* OR latest OR recent)).ti,ab	
Key content		
General	n/a *	(66)
RWE	AND (Real-world evidence OR RWE).ti,ab	
Surrogate endpoints	AND (surrogate* OR novel*).ti,ab AND (endpoint*).ti,ab	
Severity, end of life, innovation and rare disease modifiers	AND (modifier* OR severe OR severity OR end of life OR end-of-life OR innov* OR rare OR rarity OR orphan OR highly specialised OR highly specialised).ti,ab	
Discounting	AND (discount*).ti,ab	
Assessment of additional indications	AND (additional indication* OR multi-indication)ti,ab	
Patient involvement in HTA	AND ((patient*) adj2(expert* OR representativ* OR group* OR input* OR involvement)).ti,ab	
HTA remit	AND (remit* OR scope* OR mandate*).ti,ab	
Implementation of a simplified HTA procedure	AND (procedure* OR process* OR method*) adj2 (simplif* OR streamlin* OR condens* OR consolidat* OR integrat*).ti,ab	

FIGURE 14 PRISMA DIAGRAM OF RESULTS FROM THE SECOND SEARCH

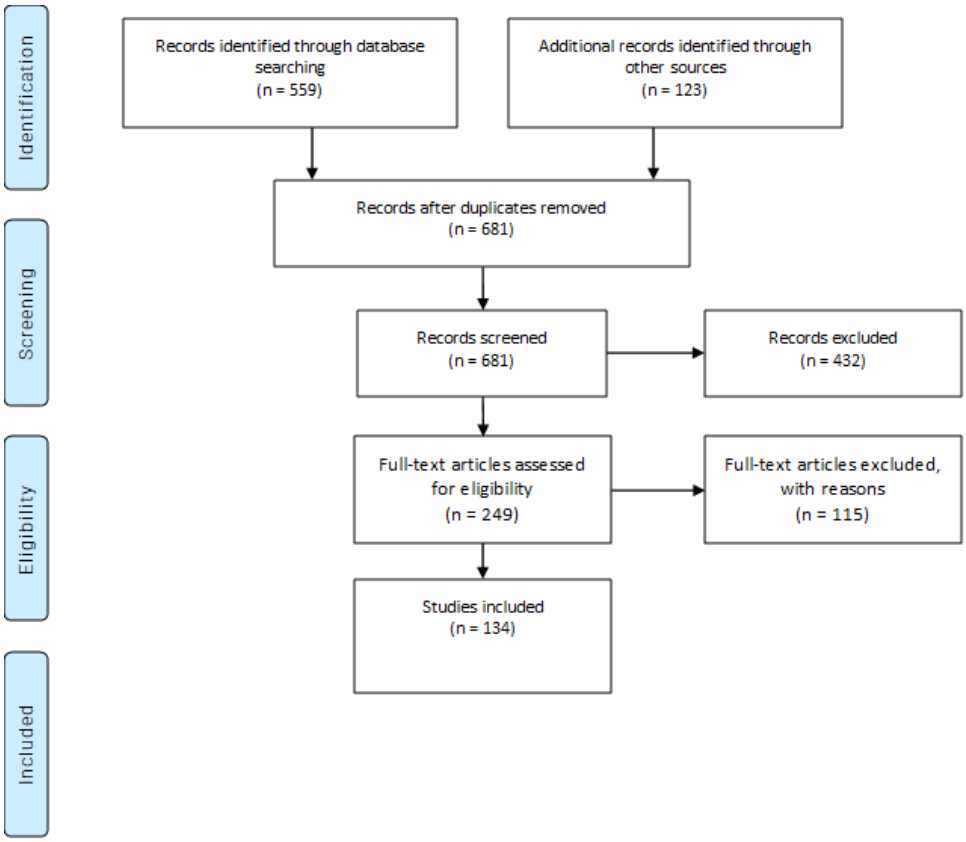


TABLE 3 COUNTRY SPECIFIC GUIDELINES AND COMPLEMENTARY SOURCES

Most relevant literature (Official HTA guidelines)		
	Official HTA guidelines	Other relevant documents from the website of the HTA agency
Australia	(PBAC, 2016a) (PBAC, 2013) (PBAC, 2008) (PBAC, 2006) (PBAC, 2002) (PBAC, 2000) (PBAC, 1995)	(Australian Government Department of Health, 2021a) (Australian Government Department of Health, 2021c) (Australian Government Department of Health, 2021d) (Australian Government Department of Health, 2021b) (Australian Government Department of Health, 2019) (Australian Government Department of Health, 2011) (Australian Government Department of Health, 2009)

		(PBAC, 2016b)
Canada	(CADTH, 2020) (CADTH, 2018c) (CADTH, 2006) (CADTH, 1997)	(CADTH, 2021) (CADTH, 2018b) (CADTH, 2018a) (CADTH, 2018d) (CADTH, 2017a) (CADTH, 2017b) (PMPRB, 2021)
England	(NICE, 2022c) (NICE, 2019) (NICE, 2018a) (NICE, 2018b) (NICE, 2017a) (NICE, 2017b) (NICE, 2016a) (NICE, 2014) (NICE, 2013a) (NICE, 2013b) (NICE, 2011) (NICE, 2009a) (NICE, 2009b) (NICE, 2009c) (NICE, 2008a) (NICE, 2006) (NICE, 2004) (NICE, 2001)	(NICE, 2022a) (NICE, 2022b) (NICE, 2022e) (NICE, 2022f) (NICE, 2021a) (NICE, 2021b) (NICE, 2020a) (NICE, 2020b) (NICE, 2016b) (NICE, 2009a) (NICE, 2008b) (NICE DSU, 2022) (NICE DSU, 2013) (DHSC and NICE, 2018)
France	(HAS, 2022). (HAS, 2020a) (HAS, 2020b) (HAS, 2012)	(HAS, 2019) (HAS, 2014)
Germany	(IQWiG, 2022) (IQWiG, 2020) (IQWiG, 2017) (IQWiG, 2015) (IQWiG, 2013) (IQWiG, 2011) (IQWiG, 2009) (IQWiG, 2008) (IQWIG, 2006) (IQWIG, 2005)	(Gemeinsamer Bundesausschuss, n.d.).
Italy	(AIFA, 2020b) (AIFA, 2018)	
Spain	(AEMPS, 2013)	(RedETs, 2016) (Puig-Junoy et al., 2014)
Secondary literature		
(Allen et al., 2017) (Angelis, Lange and Kanavos, 2018) (Balijepalli C. et al., 2019) (Bossi et al., 2020) (Charlton, 2020) (Dawoud et al., 2022) (Earnshaw and Lewis, 2008)		

(EUnetHTA, 2017)
(Favaretti et al., 2009)
(Fortinguerra et al., 2020)
(Fricke and Dauben, 2009)
(Goel, Mahajan and Chatterjee, 2020)
(Granados et al., 2000)
(Grigore B. et al., 2020)
(Hailey, 2009)
(Hofmann et al., 2021)
(Kim, Byrnes and Goodall, 2021)
(Kleijnen et al., 2016)
(Komakoma and Yi, 2022)
(Kristensen et al., 2019)
(López-Bastida et al., 2010)
(Menon and Stafinski, 2009)
(Miot and Thiede, 2017)
(Mostardt et al., 2014)
(Paris and Belloni, 2013)
(Ramsey et al., 2005)
(Ruof et al., 2014)
(Serrano-Aguilar et al., 2019)
(Skedgel, 2016)
(Sorenson, Drummond and Kanavos, 2008)
(Tarricone et al., 2021)
(Taylor and Weston, 2016)
(The Access Delivery Partnership, 2017)
(Toumi et al., 2017)
(Ubago Pérez et al., 2017)
(Wang et al., 2020)
(Ward et al., 2022)
(Zechmeister-Koss I., Schnell-Inderst P., and Zauner G., 2014)
(Zhang and Garau, 2020)
(Zhou et al., 2022)
(Zisis K., Naoum P., and Athanasakis K., 2021)

PHASE 2

TABLE 4 SEARCH STRATEGY (FIRST SEARCH)

Dimension/Item	Search command	Search [#]
Population	(Taiwan OR Taiwanese OR Singapore OR Singaporean OR Netherlands OR Dutch OR The Netherlands OR Belgium OR Belgian OR Flemish OR Denmark OR Danish OR Portugal OR Portuguese OR Sweden OR Swedish).ti,ab.	36
Intervention	AND (((health technology assessment) OR pharmacoeconomic) adj2 (guideline* OR manual* OR guidebook)).ti,ab.	
Key content	n/a *	

*#: number of documents retrieved, removing duplicates; *: no search command has been added*

FIGURE 15 PRISMA DIAGRAM OF RESULTS FROM THE FIRST SEARCH

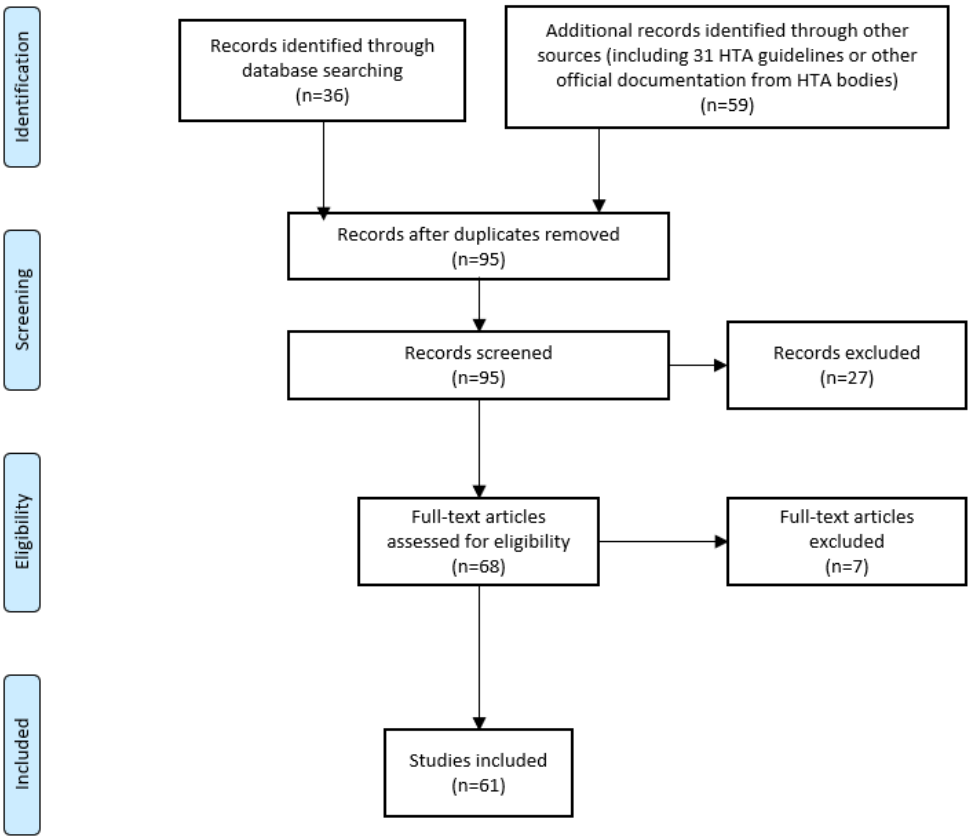


TABLE 5 SEARCH STRATEGY (SECOND SEARCH)

Dimension/Item	Search command	Search [#]
Population	(Taiwan or Taiwanese or Singapore or Singaporean or Netherlands or Dutch or The Netherlands or Belgium or Belgian or Flemish or Denmark or Danish or Portugal or Portuguese or Sweden or Swedish).ti,ab.	259
Intervention	AND ((evolution or changes or new or update* or novel or innovat* or latest or recent) and ((health technology or pharmacoeconomic) adj2 (assessment or institution* or agenc* or body or bodies or expert* or organisation* or institute* or guideline or manual or decree* or policy)) and (guideline* or manual* or decree* or policy or regulation* or rule*)).ti,ab	
Key content		
General	n/a *	(56)
RWE	AND (Real world evidence OR RWE OR real world evidence OR real life data OR real life evidence OR real-world data OR real world data OR RWD).ti,ab	
Surrogate endpoints	AND (surrogate) AND (endpoint OR endpoints OR outcome OR outcomes).ti,ab	
Severity, end of life, innovation and rare disease modifiers	AND (modifier* OR severe OR severity OR end of life OR end-of-life OR innov* OR rare OR rarity OR orphan OR highly specialised OR highly specialised).ti,ab	
Discounting	AND (discount*).ti,ab	
Assessment of additional indications	AND (additional indication* OR multi-indication OR multi indication).ti,ab	
Patient involvement in HTA	AND ((patient*) adj2(expert* OR representativ* OR group* OR input* OR involvement)).ti,ab	
HTA remit	AND (remit* OR scope* OR mandate*).ti,ab	
Implementation of a simplified HTA procedure	AND (procedure* OR process* OR method*) adj2 (simplif* OR streamlin* OR condens* OR consolidat* OR integrat*).ti,ab	

FIGURE 16 PRISMA DIAGRAM OF RESULTS FROM THE SECOND SEARCH

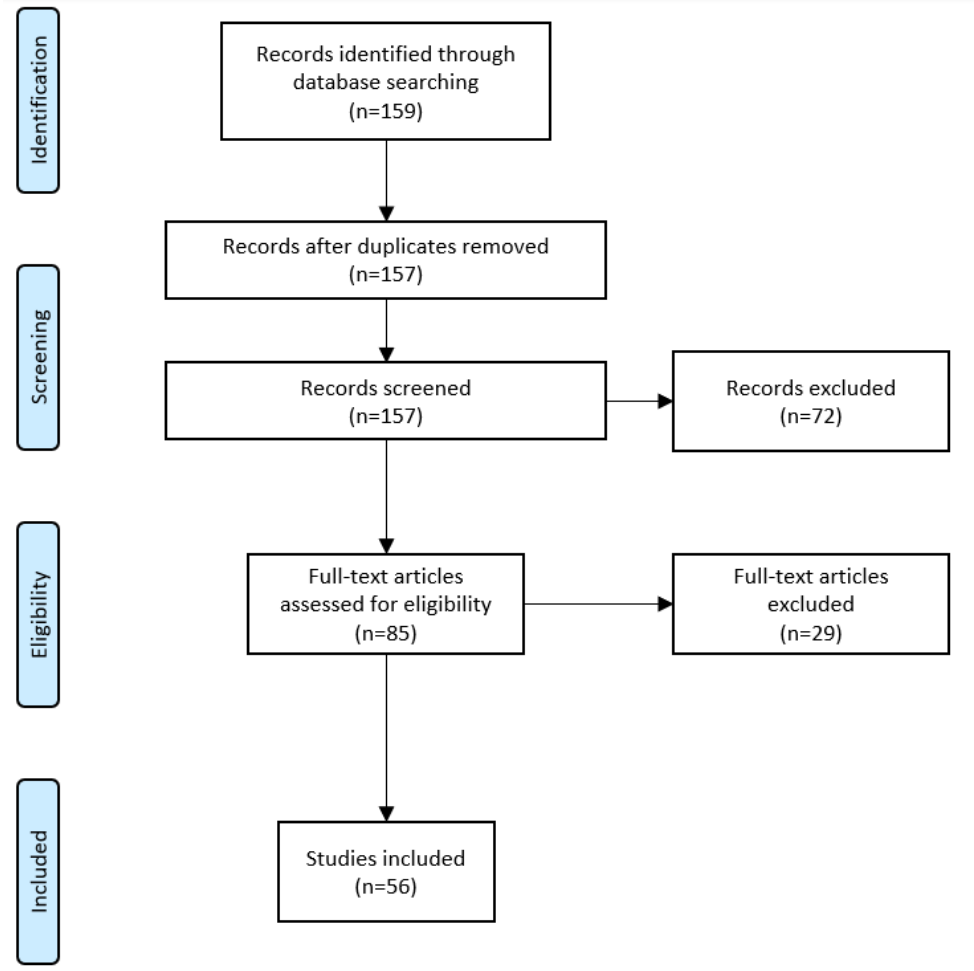


TABLE 6 COUNTRY SPECIFIC GUIDELINES AND COMPLEMENTARY SOURCES

Most relevant literature (Official HTA Guidelines)		
Country	Official HTA guidelines	Other relevant documents from the website of the HTA agency
Belgium	(Cleemput and Neyt, 2012) (Cleemput et al., 2008)	(KCE, 2022b) (KCE, 2019) (KCE, 2021) (KCE, 2022a)
Denmark	(DMC, 2021c, b; a)	(Om Medicinrådet, 2022) (Danish Medicines Council, 2022)

Portugal	(INFARMED, 1998, 2019)	N/A
Singapore	(ACE, 2021) (ACE, 2023)	(ACE, 2022b, a; c; d; e)
Sweden	(TLV, 2003, 2017)	(TLV, 2019)
Taiwan	(TaSPOR, 2006) (CDE, 2013)	(Centre for Drug Evaluation, Taiwan, 2022)
The Netherlands	(National Health Care Institute, 2016b, 2008)	(National Health Care Institute, 2018, 2016c; a)
Secondary literature		
(Chen, Chang and Chang, 2018) (Chen, Huang and Gau, 2022) (Chiu, Pwu and Gau, 2015) (Cleemput and Wilder, 2009) (Duke NUS, ACE and CoRE, 2021) (Enzing et al., 2021) (EUnetHTA, 2013) (Finansministeriet, 2021) (Heintz et al., 2014) (Hoomans T. et al., 2012) (Kao et al., 2019) (Lou et al., 2020) (Makady A. et al., 2017) (Ministerie van Volksgezondheid, 2015b) (NBHW, 2015) (Pearce et al., 2019) (Pereira et al., 2021) (PPRI, 2017) (Pwee, 2009) (Reckers-Droog, van Exel and Brouwer, 2018) (SBU, 2020) (Schurer et al., 2022) (Segar et al., 2021) (Shah et al., 2014) (Simões and Augusto, 2017) (Skedgel et al., 2022) (Tan, 2021) (Thiry et al., 2014) (Vandijck and Annemans, 2010) (WHO, 2015) (Yang, 2017)		

Interview guide: Understanding the processes and drivers of HTA reforms

Interview guide and background

Introduction

PROJECT BACKGROUND

Health Technology Assessment (HTA) is a multidisciplinary process that evaluates the properties and effects of a health technology to support healthcare decision-making. Increasingly, HTA agencies conduct their assessments according to explicit and formal methodology that stipulates which evidence should be provided and analysed, and how it should inform decisions. Some HTA agencies also have formal processes which define how the operational aspects of HTA – such as selecting technologies for assessment, timelines and milestones of the assessment, and stakeholders' involvement– should be conducted. HTA M&P are continually evolving, which poses challenges for manufacturers developing evidence in support of their submissions and for other stakeholders providing inputs to value assessments. HTA practices can have a significant impact on recommendations by HTA agencies and, therefore, affect patients, providers, industry, and society.

We are therefore undertaking a study aimed at understanding the triggers and sources that lead to reforms in M&P being adopted by HTA agencies. We define methods as the scientific approach used by HTA agencies to assess the effectiveness and cost-effectiveness of health technologies and the approach adopted by the decision committee to develop and reach a recommendation based on the evidence assessment (appraisal). We define processes as the operational practices used to undertake HTA assessments and appraisals.

Our focus is on the core value assessment process, which starts when a technology is selected for assessment and concludes with a recommendation on provision or decision on funding within the healthcare system. Not included in our scope are other activities which may sometimes be carried out by HTA agencies, including horizon scanning and pricing. Our focus is on M&P for HTA of pharmaceuticals; therefore, not in scope is HTA of other types of health technology such as vaccines, devices and diagnostics.

INTERVIEW OVERVIEW

We will be speaking to experts in HTA across a range of countries, including Australia, Canada, England, France, Germany, Italy, Spain, Singapore, Taiwan and pan-European.

The aim of these interviews is to:

Validate and fill in any gaps in our initial mapping of HTA changes over time.

Understand the motivations for and constraints to HTA reforms, both prospectively and historically.

Discuss the appetite for change of individual agencies in relation to HTA M&P and to challenges debated in the research and policy community, both prospectively and historically.

The semi-structured interview will last one hour and will be carried out virtually at a time of your convenience by two members of the OHE team. Questions will focus on your experience and understanding of HTA in your country.

You will receive a brief pre-read document in advance of the interview. The document will be used to facilitate the discussion on the relevant topics.

DATA COLLECTION AND MANAGEMENT

The interview will be recorded for research purposes only. You will be asked whether you are happy for the recording to begin before the recording starts. As well as the interviewer, there will be another member of the OHE team on the line to take notes.

The identity of the interviewees, the data from the recording, and the notes will not be shared outside of the OHE project team and will be stored in a secure folder that only the OHE project team have access to. The sponsor of the research is blinded to the identity of the interviewees. The data (transcripts, recordings, and notes taken by the notetaker) will not be shared with the sponsor of the research. When the project has been completed, the attributable recordings and the verbatim notes will be deleted. Only anonymised quotes will be used in the final report and will be identified only by country and area of expertise (i.e., specific job titles will not be used). Information provided by interviewees that could be used to identify their identity will not be included in the report.

Question outline

TABLE 7 QUESTIONNAIRE

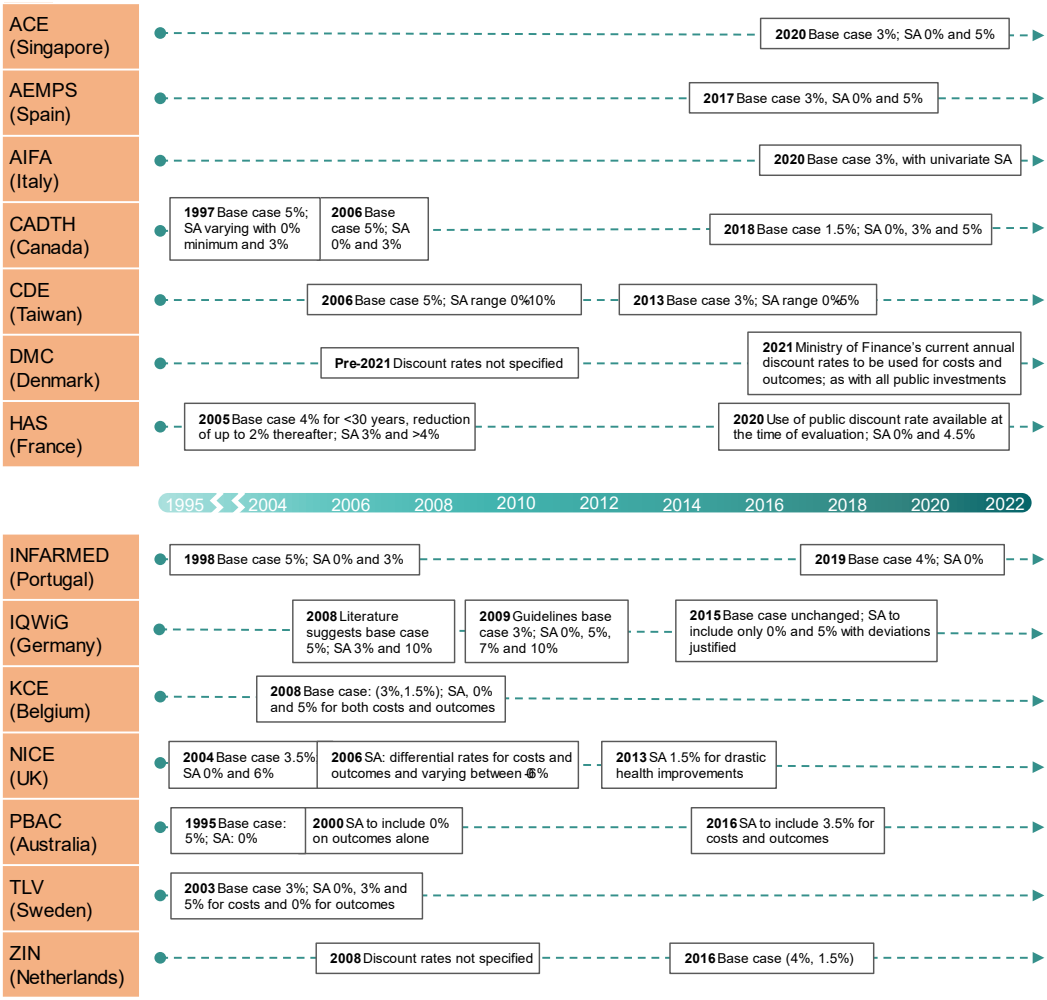
#	Question
Section 1: Introductions and background (5 minutes)	
Section 2: HTA reform process (20 minutes)	
1	Please refer to the draft process map in your pre-read. - How far does this capture the process for M&P reviews at your country's HTA agency? - Would you make any changes (in terms of indicated dates and method change)? If so, what are they? - Please provide any references or sources where possible. (These can be provided by email after the interview, and we will follow up with our requests). (Where there is uncertainty, date ranges may be useful.)
2	What are the key opportunities for industry throughout the HTA review process used at your country's HTA agency (from engagement to implementation of change)? What are the risks?
Section 3: Past and future HTA reforms (20 minutes)	
3	- Do you agree with the key method changes of your country's HTA agency that we indicate in our timelines slide of the pre-read? Are we missing any important ones? If so, what are they? - Out of the changes discussed, what were the ones with the most significant impact on HTA decisions? - Does the driver framework presented in slide 4 explain the changes discussed? Have we missed anything? Can you think of one HTA reform that has been considered but not implemented? Were there any barriers to the introduction of this change? If yes, what were they?
4	In your pre-read, we have highlighted some key drivers to specific topics within HTA methods. - Do you agree with the drivers we have pulled out from the literature? There are some missing drivers for some topics that we have highlighted in red, are you able to suggest them?

5	Are there any key HTA reforms on the horizon for your country's HTA agency? - If so, what are the attitudes within the organisation to these reforms? - Are there any other major challenges on the horizon for the agency?
Section 4: Culture relating to HTA reforms (5 minutes)	
6	How would you position your country's HTA agency in relation to leadership in HTA methods development? Why?
7	How would you position your country's HTA agency when it comes to initiating a new approach in HTA (HTA reforms)? Are you able to provide an example?
Section 5: HTA agencies influence (5 minutes)	
8	Which HTA agency/ies in your region and/or internationally do you perceive to be most proactive in implementing new approaches in HTA (HTA reforms)?
9	Which HTA agency/ies in your region and internationally do you perceive to be most influential for HTA reforms overall?
10	To what extent is your country's HTA agency influenced by the HTA debate internationally? To what extent is your country's HTA agency influenced by changes in other countries? Are HTA reforms by any specific HTA agencies particularly influential for your country's HTA?
Section 6: Wrap up (5 minutes)	
11	Are there any other thoughts you wish to share on this topic today?
12	Thank you for your participation. We will now develop a summary note of our discussions today and share this with you for your confirmation that we have accurately represented your views.

Appendix 2: Timelines

Discount rate

FIGURE 17 EVOLUTION OF HTA AGENCY POSITIONS OVER TIME - DISCOUNT RATES



Modifiers

FIGURE 18 EVOLUTION OF HTA AGENCY POSITIONS OVER TIME - MODIFIERS

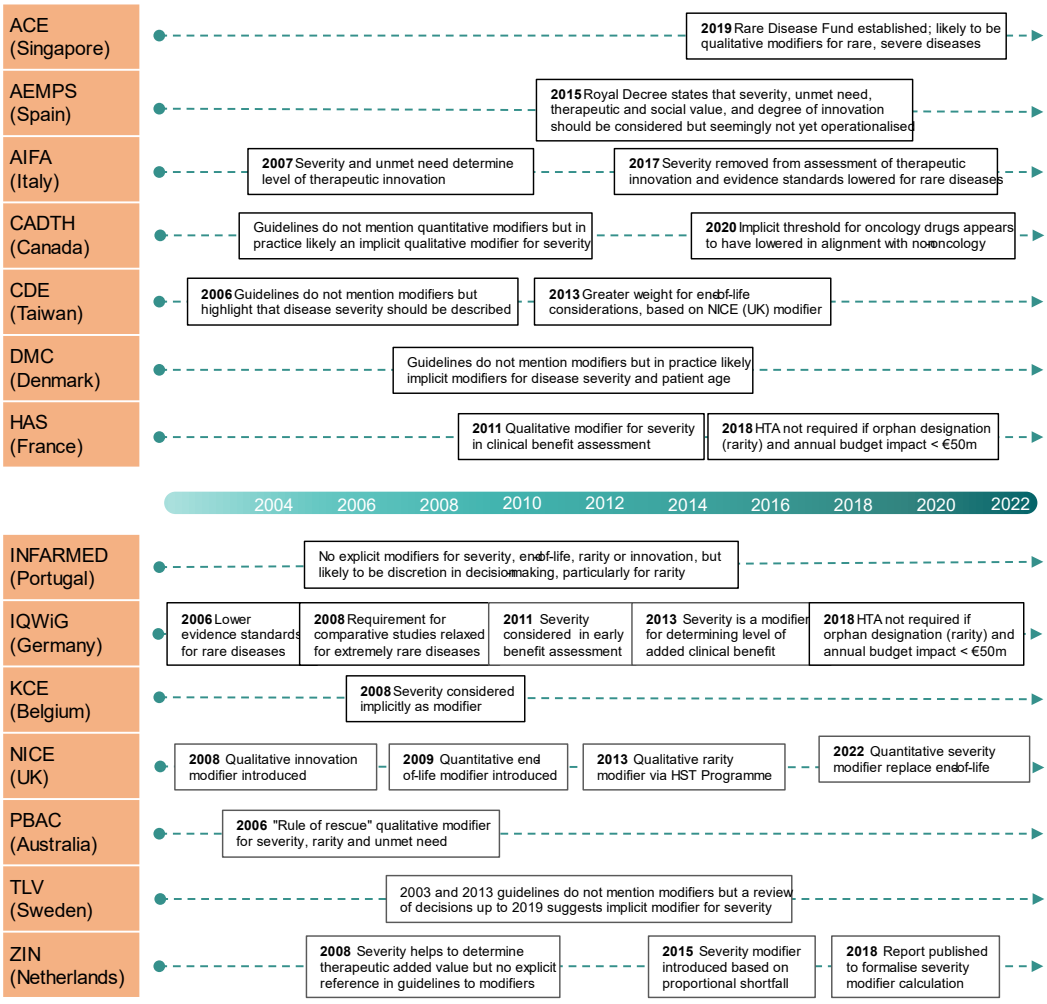


FIGURE 19 EVOLUTION OF HTA AGENCY POSITIONS OVER TIME - PATIENT INVOLVEMENT

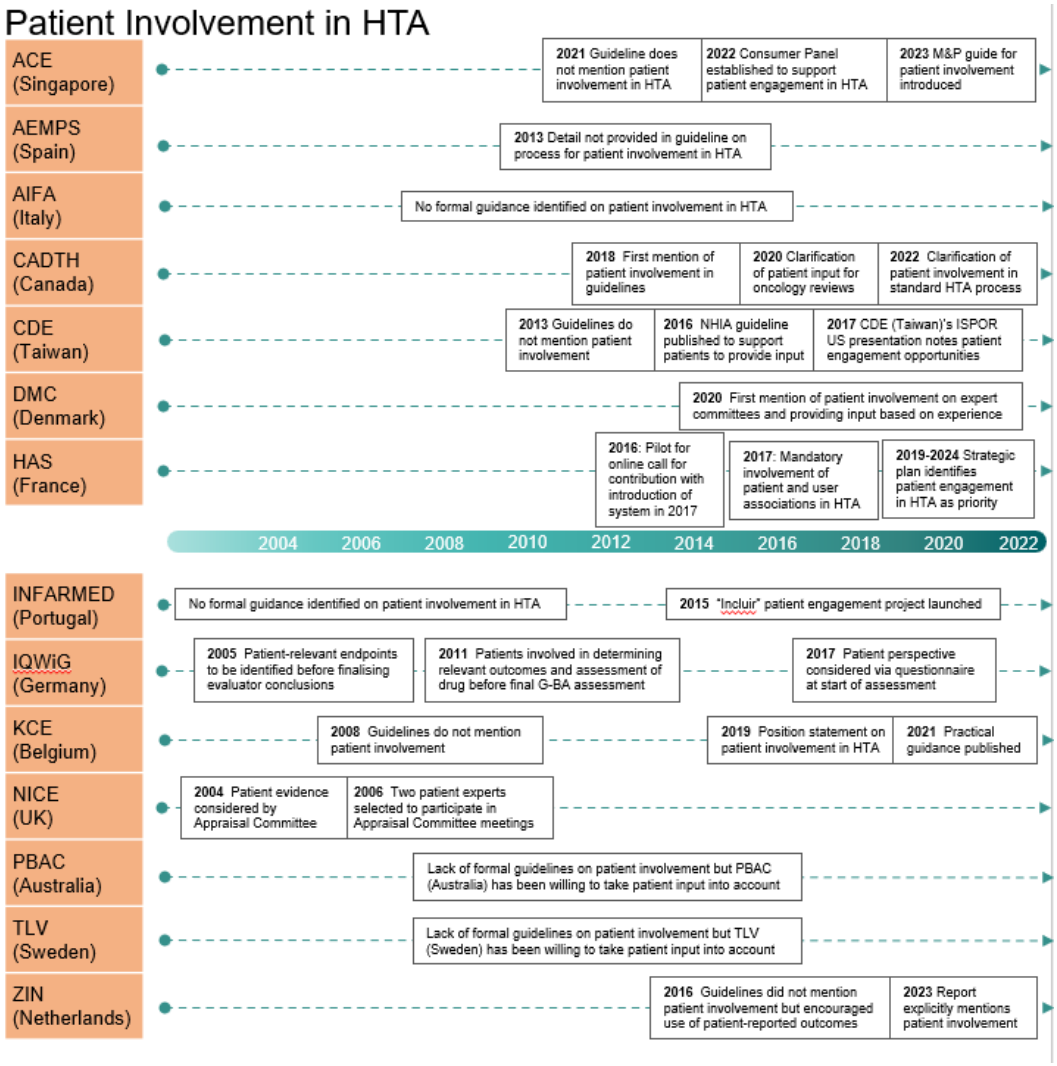
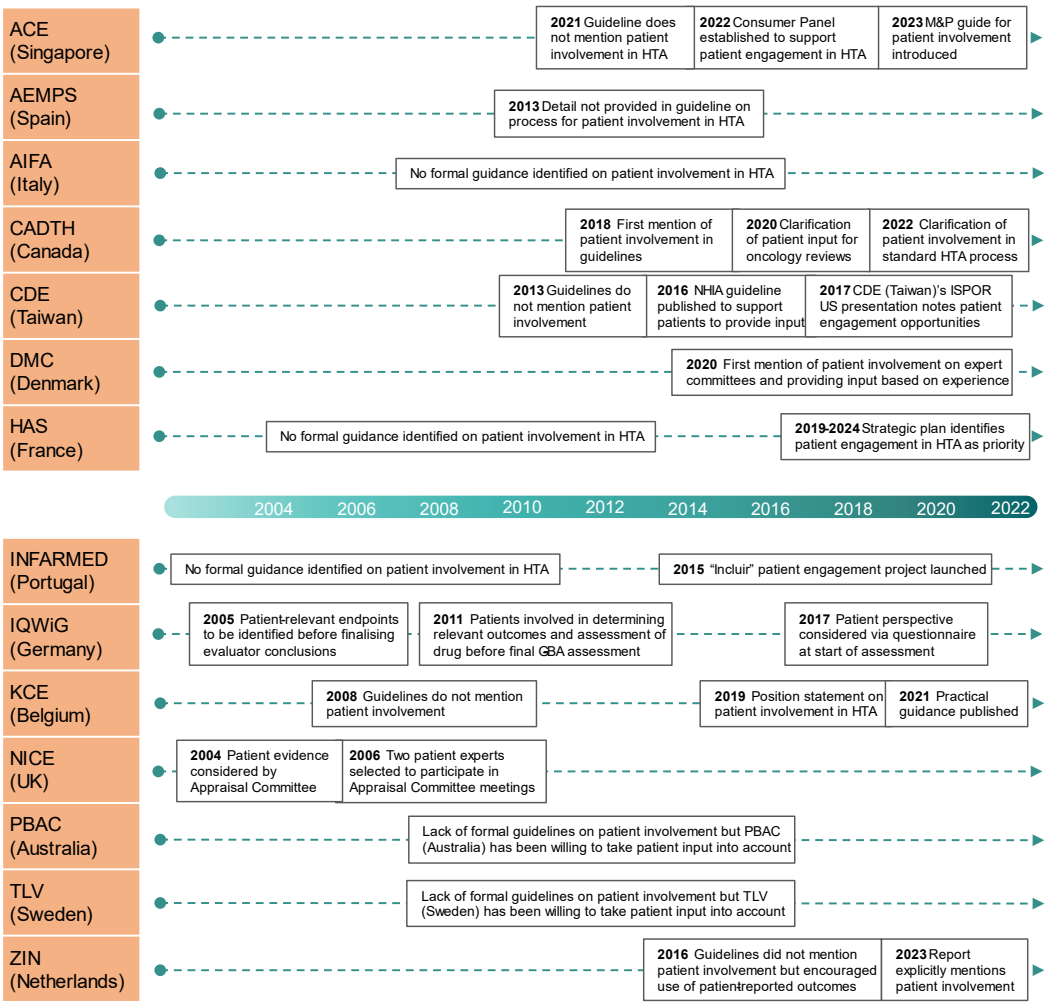
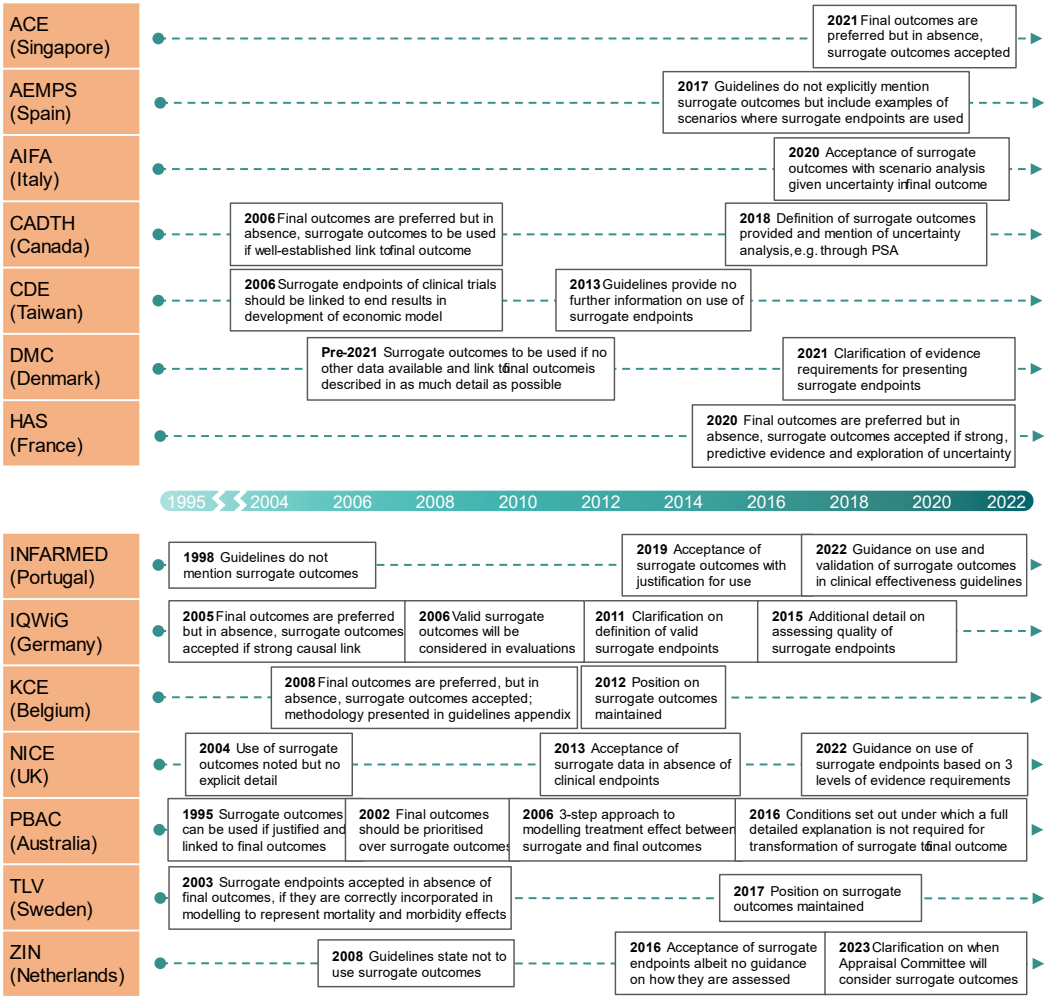


FIGURE 20 EVOLUTION OF HTA AGENCY POSITIONS OVER TIME - RWE



Surrogate endpoints

FIGURE 21 EVOLUTION OF HTA AGENCY POSITIONS OVER TIME - SURROGATE ENDPOINTS



About us
With over 60 years of expertise, the Office of Health Economics (OHE) is the world's oldest independent health economics research organisation. Every day we work to improve health care through pioneering and innovative research, analysis, and education.

As a global thought leader and publisher in the economics of health, health care, and life sciences, we partner with Universities, Government, health systems and the pharmaceutical industry to research and respond to global health challenges.

As a government-recognised Independent Research Organisation and not-for-profit, our international reputation for the quality and independence of our research is at the forefront of all we do. OHE provides independent and pioneering resources, research and analyses in health economics, health policy and health statistics. Our work informs decision-making about health care and pharmaceutical issues at a global level.

All of our work is available for free online at www.ohe.org.

Areas of expertise

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

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CONTRACT RESEARCH REPORT
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