FINAL REPORT

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A comparative analysis of the role and impact of Health Technology Assessment

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EXECUTIVE SUMMARY

Over the last ten years, Health Technology Assessment (HTA) has become an increasingly important part of the assessment system for new medicines. It is generally agreed that HTA has the potential to assist payers in making informed decisions about allocating resources (including expenditure on medicines) in the health system. However, it is also possible that a poorly designed or managed HTA process runs the risk of denying patients appropriate access to medical technologies, inefficiently allocating resources, constraining clinical freedom and sending distorted signals to medical technology providers.

To this end a considerable amount of effort has been put into developing best practice principles which demonstrate a degree of consensus between academia, payers and industry. Charles River Associates ("CRA") was asked by EFPIA, PhRMA, Medicines Australia and EuropaBio to undertake a comparative assessment of the role and impact of Health Technology Assessment (HTA) in different parts of the world. In this report, we use these principles to compare how different systems use HTA, the basis of the approach they apply, how it works in practice and the consequences for the key stakeholders.

The methodology

The objective of the project was to build upon, rather than replicate, the various published studies that have compared HTA systems in order to develop the lessons that can be drawn from different national models in the world. Hence, the project started with a literature review of existing frameworks for comparison, the use of HTA focusing on its role and impact (rather than the merits of particular methodologies). Following this we agreed a set of countries to be included in the assessment including countries which use HTA in different ways and countries with long-established systems as well as markets where HTA is still under development. The countries are set out in the Table 1 below.

Table 1: HTA in the selected markets

Country	Principle HTA agency	Objective*	HTA Separate/Part of P&R Process	Influence on Price, Reimbursement and Market Access	# in 2009
Australia	PBAC	TV,VM,BI	Part	Price and access	228 (73 major submissions)
Brazil	CITEC	TV,VM,BI	Part	Access only	14
Canada	CADTH	TV,VM,RD	Part	Access only	28
England	NICE	TV,VM,RD	Separate	Access only	17
France	HAS (transparency commission)	TV	Part	Price, reimbursement and access	657
Germany	IQWiG	TV,VM	Separate	Reimbursement and access	6
Italy	AIFA	TV,VM,BI	Part	Price and reimbursement (limited influence)	Unknown
Netherlands	CVZ	TV,VM,BI	Part	Price, reimbursement and access	41
New Zealand	PHARMAC	TV,VM,BI	Part	Price and access	58
Poland	AOTM	TV,VM,BI	Part	Price and access	66
Scotland	SMC	TV,VM,RD	Separate	Access only	82
South Korea	HIRA	TV,VM,BI	Part	Price and access	53
Spain	CAHIAQ (Catalan HTA Agency)	TV,VM	Part (regional reimbursement)	Access only	6
Sweden	TLV	TV,VM	Part	Price and access	30
Turkey	SSK	TV,VM	Part	Price and access	Unknown

Source: CRA analysis; * Therapeutic value (TV), Value for money (VM), Budget impact (BI), Regional disparities (RD)

The next step of the project was to develop a template that relates the best practice principles (drawing on the existing literature) to observable characteristics of the way HTA are undertaken and their impact. This was then completed by reviewing HTA publications, academic studies, published data, examination of a set of twelve case studies and an interview programme including industry experts and experts with the agencies responsible for conducting HTA.

The existing literature

In reviewing the literature we found it useful to consider the impact that HTA can have on different stakeholders in the market. We have reviewed the literature on the impact on payers, physicians, patients and the industry. Although there is a significant literature comparing the decisions resulting from different HTA processes, diffusion (at least in

some markets) and the impact on clinical practice, there is little on how restrictions affect patients, the impact on prices or the allocation of expenditures overall (the results of our review are set out in Table 2 below). Little of the literature examines whether the outcome of the HTA process depends on the assessment of the value of the medicine, the type of HTA or ultimately if this results in a superior allocation of scarce health resources.

Table 2: The impact of HTA by stakeholder

Stakeholder	Impact	Potential measure	Existing evidence
Patients	Allocate resources on health services that offer greatest benefits	Distribution of expenditure	No analysis that directly relates HTA to impact on allocation of resources
	Speed of access to good value medicines	Impact of HTA review on time to market	HTA clearly increases time relative to markets where manufacturers are free to launch. However, no evidence that HTA increases time relative to countries with a traditional P&R approach Results in greater restriction being imposed on reimbursement of medicines but little assessment of detriment imposed
	Availability of good value medicines	Diffusion of medicines to patient population	Mixed evidence. HTA appears to slow diffusion but a positive assessment appears to increase diffusion
Physicians	Provide information regarding best clinical practice	Awareness of changes to best clinical practice	Physician appear to value information but awareness varies considerably
	Affect clinical standards	Adoption of changes to best clinical practice, reduce variation in patterns of treatment	Mixed evidence but overall HTA is seen to have an impact on clinical standards if funding is available
Payers	Efficiency of health system	Cost savings achieved from assessing redundant or inferior technologies	No analysis that directly relates HTA to impact on allocation of resources
	Imposes a direct cost	Cost of the HTA	Broad estimates but no attempt to determine how cost vary by type of HTA
Pharmaceutical industry	Affect return to innovative medicines	Allocation of resources to products and speed of assessment	Very limited information on the relationship between HTA and price. Analysis of the French system shows HTA can associate price to value and even incorporate information over time Theoretical argument that HTA favour static efficiency over dynamic efficiency and hence lower returns to innovation
	Predictability of rewards for future	Consistency between HTA assessment and P&R decisions	Regional systems show markedly less relationship between the HTA and the ultimate P&R decision

Source: CRA analysis

Even if there was clear evidence of the benefit of HTA, the limited data on the cost of HTA (both directly on the payers but also on other stakeholders such as the industry) means we would still not be able to determine if HTA brought net benefits to society overall.

The role of HTA

We first summarise the role of the HTA in terms of whether it is a formal part of the pricing and reimbursement (P&R) process (defined as the requirement to undertake an HTA to achieve a P&R decision) and the primary influence of the HTA in terms of pricing, the reimbursement category or its role in determining access (in terms of restrictions imposed on the product). As can be seen in Table 1, 12 of the 15 HTA processes reviewed are a formal part of the P&R process.

The UK's NICE and SMC and the German IQWiG standout as separate processes that are not directly linked to determining or negotiating prices and reimbursement (although they clearly have a significant impact on usage) today. It is also important to note that some systems are still under development – this is particularly the case in Brazil and Turkey.

The objective of the HTA varies significantly between different markets, with some HTA focusing predominantly on assessing medicines in terms of their therapeutic value, while others incorporate economic factors (through an assessment of value for money and budget impact) and regional disparities.

An additional dimension of the role of HTA in the price and reimbursement process is the timing of the review. We have categorised the models based on whether the role of the HTA is ex ante - prior to the launch (and P&R decision) – or occurs after the medicine has been launched on the market and developed organograms regarding their role. This is summarised in Table 3.

Table 3: Models of HTA

Model of HTA	Countries
Ex ante relative effectiveness	France (old), Italy
Ex ante cost effectiveness	Australia, Brazil, Canada, England (new), Italy (regional), Netherlands, New Zealand, Poland, Scotland, South Korea, Spain, Turkey
Ex post relative effectiveness	US (not included in the study)
Ex post cost effectiveness	England (old), Germany (old)
Ex ante relative effectiveness & ex post cost effectiveness	France (new), Germany (new)

Source: CRA analysis

Given the significant differences in the role of the HTA it is not surprising that the number of assessments taking place in any year also varies dramatically. As can be seen from Table 3 the great majority of systems we have assessed can be categorised as an ex ante system based on cost effectiveness (although some kind of ex post review will often follow). It is also apparent that in all markets the role of HTA is still evolving. This is the case in England (as the system moves from assessing multiple medicines to focusing on single technology assessments much closer to launch), France (through the incorporation

of the economic assessments undertaken by the CEESP) and German system (through the AMNOG reforms) possibly changing category in the near future.[1]

Given both the different role of HTA, the objectives of the HTA and hence the number of HTA taking place, comparison of the decisions made, the time it takes to make decisions based on aggregate statistics are likely to be meaningless – hence our effort to base comparisons on shared case studies. We examined the assessments of 12 case studies that cover a range of different therapeutic areas. As these are recent medicines they have not yet been assessed in every market however, further limiting the comparison.

Scope and priorities

We then turn to issues associated with the scope and priorities of HTA in each country. We first examine whether the bodies conducting HTA are transparent and unbiased, whether they cover all potential technologies and how they prioritise their efforts.

There are clearly a variety of models with HTA being undertaken by independent agencies in some countries whilst in others they are conducted by committees that are clearly part of the relevant ministry's decision making process. However, even assessments undertaken on an 'independent' basis can also be affected by political concerns. Given the objective of HTA to take into account the societal perspective (discussed in the next section), the pros and cons of political accountability for the HTA is an interesting area for future consideration. We did not find concerns regarding the independence of the HTA and the regulatory assessments in any of these markets.

We examine whether HTAs are applied to the range of different technologies. In most cases there is an HTA process applied to technologies beyond pharmaceuticals (although often undertaken by a different assessment body), however, it is also the case that the rules and methodologies used vary, with more stringent approaches aimed at pharmaceutical products. While in some cases this may reflect the characteristics of the different technologies, in general the justification for this seems unclear.

Equally, many systems are intended to focus on assessing new medicines but also potentially include assessment, or re-assessment, of older technologies for potential disinvestment decisions. However, although many systems include the potential for this, in reality resources are focused on new medicines. As a consequence of the focus on budget impact this is not surprising (although the assumptions that this will be captured in a review of new medicines or that genericisation means these are unlikely to yield significant savings should be tested). In terms of prioritisation between medicines, this is clearly an important task in some markets, particularly those with a more rigorous and resource-intensive approach, but in others all products are assessed. Where prioritisation is an issue there is often a clear system for setting priorities for HTA but the transparency of the actual decisions varies. The costs of HTA should also be proportionate to potential

1 The German assessment will clearly change following the AMNOG reforms. Under the AMNOG reforms there will be an assessment of added therapeutic value of the medicine within one year, this will determine if the product enters into the reference pricing system or there is a negotiation with the manufacturers regarding a rebate. The situation in the UK is also likely to change with an increased role for HTA in pricing decisions on the introduction of Value Based Pricing. As discussed in "A new value-based approach to the pricing of branded medicines: A consultation" December 2010.

spending on the technology in question, but it appears in some cases that the costs of the HTA process are not even known.

Methodology

In most cases, the methodology applied in HTA is relatively transparent - although in countries where HTA is still under development unsurprisingly this needs to be improved. There is a concern regarding the methodology in some markets but we have not in this study attempted to contribute to the debate on issues such as the role of thresholds – where there is clearly a range of opinions and a large existing literature.

In terms of the types of information that HTA uses, all agencies consider data from published RCTs as the preferred evidence base, but there is variation in the level of acceptance of a broader approach, for example the use of data generated in observational studies or data from unpublished studies.

There are clearly divergent opinions as to whether HTA should include a full assessment of societal value. In two countries there is clearly a process for systematically allowing for these. In other systems, some effort has been made to allow the societal perspective to be taken into account in some way but this appears to have considerably less impact on decision-making than evidence on health benefits and costs to the healthcare system. In particular the relative weighting of these is opaque. On the basis of our assessment we find little evidence of societal aspects being taken into account (indeed we only find one case study where this was the case).

In terms of uncertainty, there appears to be a growing recognition of the problem associated to uncertainty at the time of assessment. The more formal the assessment process the more likely they are to recognise the degree of uncertainty and to attempt to quantify it. The use of mechanisms such as conditional reimbursement and risk-sharing are clearly still embryonic in most markets although evidence from interviews suggests that this will be an area of evolution in the near term.

Process

There is common agreement that during the HTA process there should be the opportunity for interested stakeholders to participate. We found a mixed experience in practice. The more formal HTA processes undertaken by separate agencies have more complex stakeholder programmes, whilst integrated systems, such as France and Italy, have little role for patients and only allow limited role for manufacturers. After the decision has been made the transparency regarding the decision also varies dramatically (with the result that in some countries it is difficult to assess the reasoning behind the decisions), equally very few markets have an independent appeal process if different parties disagree with the final decision.

With respect to the value of additional information, most systems allow for re-assessments to be conducted where new data is available; however, we found few examples where this occurred in practice.

Impacts

There are a range of different impacts that could be associated to the use of HTAs. We have used the case study data to look at the impact of HTA on timing, price and reimbursement and the restrictions imposed on products. The current results are

therefore based on a small sample of products and hence the current results should be treated with some caution – however, the methodologies appear robust and should be developed as more data is collected in the future.

The first issue is whether they are undertaken in a timely fashion or whether the HTA delays the process for medicines being available to patients. It is only possible to observe the length of the actual HTA process in some markets. However, it is clear that although nearly all agencies responsible for undertaking the HTA have targets, the length of the review varies significantly. HTA has undoubtedly increased the time before patients have access to new medicines in markets that were previously free pricing but it is less clear that it has added to assessment time for markets with traditional P&R systems. It is also the case that we need to look at the principles holistically, appropriate stakeholder involvement is a fundamental component of every stringent HTA system but the opportunity to interact with the process and providing transparency will affect the length of the process. There are also clearly efforts to reduce delays in market access through starting the review earlier (before market authorisation in some cases).

We have also looked at the relationship between the length of the time between marketing authorisation and the announcement of the decision and whether this varies by country (after allowing for the systematic differences by product). This supports that some HTA systems (Scotland, France, Australia and the Netherlands) are systematically faster than the other systems covered in this report. We also tested whether the speed of the review was associated to the characteristics of the product. Only in the case of Scotland (based on a small number of observations) do we find a relationship between the therapeutic value of the medicine (as proxied by the ASMR in France[2]) and the speed of the review, with higher value products progressing more quickly through the review. In other countries there is no relationship between the proxy for the assessment of therapeutic value and speed – given many markets are based on order of application this perhaps should not be surprising.

In terms of the role of HTA in the pricing and reimbursement system, we have compared relative prices for products that undergo HTA and those that do not. On the current data we do not find that the application of HTA per se systematically lowered prices. We have also examined whether HTA changes the relationship between prices and the assessment of value (as proxied by measures such as the ASMR – which itself only captures some elements of value). There are clearly a small number of systems where HTA offers greater reward for favourable assessments (through directly linking pricing freedom to the assessment of value). However, from our empirical analysis we found little evidence that HTA on average resulted in higher rewards for the higher value medicines (compared to systems that do not use HTA). There are also systems where the findings of the HTA are not always followed in subsequent P&R decisions, particularly where HTA is performed by a national agency but decisions are taken by regional bodies. We did not find any example where prices were updated due to a re-assessment.

2 This result clearly needs to be treated with caution. ASMR is only an imperfect measure of therapeutic value. It takes into account the added therapeutic benefits but does not take into account wider aspects such as severity or burden of disease. This result is also clearly based on a relatively small number of case studies.

We have examined the restrictions imposed on the case studies. This clearly varies significantly between countries (and the type of HTA), with some countries being more restrictive on average than others. Based on this analysis, Italy appears to be the least restrictive in its recommendations (although this is based only on the national assessment), and Poland and New Zealand to be the most restrictive. There is significant variation in the application of restrictions for the same products and some evidence (again based on the analysis of the case studies) that the application of restriction does appear to be related to price of the medicine rather than simply differences in clinical assessment. There also appears to be a correlation between the use of HTA and diffusion but we have not been able to test this directly with the case study analysis at this stage.

HTA has clearly increased transparency of how medicines are assessed which has benefits in terms of clinicians following best practice. However, we found little evidence that the impact of introducing the HTA process itself was closely monitored. In some cases, there are reviews that have been undertaken, however, in no cases did we find an impact assessment or cost benefit analysis of the role of HTA. A greater focus on evaluating benefits of HTA, the impact on allocation of resources and the cost of HTA would be worthwhile.

Future research

One of the objectives of the research was to set the foundation for a regular report that would allow consistent assessments of the impact of HTA to be efficiently captured over time, whilst taking into account the complexity of HTA organisations, their continuing development and the changes that are on-going in terms of co-ordination and possible harmonisation. In terms of future research we conclude:

- Given the on-going evolution of HTA we would recommend relatively high frequency re-assessments, for example, on an annual or bi-yearly basis. The number and mix of countries however appears to capture a range of different models while allowing relatively detailed comparison. We would therefore not recommend expanding the number of countries significantly.
- The methodology developed was a compromise focusing on 15 countries, a time window of 2009 and 12 case studies. This approach allows the report to make like for like comparisons across a range of dimensions and compare recent performance. In further research it will be useful to:
    - Broaden the range of case studies. A larger sample is needed to apply quantitative approaches pioneered in this paper. Given the different products assessed by different agencies, increasing the number of case studies would add considerably to the exercise;
    - Following the same case studies over time. By following the same case studies it would be possible to examine the timings of re-assessment and most importantly the impact of diffusion rates.
    - Include a focus on particular therapy areas – allowing greater detail on the justification for differences in recommendations.
- In terms of the analysis of the metrics, greater focus on patients outcome (in particular, the impact on particular patient populations, whether patients' preferences are incorporated into the assessment), the reason for the observed lack of re-

assessment, and further analysis testing the value of incorporating an explicit allowance for innovation would be worthwhile;

- The interviews undertaken for the project with the industry experts and HTA agencies were extremely useful to test how the system work in practice, recent changes and on-going trends. The template was a useful medium to have this discussion and showed that there is considerable (although not universal) agreement regarding the best practice in the application of HTA. In future research the template should also be used to gather input from other stakeholders, for example, patients and physicians groups.

Concluding remarks

It is clear from our assessment that the role of HTA varies significantly in different countries and this poses a significant challenge for comparisons across markets and the use of a single set of best practice principles. For example, where the HTA focuses only on relative effectiveness or assessing therapeutic value some principles may be less relevant. Equally, prioritisation is likely to be more important in markets where there is a time and resource consuming comprehensive review. This also has significant implications for quantitative comparisons based on the distribution of decisions and timing – which can only be meaningfully compared allowing for the types of products. For this reason an approach that makes a comparison using both a time window approach (focusing on assessment in 2009) and also compares on a like for like base (using a case study approach) is appropriate.

It is also clear that there is a trade-off in meeting different principles. No system of HTA does universally well when measured against each of these principles. Indeed, it is difficult to see how this is possible. For example, where the HTA process includes allowing a full range of stakeholders (patients, physicians, the industry) to interact at different stages and offer transparency regarding the decision-making process, this will clearly have implications for other principles. There are also areas where – although there is an apparent conflict - care needs to be taken to avoid problems emerging, for example, the independence of regulatory and HTA assessments appears an important principle, while at the same time some co-ordination of dialogue during development is valued. It appears these can both be achieved but only with considerable care.

From the industry perspective, we have looked at the role of the HTA in determining rewards and incentivising innovation. On the basis of limited data at this stage, we have not found that HTA systematically lowers price and equally, we have found no evidence that medicines receiving a more favourable assessment of therapeutic value are being rewarded – however, this clearly needs more analysis as this data set is expanded over time. To the extent that HTA informs the price of a medicine or usage of a medicine it affects the financial return to the manufacturer and hence the incentives to innovate. There is little evidence that products assessed to be therapeutically superior receive assessments more quickly. Although there is some evidence that some HTAs include innovation in their assessment the impact of this is unclear. If innovation is to be included in the assessment criteria used in HTA there needs to be significantly more research into how this should work in practice. Based on our analysis, the most significant observable impact of the HTA process is imposing restrictions on the use of a particular medicine, which appears to be related to the type of HTA and the price of the medicine.

There are clearly areas where HTA process can be improved in many markets and this would likely bring benefits to all stakeholders:

- Although there is a lot of information published, this could be improved. The agency responsible for HTA should publish performance metrics (time of review, decisions, alignment of P&R with HTA);
- There are areas where intention and application appear to differ. For example, the use of HTA for re-assessments appears to happen much less often than suggested by the HTA agency's own objectives;
- The relationship between the assessment and the speed of the review, the freedom in terms of pricing and reimbursement and ultimately how the medicine is used needs to be made more explicit.

Finally, HTA submissions often run into thousands of pages and impose a significant cost, however, there is little or no evidence looking at whether HTA has improved the allocation of scarce health care resources and whether this depends on the different models of HTA. Much more work is needed to look at whether the benefits of HTA exceed costs to different stakeholders.

1. INTRODUCTION

Charles River Associates ("CRA") was asked by EFPIA, PhRMA, Medicines Australia and EuropaBio to undertake a comparative assessment of the role of Health Technology Assessment (HTA) in different parts of the world. The goal was to develop a neutral and objective comparison based on the stated methodologies that are used in different HTA processes but which also takes into account the actual behaviour of the agencies and their observable impact. The study was intended to:

- Build upon the various published studies that have compared HTA systems and reports that look at specific HTA agencies (in terms of policies, procedures and outputs), to develop the lessons that can be drawn from different national models in the world;
- Go beyond the previous studies which predominantly focus on the best way to perform HTA and instead focus the impact (on different stakeholders but most importantly patients) and how these are related to the way that the HTA is conducted and the organisational structure; and
- Set the foundation for a regular report that would allow consistent assessments of the impact of HTA to be efficiently captured over time, whilst taking into account the complexity of HTA organisations, their continuing development and the changes that are on-going in terms of co-ordination and possible harmonisation.

The purpose of this project is to examine the role of Health Technology Assessment in the health system, comparing how HTA is used and assessing the broader consequences for stakeholders. The paper is focused on the role of Health Technology Assessments rather than the agencies that undertake them. This has a number of implications; firstly, we look at the role of HTA in health systems, noting where different agencies are involved. Secondly, we cover a wide range of countries including countries which do not have a specific HTA agency.

We have purposely focused on areas where there has been less analysis and debate. There is a vast literature on the methodologies for undertaking HTA assessment. This paper does not focus on specific methodological approaches that can be applied in the HTAs (for example the pros and cons of using explicit thresholds). Also we do not directly address the issue of internationalisation and harmonisation of HTA models or practices.[3]

1.1. DEFINITION OF HEALTH TECHNOLOGY ASSESSMENT

Before embarking on this study it is important to have a shared definition of HTA. There are a number of alternative definitions:

3 There is a significant debate regarding the application of HTA to orphan diseases and drugs for small populations and the degree to which they can be assessed with the same rigour as other drugs.

- HTA is a multidisciplinary field of policy analysis, which incorporates the medical, social, ethical and economic implications of development, diffusion, and use of health technology.[4]
- HTA is a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the formulation of safe, effective, health policies that are patient focused and seek to achieve best value. [5]
- HTA is used to systematically determine the relative 'value for money' provided by new technologies and to give providers and patients information to make treatment choices.[6]
- HTA acts as a bridge between evidence and policy-making, seeking to provide health policy-makers with accessible, useable information to guide their decisions about the appropriate use of technology and the efficient allocation of resources.[7]
- HTA is an evaluative approach that assesses the impact on society of health technologies and supports the acceptance, modification or rejection of technologies on a rational basis.[8]

HTA is therefore a 'melting pot' of the different disciplines needed to assess the benefits of a given medicine, and in some cases, also the costs. HTA experts may include epidemiologists, economists, physicians, pharmacists, and health care managers, among other professionals.[9] HTA is therefore conducted by multidisciplinary groups, using a range of analytical frameworks drawing from a variety of analytical methods.[10]

In practice HTA has come to mean a wide range of processes and assessments. For the purposes of this project we use a wide definition of HTA including any process that systematically reviews new technologies in order to provide payers with information to make decisions.

1.1.1. Relative effectiveness versus cost effectiveness

One of the most significant differences between different HTA processes is whether the focus is on an assessment of clinical attributes or whether it includes economic elements. The High Level Pharmaceutical Forum (HLPF) – discussed in chapter 2 – defined the aim

4 International Network of Agencies for Health Technology Assessment (INAHTA). http://www.inahta.org/HTA./ Accessed 31 March 2008.

5 European Network for Health Technology Assessment (EUnetHTA). http://www.eunethta.net/. Accessed 13 January 2011.

6 "The role of HTA in coverage and pricing decisions: A cross-country comparison" Corinna Sorenson, Euro Observer, Spring 2009 Volume 11, Number 1.

7 Taylor and Taylor (2009)

8 Institute of Medicine. Assessing Medical Technologies. Washington DC: National Academy Press; 1985.

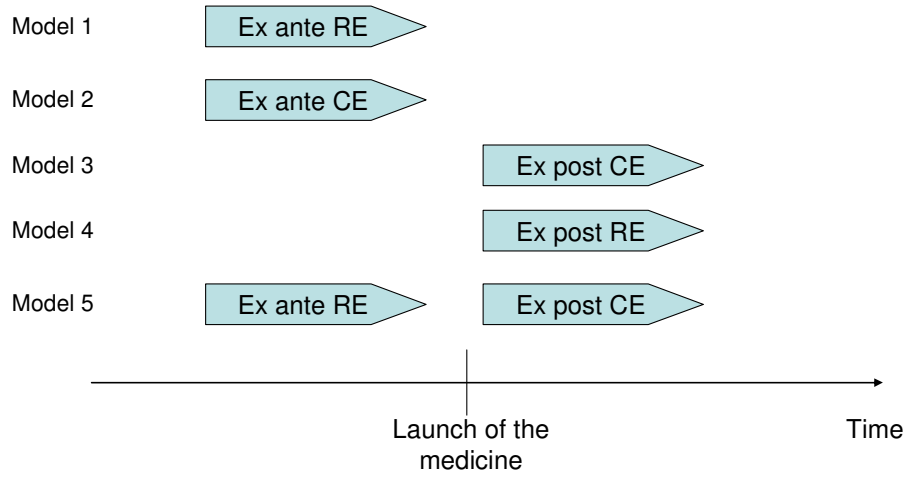
9 Garattini and Casadei (2008)

10 NICHSR, HTA Glossary

of relative effectiveness as to "compare healthcare interventions in practice in order to classify them according to their practical therapeutic value"[11]. Relative effectiveness was defined as the extent to which an intervention does more good than harm compared to one or more intervention alternatives for achieving the desired results when provided under the usual circumstances of health care practice.[12] We adopt the terminology that assessments based on clinical attributes are described as relative effectiveness throughout this report.[13] In contrast, health technology assessment in many markets is synonymous with an assessment of both clinical and economic attributes of the product. We refer to this as an HTA based on cost effectiveness (CE).[14]

The range of different HTA models can be described, at the simplest level, in terms of the nature of the assessment (RE vs. CE) and in terms of the timing of the assessment.[15] As illustrated in Figure 1 there are a range of different HTA models. This categorisation will be used later in the report as we compare different national models.

Figure 1: Common models of HTA



Source: CRA analysis

1.1.2. The process of HTA

It is also possible to categorise HTA by the activities involved in the HTA process and how this varies in different models. Figure 2 illustrates a typical HTA process. Assessments can be initiated either upon request of the policy-maker that needs support for a certain decision or can be autonomously initiated by the HTA body. The first steps to be taken are the definition of the policy question, the elaboration of a protocol to be followed and the gathering of background information. This should allow the relevant

11 High Level Pharmaceutical Forum pg. 57

12 In contrast, relative efficacy was defined as the extent to which an intervention does more good than harm, under ideal circumstances, compared to one or more alternative interventions.

13 This is referred to as "comparative effectiveness" in the United States.

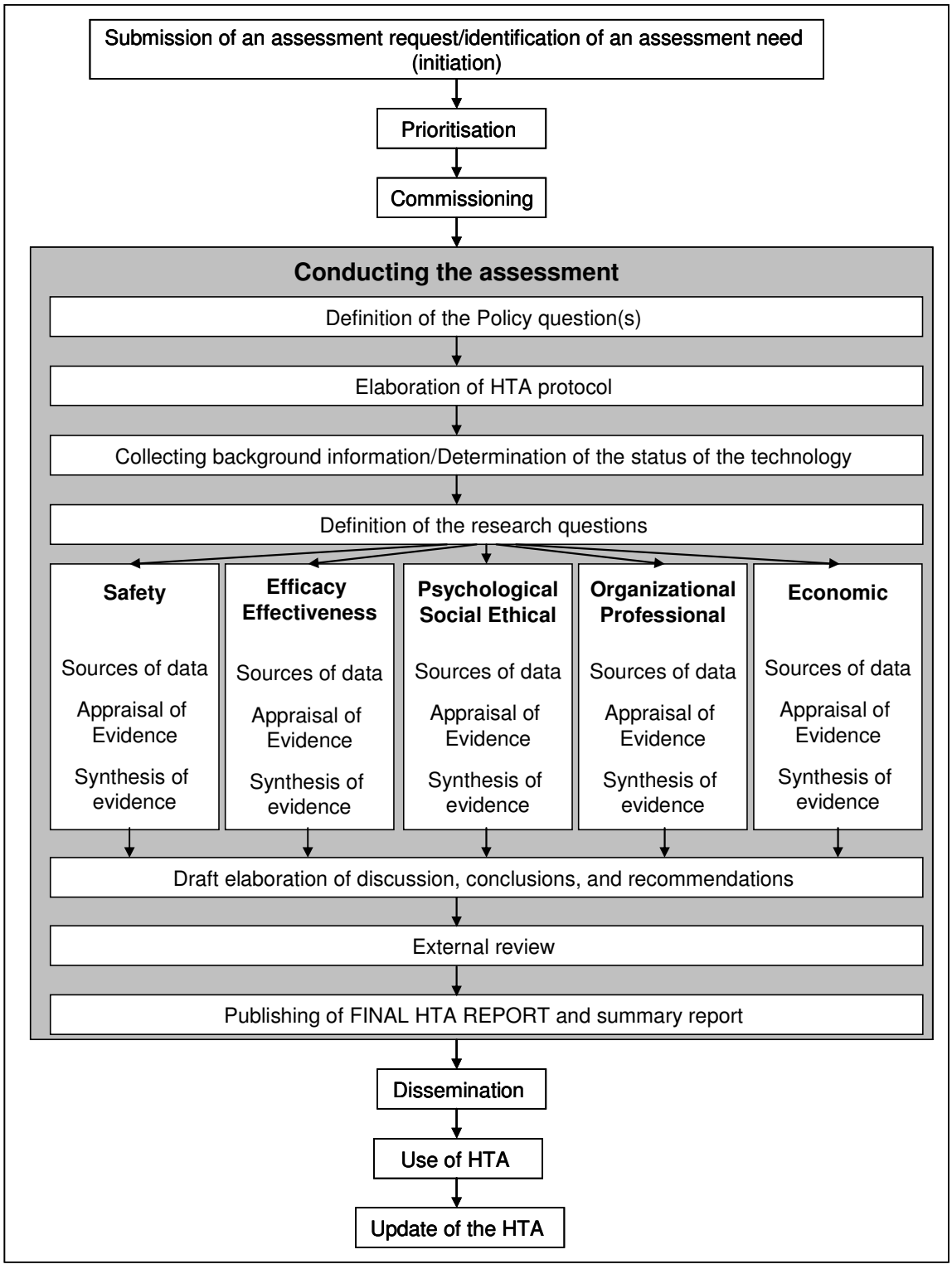
14 There are many ways in which the cost of a medicine can be included in the HTA.

15 This is clearly only one of the many ways that it is possible to categorise HTA processes. We could also look at the breadth of the assessment and whether it takes into account the perceptive of all stakeholders in society.

research questions to be defined, which may typically fall into one of the columns detailed in the figure. Although all of them could be considered in HTA, the emphasis in each one will depend on the nature of the decision-making that the assessment is intended to support.[16]

16 Busse et al. (2003)

Figure 2: The process of HTA



Source: Busse et al. (2003)

1.1.3. The use of HTA

Finally, HTA can be categorised by how the outputs of the HTA process are used. The way that HTA is used in the health system also varies significantly in different models. HTA can be used:

- As an input into the pricing and/or reimbursement process. That is the HTA forms an integral part in the decision-making process that determines the price or the reimbursement of the medicine;
- As an input into market access decision. That is the HTA determines the degree to which payers fund a medicine once it has a price and reimbursement decision
- As a determinant of the use of the medicine by affecting guidance to physicians or even possibly the patients themselves.

Although HTA is also used in other ways, for example, in the development of clinical guidelines and public health policies, the focus of this report is the use of HTA by payers in making decisions about new technologies.

1.2. METHODOLOGY

The methodology for this project had a number of key tasks:

- A review of the existing literature on the use of HTA;
- Agreement of the countries to be included in the assessment;
- The development of a template that relates 'best practice' principles of HTA to observable characteristics of the way HTA are undertaken and their impact;
- An interview programme including industry experts and experts within the agencies responsible for the HTAs in different countries;
- An assessment of case studies for medicines that have been through the HTA process in different markets and the outcome of this process.

1.2.1. Existing literature

Given the aim of this project is to develop (rather than replicate) the large information base on the impact of HTA, we began the project with a review of existing literature on both the use and the impact of HTA. There is however an enormous literature so we have focused on the literature:

- setting out a framework for comparing different HTA systems. In particular, we have examined the different principles that have been developed as to best practice in the use of HTA;
- comparing HTA according to these principles, in particular, focusing on the role of HTA in practice as well as theory;
- reviewing the relationship between the HTA, the decisions that follow and ultimately the impact on different stakeholders, notably patients.

It should be noted from the start that there is much less literature on the impact of HTA decisions on different stakeholders. Many authors have noted the lack of evidence

regarding the actual impact of HTA on policy and practice because of lack of formal evaluation studies in many countries.[17] We have not reviewed the literature on:

- The evolution of HTA in assessment of medicines;[18]
- The debate regarding detailed methodologies applied by the different HTA bodies and examples of their application.[19]

The literature related to the framework for comparison and principles associated to best practice is described in Chapter 2 whilst the existing literature on impact is set out in Chapter 3.

1.2.2. Choice of countries

An important question addressed early in the project was the choice of countries. There is clearly a trade-off in terms of the depth to which information can be collected and the number of countries included. From the outset the objective of the project was to cover a wide range of different countries that use an HTA process. The final list of countries was agreed with the project steering committee and includes a wide range of different systems which vary in terms of:

- The type of HTA: we have systems where HTA is primarily RE and where it is CE;
- The role of HTA: we have systems using HTA primarily for pricing and reimbursement and where it is primarily used in access decisions;
- The maturity of the HTA system: Some have been in place for many years, while other systems are clearly still under development (we note where there is an on-going debate regarding the role of HTA or the process is planned to change in the short-term);
- Geographical coverage: we have purely national systems, systems where a national HTA is used in regional decision making and where regional HTA is undertaken.

The result of this is an assessment based on 15 countries (but including within country regional bodies as appropriate):[20]

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17 "Health technology assessment and policy from the economic perspective" Frans Rutten, International Journal of Technology Assessment in Health Care, 20:1 (2004), 67–70. This still remains the case today, although there have been some recent significant contributions to this literature, for example, Kanavos et al., "The impact of health technology assessments: an international comparison", Euro Observer, 2010.

18 It is important to recognise that new health technologies have always been appraised in terms of safety or effectiveness, and economic evaluation methods have been used in this area for many years. To facilitate the broader assessment needed for full HTA, methods were adapted from other areas of public policy, such as the environment, where wider impact assessments were more established. Hutton et al. (2006). A good description of the history of HTA is provided in the supplement to International Journal of Technology Assessment in Health Care Volume 25, July 2009 or in "Health technology assessment and health policy-making in Europe: Current status, challenges and potential" Marcial Velasco Garrido; Finn Børlum Kristensen; Camilla Palmhøj Nielsen; and Reinhard Busse Observatory Studies Series No 14.

19 See the International Journal of Technology Assessment in Health Care which commonly summarizes particular examples of HTA for particular medicines.

20 However, this represents a fraction of the number of systems which have an interest in HTA. Indeed, we note that the International Network of Agencies for HTA (INAHTA) now has 50 members.

Table 4: Countries included in the assessment

Australia	Germany	Scotland
Brazil	Italy	South Korea
Canada	Netherlands	Spain
England	New Zealand	Sweden
France	Poland	Turkey

1.2.3. Template

Based on the literature setting out the principles of best practice we developed a template to be completed for each country. The objective of the template was to include an assessment of the stated procedures and processes used in the HTA on a comparable basis. However, we also wanted to capture, to the degree possible, measures that reflected the application of these processes in practice. This is illustrated, using the example that HTA should include a range of technologies, in Figure 3 below.

Figure 3: Example of the template

Principle	**Metrics: Relating to stated aims / processes**	**Metrics: Relating to actual activities / outputs**
HTA should include all relevant technologies	HTA is conducted for pharmaceuticals, devices, procedures, diagnostics and treatment strategies	Proportion of HTAs conducted for each of pharmaceuticals, devices, procedures, diagnostics and treatment strategies
	HTA is conducted for old as well as new technologies	Proportion of HTAs conducted for old technologies

Source: CRA analysis

The templates were completed based on the guidelines set out by each of the agencies responsible for the HTA, assessments of the HTA undertaken by government agencies and academic reviews. For each principle in the template we set out the basis for our assessment. We have used a traffic light system, with the colour coding representing:

- Green: Meets the best practice principle in terms of the HTA guidelines and evidence that it is followed in reality;
- Amber: Meets principle in guidelines and no evidence to assess situation in reality (or evidence that the system is moving towards best practice principle);
- Red: Guidelines are not consistent with best practice principles or evidence that it is not followed in practice.

The template and assessment criteria (i.e. the boundary conditions that determine whether we assess a particular country to be green, amber or red) are set out in the appendix to this report.

1.2.4. Interviews

In order to complete and test the assessment included in the templates, we have undertaken interviews with (1) industry experts working in those markets (2) interviews with the agencies undertaking the HTAs themselves.[21]

Table 5: Interviews undertaken with HTA agencies

Country	Agency	Interviewee
Australia	PBAC	Chair
Brazil	CITEC	Technical Assessor
Canada	CADTH	Ex Vice President of CDR Programme
Germany	IQWiG	Ex Head of Medicines Evaluation
Italy	4Commission for Reimbursement, Lazio Region	Member of Regional Reimbursement Commission
New Zealand	PHARMAC	Manager, Analysis and Assessment
Poland	AOTM	Ex-member of Consultative Council
Spain	Catalan Agency for Health Information, Assessment and Quality	Director of HTA
UK (NICE)	NICE	Programme Director for Technology Appraisals
UK (SMC)	SMC	Chair

Source: CRA analysis

The templates completed for this project form part of the final output of the project. These are the basis for the assessment presented in chapter 4.

1.2.5. Comparison of actual assessments

The final element of the project is a review of actual assessments made in the different countries. This is an important data source to assess whether the reality of the HTA process matches up to the guidelines. In order to assess and compare the outputs and outcomes of the HTA process in the different countries, there were two possible approaches:

- Time window approach: Analysis of all assessments conducted within a period of time; or
- Case study approach: Analysis of assessments conducted for a set of selected products.

21 Requests were made to all agencies responsible for HTA between September 2010 and November 2010. We also requested an interview with DG Sanco of the European Commission. We would like to thank all those who participated in the interview programme and commented on the templates.

Arguments for and against the time-window approach

The time window approach has the advantages of being more objective (as we do not need to select particular case studies), providing a comparison of recent behaviour (whereas case studies may occur over time) and allowing the assessment to be updated easily over time. We still need to choose the particular window to be examined. However, this approach also has disadvantages. Because the products assessed during a given period will vary from country to country, the approach does not allow a fair comparison of like-for-like products between countries, particularly for assessment criteria such as the type of information assessed or whether societal benefits have been considered. In addition, the time window approach may not include products covering key therapy areas.

In contrast the case study approach allows us to make like for like comparisons and select products that cover different therapeutic areas and have different attributes. If we base the analysis primarily on case studies, we would need a rule to choose the case studies so they are representative. However, the main disadvantage of this is that this could be criticised for comparing assessments made at very different times and not reflect the 'typical' output of the HTA process.

The methodology used in this study is a compromise using elements of both the time window and the case study approach. We first focus on a time window approach comparing the assessments made in 2009. This has the advantage of representing recent assessments and hence allowing for the recent evolution of HTA in some markets. However, this also means we do not include diffusion analysis of the case studies but base the assessment on existing diffusion studies.

This is then supplemented by a limited basket of case studies that would allow like for like comparisons. The case studies were chosen based on:

- the overlap in assessments undertaken by NICE in England and HAS in France. As the French system is ex ante and England's is ex post this was seen as a method to capture a range of medicines – this resulted in 6 case studies;
- to capture a wider range of medicines we also included the overlap in assessments undertaken by SMC in Scotland and HAS in France (which assess all new medicines) – this resulted in an additional 6 case studies.

The case studies are important as they allow us to examine differences in the decision, the timing of the appraisal, the impact on reimbursement and prices. This results in a group of 12 medicines in a range of different therapy areas:

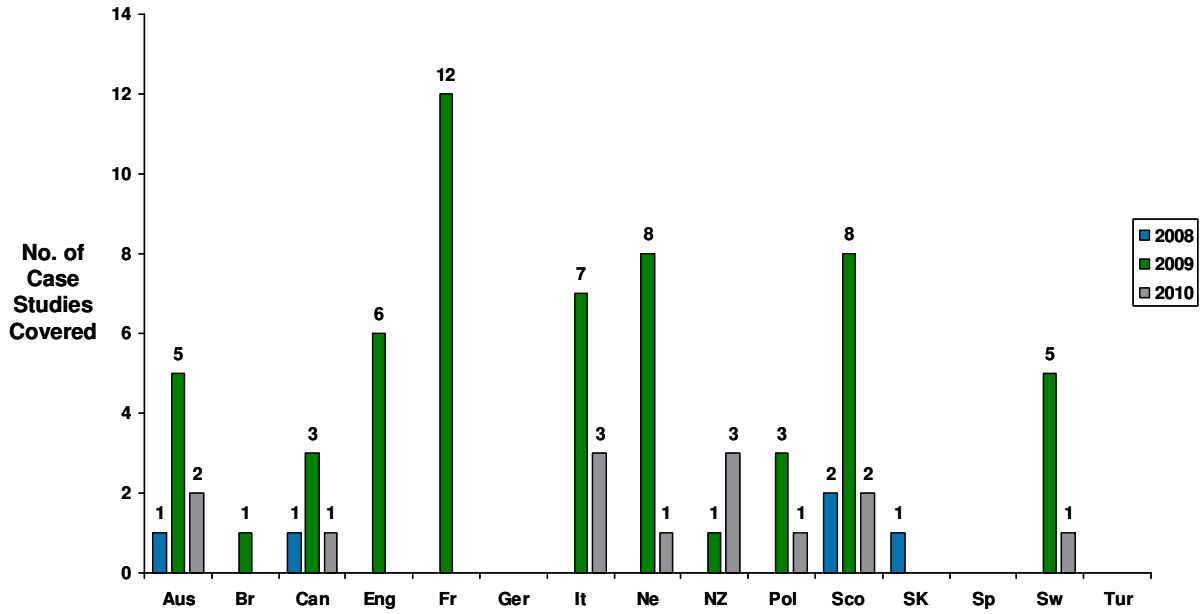
Table 6: Case study medicines

Alitretinoin (eczema)	Rivaroxaban (venous thromboembolism)
Cetuximab (colorectal cancer)	Romiplostin (Idiopathic thrombocytopenic purpura)
Degarelix (prostate cancer)	Sapropterin (hyperphenylalaninaemia)
Doripenem (intra-abdominal infections and	Sugammadex (anaesthesia)

pneumonia)	
Lacosamide (epilepsy)	Tenofovir disoproxil (Hepatitis B)
Prasugrel (ACS)	Ustekinumab (psoriasis)

The result of this is that we have assessed reviews that have been published across a number of years as illustrated in Figure 4. This clearly illustrates the degree to which different products are being assessed at any point in time and the potential pitfalls of a time-window approach.[22]

Figure 4: Coverage of Case Studies by Year of Publication of Recommendation



Source: CRA analysis

It should be noted that the purpose of the case studies is to allow us to compare the same basket of products. We do not focus on the specific issues associated with any particular product.

1.3. STRUCTURE OF THE REPORT

The report is structured as follows:

- Chapter 2 sets out the framework for the comparison;
- Chapter 3 reviews the existing literature on the impact of HTA;

22 The trade-off between the time-window and the case study approach is also clearly demonstrated in the analysis by Kanavos (2010). In their study they examine 6 countries examining assessment made between 2007 and 2009. They find 293 appraisals and only 7% of this or 20 drugs that are assessed by all six agencies.

- Chapter 4 sets out our results and conclusions;
- Chapter 5 discusses our recommendations for future assessments.

2. THE FRAMEWORK FOR THE COMPARISON

In this chapter we set out the framework for the assessment of the role and process of different HTA systems. This draws extensively on the existing literature regarding how to compare different HTA systems and the principles for best practice in HTA and attempts to consolidate the different principles into a single list.

2.1. CLASSIFICATION OF HTA

One of the first papers to focus on assessing the role of HTA (rather than debating HTA methodologies) was Hutton et al (2006). This aimed to establish an analytical framework within which the HTA systems in European countries can be described and classified.[23] It distinguished between:

- *Policy implementation level*: the establishment of the HTA system as a policy decision of government, the policy objectives of the system, its legal status, and its relationships with the remainder of the health system, with other public sector bodies, and with other stakeholders, such as industry and patient groups.
- *Individual technology decision level*: the processes by which individual technologies are dealt with by the system, for example, assessment processes, how decisions are made, and how they are implemented.

2.1.1. The policy implementation level

The purpose of the policy implementation level is to set out the role of HTA and its position in the health system. This focused on issues such as who set up the system; what was the objective; whom does it advise; and who assesses its performance.

In determining the position of HTA in the policy implementation level we have found it useful to distinguish between:

- Whether the HTA is undertaken by a separate body or part of the pricing and reimbursement process: Hutton distinguishes between systems built on special institutes and committees created to manage some parts of the system. For example, NICE in England and Wales, receive their budgets from the Department of Health, which also reviews performance. In contrast in social insurance–funded health systems, such as the Netherlands and Belgium, the fourth hurdle systems are driven by the insurance organizations, which are not public bodies. *We define the HTA process as separate from the pricing and reimbursement system if a medicine can achieve a price and reimbursement status without HTA.*
- The objective of the HTA: Hutton et al distinguishes between the objective to control health expenditures through pricing and utilization of technologies, and classification of medicines such as determining whether technologies are inside or outside the reference pricing system. This also includes the inclusion criteria such as the type of

23 "Framework for describing and classifying decision-making systems using technology assessment to determine the reimbursement of health technologies (fourth hurdle systems)" International Journal of Technology Assessment in Health Care, 22:1 (2006), 10–18.

technology that will be appraised. *We have collected the stated objective of each of the HTA processes.*

- The implementation of decisions: This refers to the stage in the process where the outputs of the HTA process are used. Hutton notes that often, the implementation is within the control of the health ministry or insurance organization, relating to the level at which reimbursement is paid for a drug or other technology. It is particularly important to distinguish between the roles HTA can play in various phases in the diffusion of a health technology, notably when the decision on reimbursement of the technology is taken (or revised) and when recommendations on its use are made to the professionals using the technology.[24] *We have followed Hutton in developing a schematic illustrating the point where the HTA is influential.*

Table 7 illustrates the information collected to describe the policy implementation level of each HTA.

Table 7: Elements at policy implementation level

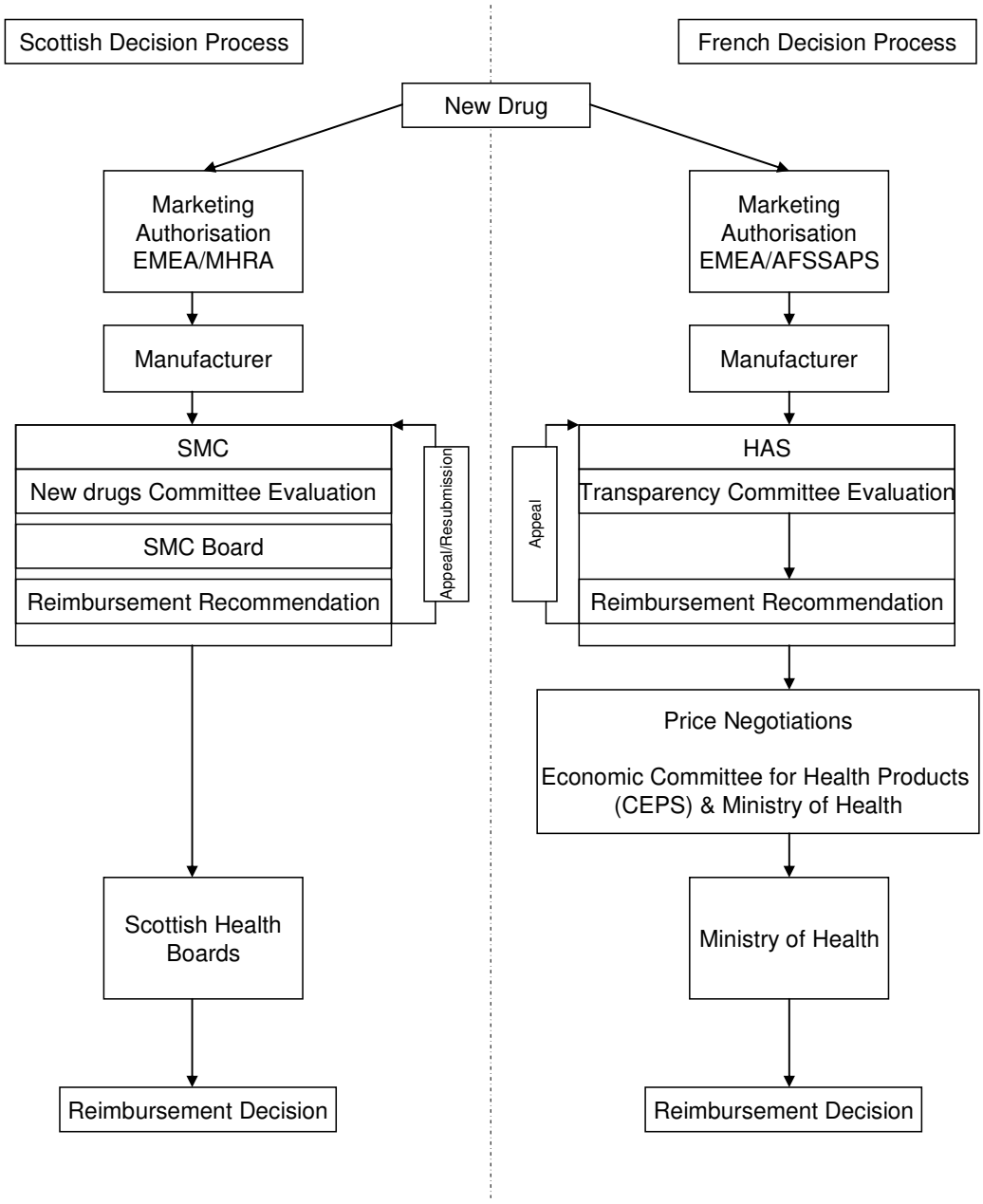
	Criteria
Establishment	Relationship to health ministry
Stated objectives	Nature of objectives
Implementation	Role of advice (role in pricing and reimbursement); number of stages in assessment; pre or post P&R decision

Source: Modified from Hutton et al (2006)

Figure 5 illustrates the position of HTA in the appraisal of new medicines graphically for the Scottish and French processes systematically. Similar schematics have been created for all of the HTAs under consideration and are in the appendix to this paper.

24 "Health technology assessment and policy from the economic perspective" Frans Rutten, International Journal of Technology Assessment in Health Care, 20:1 (2004), 67–70.

Figure 5: The role of HTA in assessing a new medicine



Source: Hutton et al. (2010)

2.2. EXISTING PRINCIPLES

The second part of the assessment focuses on the appraisal process itself and the impact of the HTA. Rather than create an assessment criteria from scratch we have reviewed existing sets of best practice principles. These have been identified by forums such as the High Level Pharmaceutical Forum, industry trade associations, academics and individual companies.

It is important to note we have focused on principles regarding the role of HTA. There is a vast literature on how HTA should be undertaken and the appropriate methodology to use in undertaking an HTA. This work is beyond the remit of this study.[25]

2.2.1. The International group principles

There have also been a number of academic reviews of the subject of best practice principles. The most well known are the principles elucidated by The International Group for HTA Advancement (which we refer to as the International group). Figure 6 summarises the 15 principles for best practices in health technology assessment (HTA).[26]

Figure 6: Principles of HTA from an academic perspective

- Principle 1: HTAs should have explicit and relevant goals and scope
- Principle 2: HTAs should be unbiased, rigorous and transparent
- Principle 3: HTAs should include all relevant technologies
- Principle 4: HTAs should have a clear system for setting priorities
- Principle 5: HTAs should incorporate appropriate methods for assessing costs and benefits
- Principle 6: HTAs should consider a wide range of evidence and outcomes
- Principle 7: HTAs should consider a full societal perspective
- Principle 8: HTAs should explicitly characterise uncertainty surrounding estimates
- Principle 9: HTAs should consider and address issues of generalisability and transferability
- Principle 10: HTAs should actively engage all key stakeholder groups
- Principle 11: Those undertaking HTAs should actively seek all available data
- Principle 12: The implementation of HTA findings needs to be monitored
- Principle 13: HTA should be timely but separate from other regulatory review
- Principle 14: HTA findings need to be communicated appropriately to different decision makers
- Principle 15: The link between HTA findings and decision making processes needs to be transparent and clearly defined

Source: The International Group for HTA Advancement

The International group principles are a useful starting point for the assessment criteria. As the International group makes clear their intention of principles was for them to be used in assessing existing HTA activities. The International group principles are useful as they clearly consider the link between the HTA and the decision that will follow. The principles are organized into four sections: (i) “Structure” of HTA programs; (ii) “Methods” of HTA; (iii) “Processes for Conduct” of HTA; and (iv) “Use of HTAs in Decision Making.” We have adopted a similar structure in our assessment.

However, it is clearly the case that there is no consensus on the use of HTA principles. In the early interviews undertaken for this project it is clear that the HTA agencies do not

25 For an example of this literature Busse R et al. Best practice in undertaking and reporting health technology assessments. International Journal of Health Technology Assessment, 2002, 18:361–422. The outcomes of this process are described in “Practical tools and methods for health technology assessment in Europe: Structures, methodologies, and tools developed by the European network for Health Technology Assessment, EUnetHTA” International Journal of Technology Assessment in Health Care (2009), 25: 1-8.

26 “Key principles for the improved conduct of health technology assessments for resource allocation decisions” International Journal of Technology Assessment in Health Care, 24:3 (2008), 1–15.

necessarily recognise the principles as relevant to them. Following the publication of the principles by the International group there was considerable academic debate (as discussed in the subsequent paper by the International group).

Based on this debate we have made some changes to the principles. For example, it is important to recognise that HTA itself takes resources and thus should be applied proportionately taking into accounts its costs. We have therefore modified principle 11 that recommends that all available data is sought; so that instead HTAs should consider a wide range of evidence and outcomes.

Unlike any of the other principles considered, the International group has also applied these principles to a range of countries. Drummond et al (2010) investigated the extent to which each of the fifteen principles have been supported and implemented by fourteen HTA organisations. By "supported," they meant that the organization embraced the principle in written guidelines or other forms, regardless of whether they actually followed it. By "implemented," they meant that published reports and decisions based on these reports demonstrate adoption of the specific principle.[27] The results for the countries included in this study are summarized in Table 8 below.

Table 8: Assessment of HTA Principles across selected organizations

Principles	NICE (UK)	IQWiG (Germany)	TLV (Sweden)	CADTH (Canada)	HIRA (Korea)	PBAC (Australia)	ANVISA (Brazil)
1	++	++	+	++	++	++	+
2	++	++	++	++		+	+
3	++	++			+		+
4	++	+	+			++	
5	++	+	++	++	+	++	+
6	++	++	++	++		+	+
7			++	++	+		
8	++	+		++	+	++	+
9				++	+	+	
10	++	++	++	++		+	
11	++	++		++	+	++	+
12	+					++	
13	+	++	++	+	+	+	+

27 Drummond et al. (2010), "Are Key Principles for improved health technology assessment supported and used by health technology assessment organisations?", International Journal of Technology Assessment in Health Care, 26:1, 71–78. Available at: http://journals.cambridge.org/action/displayFulltext?type=1&pdftype=1&fid=7029668&jid=THC&volumeId=26&issueId=01&aid=7029660

14	++	++	+	++		+	+
15	+	+	++	++		++	

Source: The International Group for HTA Advancement; "+" signifies that the organization "supported" the principle in question in written guidelines or other form, regardless of whether they actually follow it. "++" means that the organization "implemented" the principle in published reports and decisions based on these reports demonstrate adoption of the specific principle.

The approach adopted to complete this assessment was a review of the agency's HTA website, their mission, and activities of the organization in question. In many cases, the author conducting the evaluation had participated in technology assessments for the organization and/or had written about the HTA process at the organization and about particular decisions. The International group did not ask the respective organizations either to self-evaluate or to review and comment on their assessments.

Based on their assessment, it would appear that the best performing HTA organisations are NICE in the UK and the CADTH in Canada.[28] These are then closely followed by the PBAC in Australia and the German and Swedish organisations.

The international group encourage other researchers to conduct their own studies of HTA principles and HTA organizations. In particular, they recommend quantifying more precisely the criteria for achieving a positive verdict on support and use of the principles. For example, they suggest an evaluation of whether an HTA organization has successfully implemented principle 13 ("timely HTA") might stipulate a period (e.g., 6 months) for producing HTA reports, and a criterion (e.g., that 75 percent of reports must have been done within the 6-month window) for an HTA to achieve a favourable evaluation. In our paper we have attempted to build on this recommendation in our methodology.

We have therefore used the International group principles as the starting point of our assessment criteria. However, to reflect some of the debate that followed we have also drawn upon some of the other principles developed.

2.2.2. The High Level Pharmaceutical Forum principles[29]

The High Level Pharmaceutical Forum (HLPF) was a three year process involving the European Commission, national government and stakeholder groups (including the pharmaceutical industry, patients, physicians and payers). HLPF set out a range of principles for undertaking reviews of relative effectiveness.[30] These are described in Figure 7. It endorsed the aim of relative effectiveness assessment to compare healthcare

28 With respect to 'best performing' it may be worth pointing out that most literature on this topic would define 'best performing' as achieving 'best value for money' on behalf of their national health system (patients & payers). It is axiomatic that the lower the price the better value for money a medicine will be. An interesting facet of this study should be to seek out any explicit or implicit statement of principle or criterion in which pursuit of best value for the demand side should be constrained by considerations of the rewards/returns to the innovator.

29 Recommendation 5: Implement agreed good practice principles for Relative Effectiveness assessments in Final Conclusions and Recommendations of the "High Level pharmaceutical Forum"

30 The HLPF distinguished carefully between "the scientific assessment of the relative effectiveness of medicinal products and health-economic assessments of their costs and benefits."

interventions in daily practice and classifying them according to their added therapeutic value.[31]

Figure 7: The HLPF relative effectiveness principles

1. Individual Member States may use RE assessments for different purposes. Decisions on the detailed operation of RE assessments, including methods and relevant stakeholders, are most appropriately made at a national level.
2. RE assessment processes, selection of products to be assessed, working methodologies and quality assurance processes should be transparent to all parties and evidence-based.
3. Relevant stakeholders should be able to contribute to the development of assessment methodologies. The purpose of RE assessment and the organisation(s) responsible for its conduct should be clearly identified.
4. RE assessment processes should remain separate from product market authorisation procedures (though this does not mean that they are necessarily performed by different organisations).
5. RE assessment processes should be time-framed, and should minimise or avoid causing unnecessary procedural delays consistent with any associated Transparency Directive requirements where applicable.
6. RE assessments should be capable of addressing transparently uncertainty in the evidence base, and the methodological challenge of translating evidence on relative efficacy and other appropriate available data into conclusions on relative effectiveness.
7. The sources of evidence which are to form the relevant RE input should be specifically discussed among the identified key stakeholders, who should each be able to submit evidence or argumentation for appraisal.
8. RE assessment should include comparison with the most appropriate healthcare interventions. Such comparison should build on the results of active controlled clinical trials, where available.
9. When concluded, outcomes should be communicated in a clear and timely manner to all interested parties. Communication by means of publishing the supporting evaluation on a publicly accessible website is strongly encouraged.
10. RE assessments should be capable of subsequent revision and updating as the evidence base develops.
11. RE assessments should aim to identify areas in which the evidence base on an intervention could most usefully be developed in the future.

Source: HLPF Final recommendations pg. 58

The HLPF principles are important as they recognise that RE assessments can be undertaken for a range of purposes whilst maintaining transparency, an open process to different stakeholders and flexibility to information being included over time. They also explicitly recommend that RE assessments should draw on information presented in other assessments and that decisions are communicated publicly.

2.2.3. Industry principles[32]

The third set of principles reviewed for this project were those developed by EFPIA (the European trade association for the innovative pharmaceutical industry) (see Figure 8). We have also reviewed principles developed by individual pharmaceutical companies – these are largely similar to the industry's principles and hence we do not report them separately.

31 The HLPF recommended "Member States and stakeholders are encouraged to implement the agreed best practice principles for relative effectiveness assessment and to regularly communicate and exchange information on their adoption, where appropriate".

32 EFPIA Key Principles on "The Use of Health Technology Assessments (HTA) to evaluate Medicines"

Figure 8: EFPIA's HTA principles

- HTAs should be based on a clear, sophisticated and differentiated view of what constitutes value
- HTAs should be transparent and balanced
- HTAs should be based on early and inclusive dialogue, including with patients
- Evaluations should allow new data to be considered
- Flexibility is required in handling uncertainty
- Comprehensive understanding of the benefits of a drug in disease management is needed
- Payers should commit to rewarding added value
- HTA outcomes should be implemented
- HTA should apply to all healthcare interventions
- Assessment should take place at national level
- HTA should remain separate from regulatory review
- Evaluations should take into account indirect benefits

Source: EFPIA Position Paper

These are similar to the principles promoted by Medicines Australia in the recent review of HTA in Australia.[33] They advocated:

- maintaining the separation of the registration and reimbursement processes;
- a preference for HTA to be conducted from a broad societal perspective rather than a narrower "payer's" perspective;
- HTA, as a technical analysis, to be one input into the decision to reimburse a technology, along with other considerations including clinical need, prevalence of disease, ethical and equity issues, and incentives to drive technology innovation;
- appropriate transparency around the assessment, appraisal and decision making processes, including the criteria used to make a recommendation
- ensuring that there is appropriate separation of powers between payers, policy-makers, program administrators, evaluators and decision-makers.
- wide stakeholder input into the HTA appraisal and decision making, including from consumers and consumer organisations, health professionals and industry;
- public disclosure of decisions and reasons for recommendations to reimburse or not reimburse a technology, and
- appropriate accountability measures, including an appeals procedure, quality assurance programs/audits of evaluations, and the publication of system performance indicators.

From the industry's principle we have included that evaluations should allow new data to be considered (one point that was not included in the international group principles). Other elements of the principles have been incorporated into our assessment as key measures (for example, the existence of an appeals mechanism or whether an assessment of added value is ultimately rewarded in the reimbursement process) that are used to assess existing principles.

33 "Submission to Australian Government Review of Health Technology Assessment (HTA) in Australia" May 2009, Medicines Australia - Submission to Australian Government Review of Health Technology Assessment (HTA) in Australia

2.2.4. Other academic studies on HTA best practice

Finally, we have reviewed the wider academic literature of best practice principles. Of particular note is Haas et al (2008).[34] This paper reviews and describes different approaches to HTA used in Australia and in other countries and identifies the features of best practice in HTA (with particular reference to those likely to be most relevant to HTA at a local (i.e. state/regional) level). This is notable as it:

- Focuses on the regional characteristics of the HTA;
- Explicitly identifies avoidance of duplication and overall cost of the process;
- Its focus on adoption and diffusion of the technology.

Finally, the paper presents a template for associating principles to measures. We have adopted this approach as described below.

2.3. THE RESULTING FRAMEWORK FOR ASSESSMENT

Based on the review of the literature above and early interviews undertaken for this project we developed our own list of principles to be taken into account in the assessment. These are summarised in Table 9 below. This included some differences to the International Group (from which they are based):

- We added that the HTA should be proportionate in Principle 3;
- We have modified Principle 4 to focus on appropriate methods rather than referring to costs and benefits. It is clear from the HLPF that different systems are used for very different purposes and some HTA processes do not include any evaluation of costs.

34 Haas M, Hall J, Viney R et al (2008) A model for best practice HTA. CHERE Working Paper 2008/1. Centre for Health Economics and Evaluation, Faculty of Business, University of Technology, Sydney

Table 9: The framework for assessment

Structure	Category	Principles	Principles
Individual technology decision level	Scope and Prioritisation	1	HTA should be an unbiased and transparent exercise
		2	HTA should include all relevant technologies
		3	A clear system for setting priorities for HTA should exist and the costs of HTA should be proportionate
	Methods	4	HTA should incorporate appropriate methods depending on its goal
		5	HTAs should consider a wide range of evidence and outcomes
		6	A full societal perspective should be considered when undertaking HTAs
		7	HTAs should explicitly characterise uncertainty surrounding estimates
	Process	8	Those conducting HTAs should actively engage all key stakeholder groups
		9	HTA findings need to be communicated appropriately to different decision makers
		10	Evaluations should allow new data to be considered
		11	HTA should identify areas in which the evidence base on an intervention could most usefully be developed in the future
	Impact	12	HTA should be timely
		13	Pricing reimbursement and market access decisions should reflect the HTA assessment in a transparent, clearly defined way and be implemented as intended
		14	The impact of HTA findings and how they are used needs to be monitored

Source: CRA analysis

In the majority of interviews with HTA agencies these principles were seen as reasonable and comprehensive. However, it is important to note that some agencies objected to particular principles. In particular, where the objective of the HTA was narrowly defined, they felt it was unreasonable to apply principle 6. We have attempted to take into account in the assessment when other processes beyond the HTA allows for these considerations.

These principles attempt to draw together the best elements from the debate thus far. However, these principles share some of the same problems. They do not take into account that the HTA systems are evolving and therefore should only be seen as an assessment at a point in time (we do however attempt to note where changes are imminent). Any set of principles implies that the principles are equally important – this is clearly not the case. In reality some principles are clearly more important than others, the

implications of this are that it is not possible to 'add-up' the different categories but instead the principles should be seen as a package.

2.4. PRINCIPLES AND METRICS

Using the principles as the framework for assessment we created a template. The objective was to incorporate information from official documents, guidelines etc for each agency but to the extent possible set out observable measures to determine when the principle was followed in practice. Where possible we have based measures on quantifiable metrics. The criteria for our assessment are set out in the template in the appendix to this report.

The templates were completed from background research, academic studies and analysis of the published data and the case studies (described in the previous chapter). Where HTA bodies agreed to be interviewed for the purposes of this project the template was shared with them and comments included.

3. EXISTING LITERATURE ON THE IMPACT OF HTA

We were asked to focus particular attention on what was the impact of HTA upon stakeholders within healthcare generally and on the patient in particular. It has been noted that a disproportionate amount of HTA research to date has focused on HTA structures and processes rather than on the impact that HTA has had on healthcare systems and societal health outcomes.[35] In this chapter we review the literature on the relationship between the application of various forms of HTA across the selected countries and the interests of the core stakeholder groups, (i.e. patients, clinicians, paying or budget holding administrators and industry) drawing on the experience in a range of international markets and also consider the methodological challenges with measuring the impact of HTA.[36]

It is important to note that the expected impact will depend on the role and objectives of HTA. For example, the United Kingdom's National Institute for Health and Clinical Excellence (NICE) currently produces mandatory government guidelines. It is reasonable to expect its recommendations to have a significant impact on usage of different medicines. In other systems, HTA might have a role which is limited to the price and reimbursement decision, in which case, once the product is approved it is unreasonable to expect the same type of effect on usage.

We first set out the different perspectives that different stakeholders have on the impact of HTA before turning to each of these potential impacts in turn. These include the role of HTA in market access, the pricing and reimbursement of the medicine and decisions, usage of the medicine, development of clinical practice guidelines and communication with prescribers, the impact on incentives to innovate and finally the direct cost that HTA itself imposes on society.

3.1. THE IMPACT OF HTA FOR DIFFERENT STAKEHOLDERS

Stakeholders can be classified into many different segments, with varying degrees of complexity and sophistication. Much depends upon the context and issues under examination.[37] Here we consider patients, physicians, payers and innovative pharmaceutical companies; a more comprehensive list would include a broader range of

35 Among the literature that does exist, a significant proportion is focused on the UK, and in particular on the impact of NICE.. O'Donnell et al., "Health Technology Assessment: Lessons Learned from Around the World – An Overview", Value in Health 2009. This is illustrated by a review of the articles in the International Journal of Technology Assessment in Health Care, which reveals that of 848 articles published between 2000 and 2010, over 10% or 94 are about the UK. Where 94 articles include the terms "NICE", "UK", "United Kingdom" or "England" in the title or abstract.

36 In particular this draws on Gerhardus et al., "What are the effects of HTA reports on the health system? Evidence from the research literature" in Health Technology Assessment And Health Policy-Making In Europe: Current status, challenges and potential, European Observatory on Health Systems and Policies 2008

37 In this report we are focusing on the impact within the country where the HTA was undertaken. The HTA could clearly impact on other markets but this is beyond this study. This was looked at in "THE EFFECTS OF NICE HTA ON DRUG PRESCRIBING AND EXPENDITURES IN THE US" Sepulveda B, Doyle JJ, White C Quintiles Consulting, Hawthorne, NY, USA, May 18, 2009.

stakeholders including, for example, pharmacists and generic pharmaceutical manufacturers, but this lies beyond the scope of the project. In addition to sharing the aims of advancing healthcare for the benefit of patients and society as a whole, each stakeholder could be affected by HTA in a number of ways:

- Patients: At the individual level, patients are concerned with their own personal access to the best available diagnostics and treatments. At a higher level disease sector specific patient associations in effect compete for resources and funds for their disease, be it breast cancer, Alzheimers or diabetes. At the highest level all associations and umbrella associations subscribe to arguments for higher levels of resource and funding for healthcare per se. The reality of this hierarchy of interest is a substantial diversity of opinion on what the proper or appropriate use of HTA should be; a public debate which is constantly played out in the media. HTA can therefore ensure resources are used to finance the best medicines, using the best clinical practice but it can also act as a barrier to access by delaying access to the medicine or limiting its use;
- Physicians: In an ideal world physicians would optimise the treatment of individual patients without regard to costs or resource constraints. This has never been the case in reality. As patient demands and the choice of new technologies have escalated many clinicians, cognisant of financial realities, concede, or at least tacitly accept the need for higher level over-arching models, and decision-making processes which seek to fairly and efficiently set priorities in adopting innovations across different clinical disciplines. However, as for patients, this does not preclude them competing strongly for the optimal allocation of funds for their speciality. Hence HTA may affect the medicines that physicians have to choose from but may also influence the formulation of best practice guidance in their use;
- Payers: Payers in the form of national pharmaceutical agencies involve complex systems of clinicians, administrators and other advisors, the composition of which will vary depending upon the issue to be addressed. It is within their compass to recommend to their political leaders policies on HTA itself, what forms should be adopted, how that will be integrated into the broader framework of health legislation and how it will be administered in practice. In the light of this, HTA is used to allocate resources to get best value for the health system but also clearly imposes a direct cost on them (as well as indirect cost on other stakeholders).
- Innovative pharmaceutical companies: Companies seek legitimate return on their R&D investments. A key relationship is therefore between the metrics of comparative HTA assessments and the reward to innovators. In principle, HTA can focus resources on rewarding the most valuable products as quickly as possible (increasing the incentive to innovate) alternatively it could impose an administrative burden and delay and if applied inappropriately distort the rewards for developing innovative medicines.

This is summarised in Table 10 below.

Table 10: The impact of HTA by stakeholder

Stakeholder	Impact	Potential measure
Patients	Allocate resources on health services that offer greatest benefits	Distribution of expenditure
	Speed of access to good value medicines	Impact of HTA review on time to market
	Availability of good value medicines	Diffusion of medicines to patient population
Physicians	Provide information regarding best clinical practice	Awareness of changes to best clinical practice
	Affect clinical standards	Adoption of changes to best clinical practice, reduce variation in patterns of treatment
Payers	Efficiency of health system	Cost savings achieved from assessing redundant or inferior technologies
	Imposes a direct cost	Cost of the HTA
Pharmaceutical industry	Affect return to innovative medicines	Allocation of resources to products and speed of assessment
	Predictability of rewards for future	Consistency between HTA assessment and P&R decisions

Source: CRA analysis

Table 10 sets out the range of possible impacts affecting different stakeholders; we use this to structure the rest of this chapter.

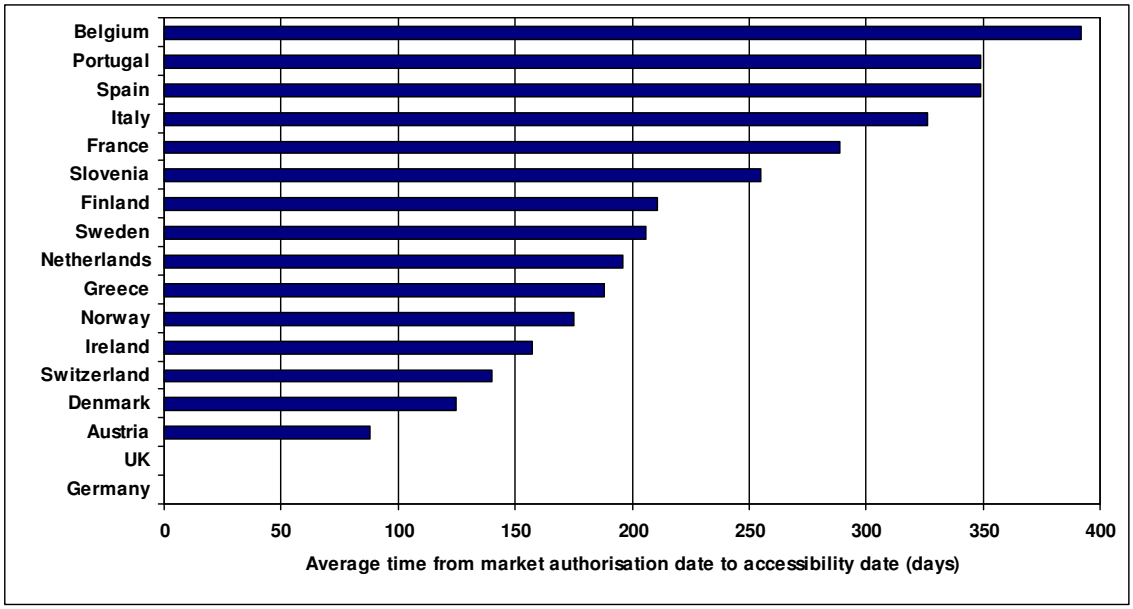
3.2. MARKET ACCESS

The first issue to address is whether HTA affects the speed at which decisions are made and when patients have access to medicines. In principle, HTA could target resources ensuring the highest value medicines are available to patients as quickly as possible. Equally, by introducing an additional step into the decision making process around market access, access to new drugs may be delayed. HTA processes are time consuming because of the process that must be followed and the complexity derived from its multidisciplinary nature. Processes may be longer if HTA bodies with limited resources have to deal with increasing number of applications.

To measure the time it takes for a medicine to become available on the market there are a number of data sources. The Patients WAIT Indicator produced by EFPIA reports the average time between marketing authorisation and patient access for new medicines. This is measured by the number of days elapsing from the date of EU marketing authorisation to the day of completion of post-marketing authorisation administrative processes, including pricing and reimbursement processes (see Figure 9). For countries where HTA assessment plays a role in formal pricing and reimbursement processes (e.g. France, Netherlands, Sweden) this measure gives an indication of the delay to market access imposed by HTA (although this could also be due to other factors). However, for countries where HTA is not part of the pricing and reimbursement process and takes

place after product launch (e.g. UK, Germany), the measure does not capture the impact of HTA on the speed at which medicines are available.

Figure 9: Average time from EU market authorisation to accessibility date for medicines with first EU marketing authorisation in the period 2007-09



Source: Patients WAIT Indicator 2010, EFPIA

We have found relatively few studies that look at the length of the HTA process itself. Table 11 reports the studies we found that estimated the length of HTA processes conducted by agencies in several countries.

Table 11: Length of HTA processes in different countries

	Australia	Canada	Germany	UK	UK	France	Spain
HTA agency	PBAC	CADTH	IQWiG	NICE	SMC	HAS/CEPS	Regional bodies
Applications	60-70 per year	20-24 per year	29 per year	44 per year	n/a	n/a	n/a
Length of Review Process	16-17 months	6-12 months	2-28 months	9-18 months	5 months	6-30 months	6-24 months

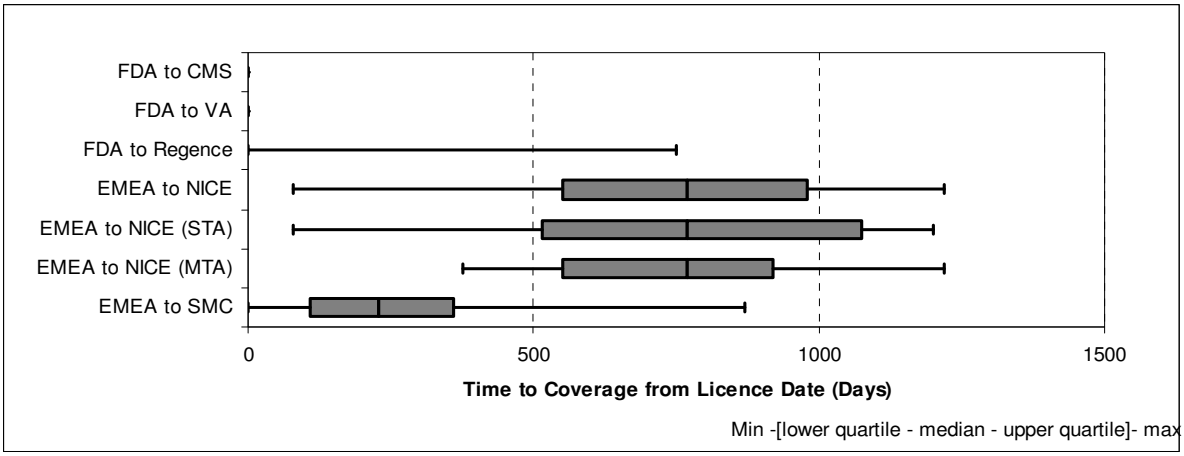
Source: Perez Pugatsch (2009), Taylor and Taylor (2009), Cargill (2009)

Although this is useful, as it does not tell us when the review started this does not directly relate to patient access.

A study by Mason et al. examined the delay imposed by HTA processes in a comparison of anticancer drug coverage decisions made by payers that use HTA in decision-making versus those that do not. The study covered decisions made by payers in the US and UK for the 59 anticancer drugs approved by the FDA between 2004 and 2008. Included in the analysis were decisions made by NICE and the SMC in the UK and by the Centers for

Medicaid and Medicare Services (CMS), Department of Veterans Affairs (VA) and the Regence Group[38] in the US. Of these, NICE, the SMC and the Regence Group routinely use HTA in decision making, while CMS and the VA do not. The analysis showed that CMS and the VA covered all 59 drugs from the FDA license date, while time to coverage for the Regence Group ranged from 0 to 771 days. In the UK, median time from European licence date to NICE decision was 26 months (783 days), with the SMC making decisions more quickly at an average of 8 months (231 days). Analysis of NICE decisions showed that the single technology appraisal process (STA) was not significantly shorter than the multiple technology appraisal process (MTA) (see Figure 10).[39]

Figure 10: Comparison of Time to Coverage of Anticancer Drugs in the US and UK



Source: Mason et al. (2010)

The Fraser Institute has investigated the delay in access to medicines imposed by HTA processes in Canada, where the decision made by CEDAC in the Common Drug Review (CDR) process provides guidance to the individual provincial public drug plans which make their own decisions on drug coverage. On average, in the period 2004-2005, the delay from Canadian regulatory approval to positive recommendation by CDR was 257 days for pharmaceutical medicines and 186 days for biological medicines. Provincial reimbursement decisions took an additional average 201 days for pharmaceutical medicines and 187 days for biologics. It is interesting to note that in Quebec, the only province not to participate in the CDR process, the total length of time from regulatory approval to provincial reimbursement approval is similar to that in the other provinces, indicating that the introduction of the CDR process has not increased the overall time it takes to reach a decision on provincial reimbursement.[40]

38 A private insurance network using HTA in coverage decisions for anticancer drugs covered by the pharmacy benefit (oral and subcutaneous) but not anticancer drugs covered by the medical benefit (Intravenous drugs delivered in the hospital / physician's office).

39 Mason et al, "Comparison of anticancer drug coverage decisions in the US and UK: does the evidence support the rhetoric?", Journal of Clinical Oncology, July 2010.

40 Skinner et al, Access Delayed, Access Denied, March 2007.

There is little evidence regarding whether the speed of the HTA varies depending on the type of HTA or whether HTA mean that products that bring the greatest value to patients are reviewed more quickly.

The studies described demonstrate some of the difficulties in looking at time to access:

- The different approaches and aims of HTA bodies mean that time lengths may vary. Where HTA is used to evaluate all products many of these might be simple assessments that can be completed in one month. If HTA is focused only on the more complex cases it can clearly take over a year. This demonstrates the need to standardise on a comparable group of products.
- The duration of the HTA is likely to be related to some of the other principles. In particular, an extensive consultation with stakeholders may lengthen the process. This must be balanced with the need to ensure that access to innovative treatments is granted in a timely manner.
- The comparisons do not allow for attempts to introduce fast-track assessments by several authorities (SBU in Sweden, HAS in France, FinOHTA in Finland, NICE in UK and OSTEBA in the Spanish Basque country). However, fast track assessments reduce the opportunity for consultation and may lead to further delays if any discrepancies need to be addressed later in the process.[41]

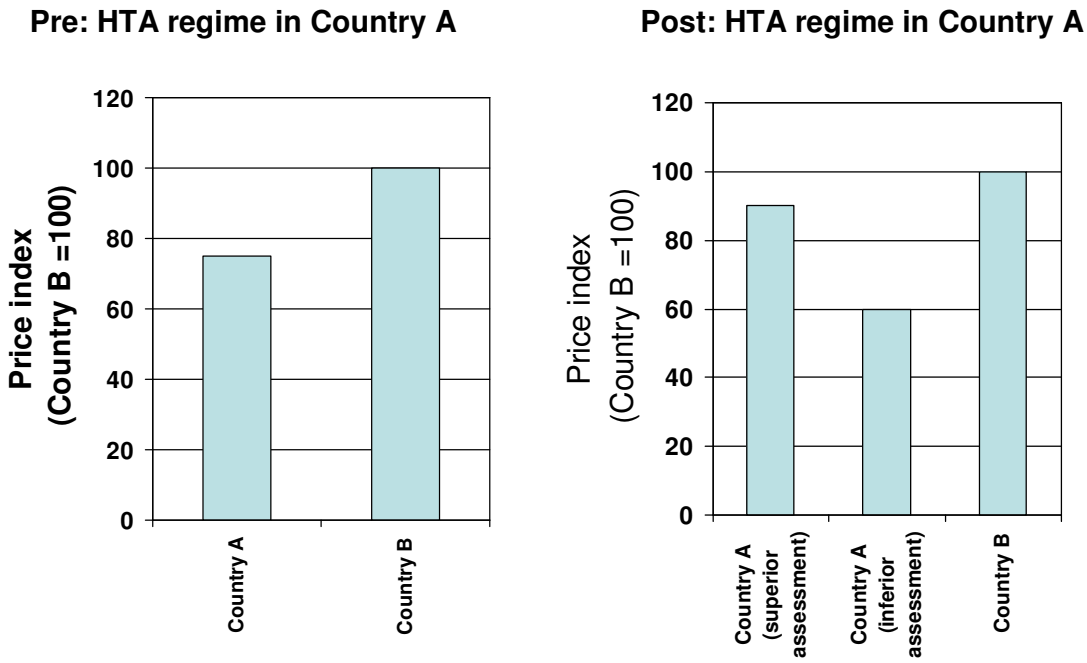
3.3. PRICE AND REIMBURSEMENT OF MEDICINES

One of the most common uses of HTA is to support pricing and reimbursement decisions. An HTA system, that is intended to feed into P&R decision, should encourage a positive reimbursement decision for those medicines which provide greater value than existing alternative treatments and allow premium prices. However, a system of HTA that is focused primarily on constraining costs might do the opposite and penalise products that would be most beneficial to a broad group of patients and therefore impose a higher burden on the public purse.

In general, where HTA is involved in decision of how to reward innovative medicines through its role in the P&R process, a favourable HTA assessment (demonstrating added value) should result in higher percentage of positive reimbursement decisions and a better price than an unfavourable HTA assessment (see Figure 11).

41 Sorenson et al. (2008)

Figure 11: Illustrative impact on price and reimbursement



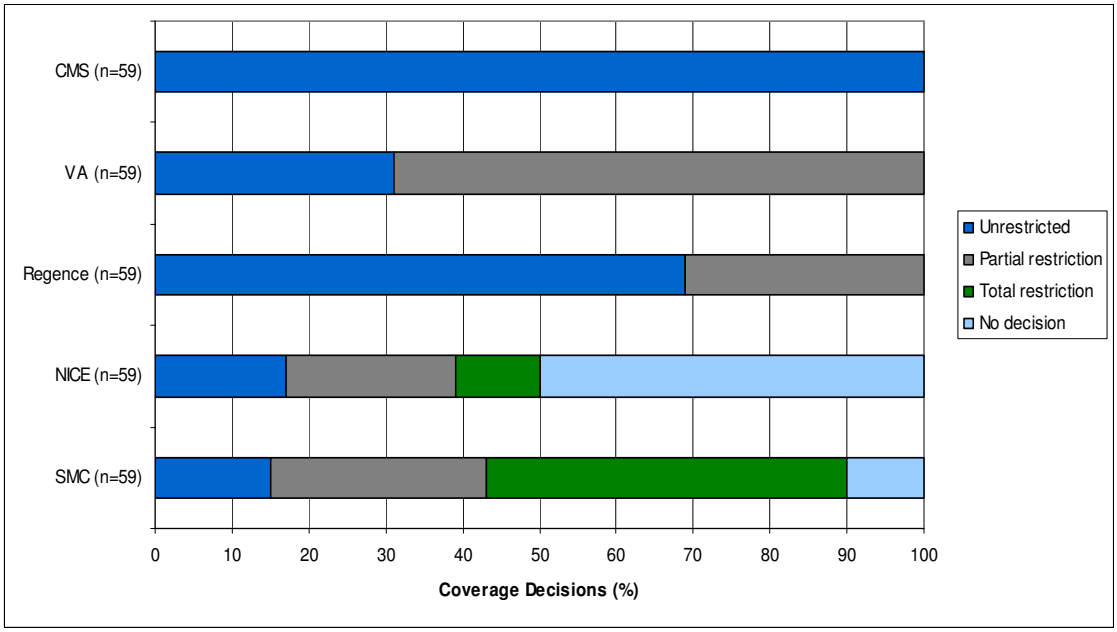
Source: CRA analysis

3.3.1. Reimbursement of medicines

To look at the impact of HTA on access to drugs we can compare decisions made where there is a HTA review with ones where there is not. Mason et al.'s comparison of anticancer drug coverage decisions in the US and UK (see details above) compared coverage decisions between payer bodies for the 59 anticancer drugs approved by the FDA from 2004-2008. The decision-making bodies in the US (CMS, VA and the Regence Group) covered all approved drugs, with some subject to partial restrictions such as prior authorisation requirements. In the UK, only 46 of the 59 drugs were licensed for use by the EMA. NICE and the SMC made positive recommendations for less than half of the licensed drugs, at 39% and 43% respectively. Of the drugs with positive recommendations, 22% were subject to restrictions by NICE and 28% by the SMC.[42] This suggests HTA imposes greater restriction on reimbursement than non HTA based approaches.

42 Mason et al, "Comparison of anticancer drug coverage decisions in the US and UK: does the evidence support the rhetoric?", Journal of Clinical Oncology, July 2010.

Figure 12 Comparison of anticancer drug coverage decisions in the UK and US

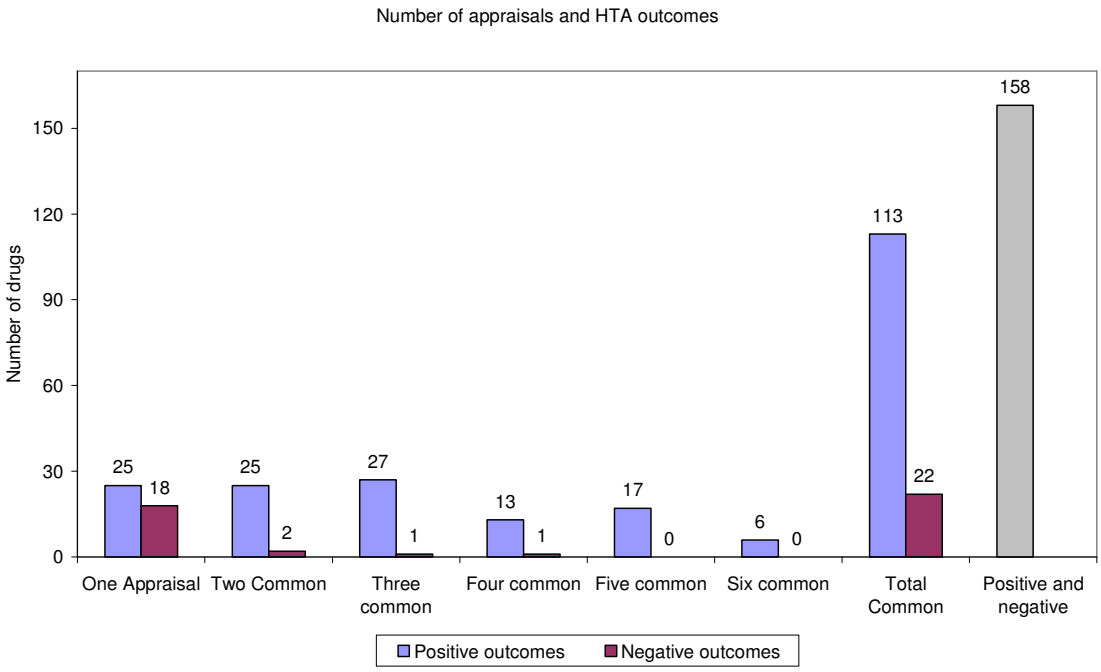


Source: Mason et al. (2010)

A number of studies have compared coverage decisions made by different HTA agencies, indicating how the varying objectives of HTA and approaches employed impact on outcomes.

Kanavos et al. examined all decisions made by the HTA agencies in Australia (PBAC), Canada (CADTH), England (NICE), France (HAS), Scotland (SMC) and Sweden (TLV) over the period 2007-2009, looking at a total 293 appraisals. A significant degree of heterogeneity was found across the decisions made by the different agencies, with almost two thirds of drugs assessed by more than one agency receiving a mix of positive and negative recommendations (see Figure 13).

Figure 13: Number of appraisals and HTA outcome

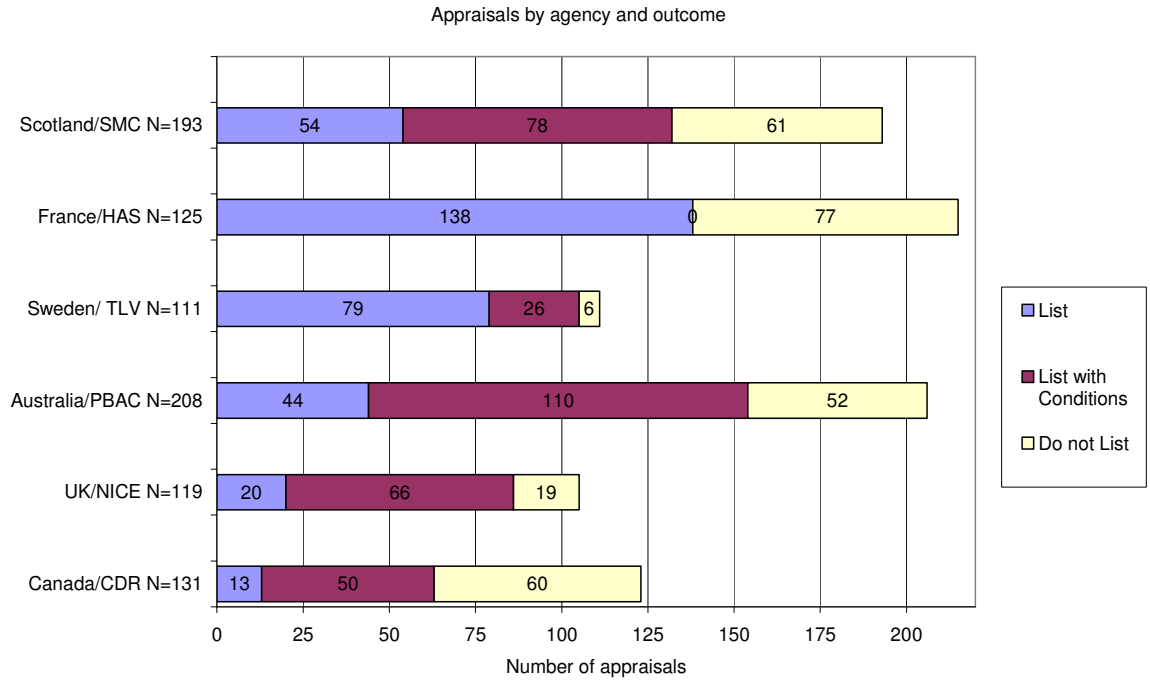


Source: Kanavos et al. 2010

The TLV in Sweden had the highest proportion of positive recommendations (95%), and the CADTH the least (48%) (see Figure 14). An evaluation of the priorities, methodologies and processes of the different agencies identified drivers of the disparities in decisions, including differences in:

- Clinical and economic evidence requirements;
- Preferred clinical endpoints
- Data interpretation;
- Choice of comparator; and
- Use of cost-effectiveness thresholds.

Figure 14: Appraisals by agency and outcome



Source: Kanavos et al. 2010

A comparison of the rigour of the process employed by the different agencies indicated that NICE, PBAC and HAS require the greatest amount of clinical evidence and perform the most rigorous assessments. There did not appear to be a correlation between stringency of requirements and the resulting recommendations, although the authors note that rigour of assessment does have an impact on the time taken for assessment.[43]

A comparison of drug coverage decisions by NICE in England, the common drug review (CDR) in Canada and PBAC in Australia looked at all publicly available assessments from the three agencies as of the end of 2008. NICE gave positive recommendations for 87% of submissions (174 of 199), compared with 50% (60 of 121) for CDR and 54% (153 of 282) for PBAC. There were 91 cases where the same drug was reviewed for the same indication by one or more of the agencies. There was poor agreement between funding recommendations made by CDR and PBAC, and by NICE and PBAC, and moderate agreement between CDR and NICE. For the subset of 19 common drugs considered by all three agencies, NICE was more likely to recommend funding than the other agencies. One of the most common reasons for discrepancies in listing recommendations was a tendency by NICE to find limited niches where drugs were cost-effective rather than giving an overall negative recommendation.[44] This clearly demonstrates the weakness of focusing on only acceptances and not examining the breadth of the approval.

43 Kanavos et al., "The impact of health technology assessments: an international comparison", Euro Observer, 2010

44 Clement at al., "Using effectiveness and cost effectiveness to make drug coverage decisions", JAMA 2009

A comparison of the outcomes of the French and English/Scottish HTA processes allows an insight into the impact of using a cost-effectiveness approach (as used by NICE in England and SMC in Scotland) versus one focused on clinical effectiveness (as used by HAS in France). Ng-Haing reviewed market access decisions for a set of oncology drugs made by the Transparency Commission in France and NICE in England, finding that virtually all were granted market access in France while only about half received positive recommendations from NICE (see Table 12).[45]

Table 12: Decisions of the Transparency Commission in France and NICE in England for 12 oncology drugs

	Positive Market Access Decision	**Negative Market Access Decision**	**Not Reviewed**
England: NICE	Revlimid, Sutent, Tarceva (NSCLC only), Velcade, Glivec	Torisel, Nexavar, Tyverb (interim decision)	Tasigna, Atriance, Sprycel, Evoltra
France: Transparency Commission	All drug indications, except Tarceva for pancreatic cancer	Tarceva (metastatic pancreatic cancer)	

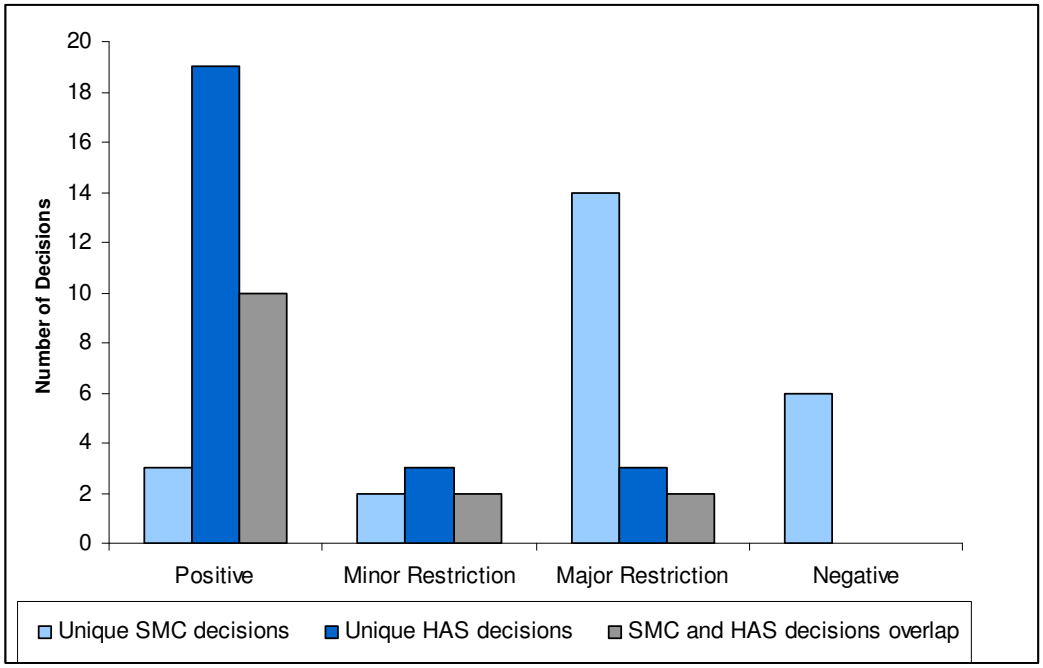
Source: Ng Haing et al, 2010

A study by Bending, Hutton and McGrath looked at 39 common medicine evaluations between 2005 and 2009 by the HAS and SMC. Comparing recommendations showed that the recommendations were the same for 14 of the 39 common evaluations. The SMC had more restrictive listing advice than HAS for 16 medicines and HAS was more restrictive than the SMC in three cases. In six cases, the SMC gave a negative recommendation where HAS gave a positive recommendation (see Figure 15).[46]

45 Ng-Haing et al., presented at ISPOR International meeting 2010

46 Bending MW, Hutton J, McGrath C, “Comparative-effectiveness versus cost-effectiveness: A comparison of the French and Scottish approaches to Single Technology Appraisal", Monday May 17th 2010, ISPOR International, USA

Figure 15 Distribution of decisions by HAS and SMC for 39 common medicine evaluations



Source: Adapted using evidence from Bending, Hutton and McGrath (2010)

The existing analysis of reimbursement decisions would seem to support that systems based on HTA are more likely to impose reimbursement restrictions than those that don't have HTA. HTA based on cost effectiveness appear more restrictive than systems based on an evaluation only of the clinical merits of the medicine.

However, the difficulty with the analysis described above is that from a social perspective it is unclear whether the products with restrictions imposed were those offering the least or the greatest benefits to society. Therefore although it seems clear that HTA affects reimbursement it is difficult to assess whether this is beneficial or harmful.

3.3.2. Pricing of medicines

The next question is whether HTA positively or negatively impacts on the price of new medicines. Few studies have looked at the impact of HTA decisions specifically on pricing.

Kanavos et al. examined price changes following HTA decisions in Canada, England, France Scotland and Sweden, based on a sample of 293 appraisals conducted in the six countries, the results of which is shown in Table 13 below. [47]

Table 13: Price changes following HTA decisions

	Impact of HTA decision on price

47 Kanavos et al., "The impact of health technology assessments: an international comparison", Euro Observer 2010

Canada	CDR recommendations usually associated with upward price volatility for several quarters after recommendation publication
England/ Scotland	Trend effect of immediate increase in price following recommendation, moderating after 6-9 months
France	No visible effect of either positive or negative recommendations on price
Sweden	Some volatility in either direction following TLV recommendation

Source: Kanavos et al. (2010)

The data in Table 13 is surprising. However, the data used to make this assessment and whether it is statistically significant is not disclosed.

Drummond (2010) examined the impact of reference pricing versus health technology assessment on initial price and reimbursement status for innovative drugs in Germany, Netherlands, Sweden and the UK. Drugs in four therapy areas were considered: hyperlipidaemia, diabetes, rheumatoid arthritis and schizophrenia. Most of the decisions following HTA did not represent a straightforward acceptance or rejection of the new drug, but rather limited the use of the drug to indications or patient populations in which it is most cost effective. There was no clear finding regarding the impact of HTA on price, and no pattern was observed in cross-country price differences, which is not unexpected considering that HTA is not used in the context of pricing decisions in the countries in question. However, the report notes that there are examples of manufacturers offering deals that amount to price reductions as part of discussions surrounding HTA, such as risk-sharing agreements and patient access schemes.[48] Therefore even if list prices are the same (or greater) in markets with HTA, the impact of risk-sharing would need to be taken into account.

A study of decisions around funding of expensive drugs notes this indirect impact of HTA on prices, particularly in cases where the drug does not reach the level of cost-effectiveness usually required by HTA agencies. As well as risk-sharing schemes in the UK, the author notes a mechanism used in New Zealand where manufacturers can negotiate price reductions across other products in their portfolio in order to attain market access.[49] Furthermore, an analysis of the impact of HTA on cancer drugs found that some HTA agencies, particularly those in Canada and Australia, exert pressure on manufacturers during the HTA process to decrease pricing thereby increasing the likelihood of a positive reimbursement decision.[50] A final example of the impact of HTA on price is the case of short-acting insulin analogues in Germany, where IQWiG's assessment that the analogues were not superior to human insulins led to discount

48 Drummond et al., "Reimbursement of pharmaceuticals: reference pricing versus health technology assessment", European Journal of Health Economics, August 2010

49 Raftery, "Paying for costly pharmaceuticals: regulation of new drugs in Australia, England and New Zealand". Pharmaceuticals and Prescribing, January 2008

50 Pomedli, "HTA and access to cancer medicines", Euro Observer 2010.

contracts regarding the price of the analogues between sickness funds and the affected pharmaceutical companies.[51]

Even once the price is set, it may be revised over time as part of a scheme agreed between the manufacturer and HTA agency. One of the best documented examples of a scheme of this type is that established in the UK in 2002 for interferon beta and glatiramer acetate in multiple sclerosis (MS). Following NICE's initial recommendation against use of the drugs, a risk sharing scheme was set up under which prices for the drugs were to be reduced if patient outcomes were less than those required to meet a cost per QALY of £36,000. In this case, the prices of the drugs included in the scheme have not been reduced, despite outcomes data showing that the drugs were not effective in preventing disease progression, but the decision not to cut prices has been widely criticised.[52] [53] The increased use of patient access schemes has added complexity to the HTA process. For example, companies advise the Department of Health (DoH) of an impending launch, the DoH may choose to refer them to NICE. NICE commissions an independent HTA study. If there is a negative recommendation, the companies can choose to discuss an arrangement with the DoH (using a template developed by NICE) about the price and/or a patient access plan such that the medicine would be judged to be cost effective.[54]

Finally, the impact of HTA on price has been examined in France, where as part of the HTA process, products are assigned a score based on the improvement in medical value they provide (ASMR score) which is then used to inform pricing decisions.[55] A comparison of prices in the major European pharmaceutical markets by ASMR rating showed that for medicines assessed as the most innovative (ASMR I/II), the prices were on average higher in France than in Spain or the UK, but lower than those in Germany or Italy. Medicines with ASMR III had average prices close to those in Italy and Spain, and ASMR IV medicines had the lowest prices in France compared with the other countries.[56] While it is difficult to draw clear conclusions from this, the results indicate that products with a better HTA recommendation achieve price premiums in line with higher priced countries.

Additional evidence of the impact of HTA on price in France comes from a study on the influence of post-registration studies for reimbursement renewal. For certain drugs, request for a post-registration study is made by the Transparency Commission (CT) or Committee for Pricing of Healthcare Products (CEPS) at the time of the original reimbursement decision in order to develop the evidence base. The results of these studies are then used in subsequent re-evaluations. A review of the 134 requests for post-registration studies made between 1997 and 2008 found that results from 15 of the studies were incorporated into the CT's opinion on the drug in question and impacted on

51 Fricke and Dauben, "Health Technology Assessment: A Perspective from Germany", Value in Health 2009

52 Raftery, "Costly failure of a risk sharing scheme", British Medical Journal June 2010

53 McCabe et al., "Continuing the scheme is unjustified", British Medical Journal June 2010

54 The use of patient access schemes may change with the implementation of value based pricing.

55 ASMR scores range from 1-V, with ASMR I assigned to most innovative products and ASMR V to the least.

56 Geoffard and Sauri, "Comparison internationale des prix des nouveaux medicaments" 2008

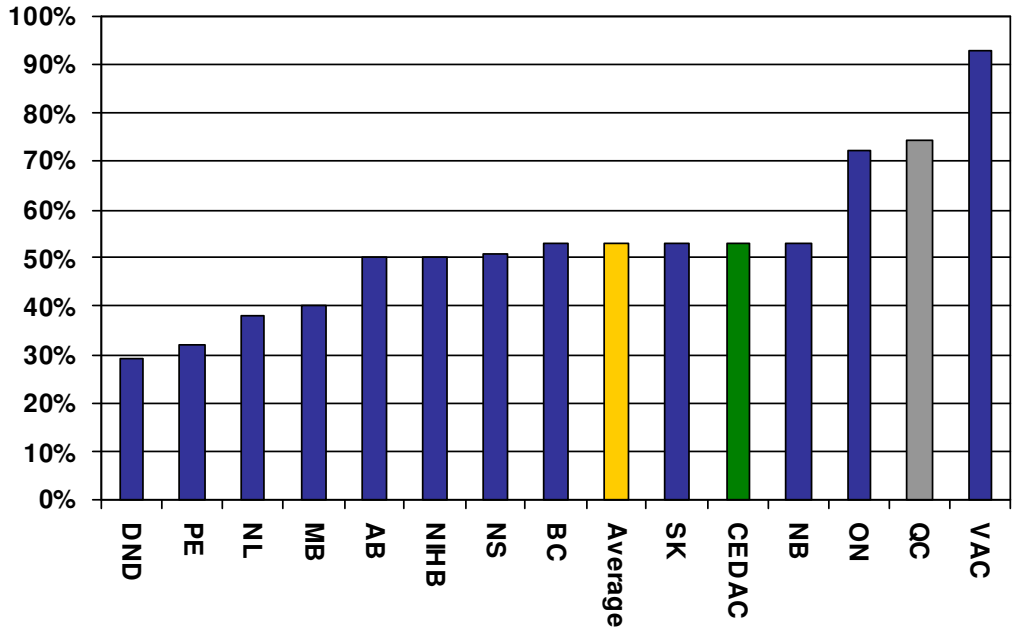
the price of the product in a proportion of these.[57] [58] This shows that HTA can, at least in principle, affect the price at launch and affect the price later during the product lifecycle as new information on the value of the product is brought to light.

3.3.3. Regional decision-making

In some jurisdictions, the national HTA agency's decisions may not be followed by regional decision-makers either because the national decisions are not binding on these decision-makers or because there are barriers to implementation such as local budgetary constraints. This can lead to regional variation in access to drugs, which is of particular concern given that standardising access to medicines is an explicit goal of HTA in many countries.

In Canada, the decision made by CEDAC in the Common Drug Review (CDR) process is intended to provide guidance to the individual provincial public drug plans which make their own decisions on drug coverage. A report by Rx&D, the Canadian pharmaceutical industry association, examined reimbursement status of 82 drugs in Canada in 2009. CEDAC had given a positive reimbursement decision for 56% of the drugs and average reimbursement by the provincial plans was slightly lower than this with significant variation between plans (see Figure 16).[59]

Figure 16: Percent public positive reimbursement of 82 drugs by province, 2009



Note that Quebec does not participate in the CDR.

Source: The Rx&D International Report On Access To Medicines, 2008/2009

57 Molimard et al., "Value of Post-Registration Studies for Reimbursement Renewal", Therapie 2009

58 Maugendre, Rencontres HAS 2008

59 The Rx&D International Report On Access To Medicines, 2008/2009

In England, PCTs are currently legally responsible to implement positive NICE guidance within three months of it being issued but in the case of negative guidance, or in cases where it has not been published, PCTs can make their own decisions on funding. A 2005 Audit Commission study of all NHS trusts in England found only 25% of sites could verify that NICE appraisals were implemented within the three month deadline.[60] More recently, an NHS Information Centre report on use of NICE appraised medicines showed significant variation between PCTs in drug usage. For example, use of ezetimibe in 2008 ranged between PCTs from approximately half to three times the level modelled as appropriate by NICE.[61] Sheldon et al.'s 2004 study of the impact of NICE guidance on clinical practice identified features of organisations that are associated with high compliance with NICE guidance, including appropriate funding for implementation and a recognition of the legitimacy of NICE.[62]

There is a consistent picture emerging from systems with regional budget responsibility but centralised HTA. Where HTA is undertaken at a different level of the budget holder the degree of consistency between decisions and actual reimbursement decreases significantly. The result of this is that the HTA assessment is not predictive of an ultimately favourable price and reimbursement assessment.

3.4. DIFFUSION OF MEDICINES

HTA could affect the uptake of the medicine. This could be directly because there is a requirement for physicians to adopt the decision of the HTA or through dissemination of information about the medicine (which could in principle affect local payers, physicians or even patients). Equally, HTA could constrain diffusion by limiting the usage of the medicine to niche markets.

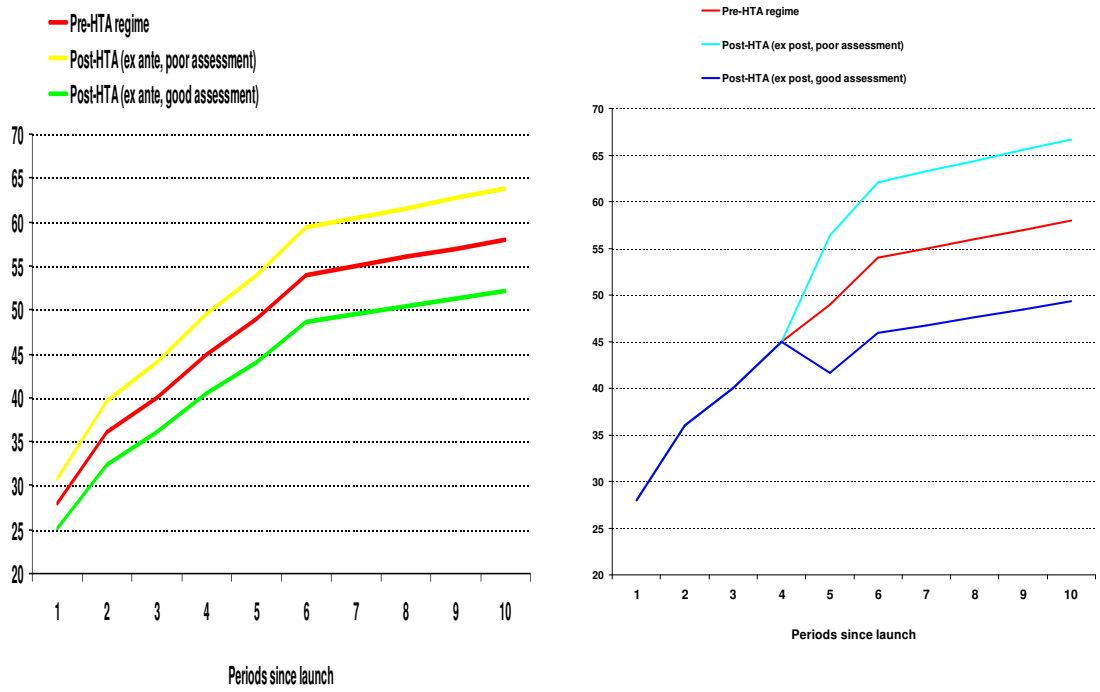
Figure 17 illustrates one of the challenges of observing the impact of HTA decisions, for ex ante systems we cannot observe the diffusion rates that would have happened without the HTA system. The impact of HTA decisions is therefore more easily observed in ex post systems.

60 Managing the financial implications of NICE guidance

61 Use of NICE appraised medicines in the NHS in England, NHS Information Centre 2009

62 Sheldon et al., "What's the evidence that NICE guidance has been implemented?", British Medical Journal, October 2004

Figure 17: Illustrative impact on diffusion



Source: CRA analysis

The impact of HTA decisions on the utilisation and speed of take-up of a product has been considered in a number of reports. In Morgan et al.'s comparison of listing decisions and their impact on cost and use in Australia, Canada, New Zealand and the UK, the impact of restricted coverage decisions varied between countries, attributed to the varying types of restrictions imposed in each case. As expected, however, rates of use were generally highest in countries with a national positive listing decision and lowest in countries with a national negative listing decision. In Canada, of the four drugs that had positive listing in all provinces, three had below-average use relative to the other countries in the study, a reflection of the fact that a minority of drug spending in Canada is paid for by the government and therefore impacted by HTA.[63]

In the UK, a report commissioned by the Secretary of State for Health examined the extent and causes of international variations in drug usage. The study examined uptake rates of drugs in a number of disease areas across 14 countries, of which ten are in the scope of this project .[64] The impact of HTA on drug uptake was considered and to what degree it contributed to variations in uptake across countries, with a focus on the impact of NICE guidance on drug uptake in the UK relative to the other countries in the study.

Countries with broadly similar HTA processes based on assessment of cost-effectiveness (Australia, Canada, Sweden and the UK) were found to have similar levels of uptake

63 Morgan et al., "Centralized Drug Review Processes in Australia, Canada, New Zealand and the UK", Health Affairs, 2006

64 Australia, Canada, Denmark, France, Germany, Italy, New Zealand, Spain, Sweden and the UK

across some disease areas. NICE positive guidance did not always result in higher than average use of medicines, but negative guidance generally translated to low uptake. The clearest impact of NICE guidance was in situations where NICE had recommended one drug within a category but not another.

The impact of guidance restricting use to a subgroup of patients or to a defined position in the treatment pathway was most apparent in the variation in the use of biologics for the treatment of rheumatoid arthritis, where the UK uptake was 73% of the all-country average. This was attributed to more stringent disease activity thresholds being applied in the UK, more selective guidance on some drugs and negative and/or pending guidance on others. The study concludes that HTA processes have a significant impact on levels of drug usage, but cannot alone explain international variations.[65]

Although this study points to some interesting results, there are weaknesses in the methodology employed. As recognised in the report, although efforts were made to minimise errors, there are issues with the completeness and reliability of the data sourced from IMS Health, Furthermore, findings on the cause of variation in uptake between countries (including use of HTA) were based on discussions with experts on their interpretation of the data rather than on any statistical analysis,

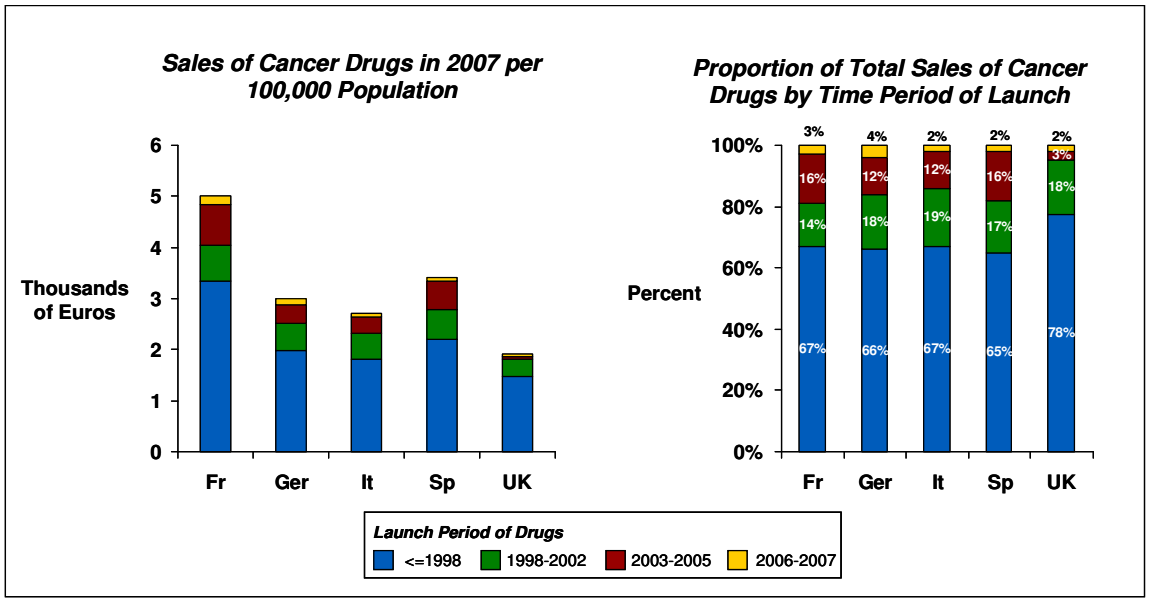
(as measured by defined daily doses per head of population allowing for prevalence where possible) for 14 markets

Wilking and Jonsson's comparison of patient access to cancer drugs in Europe found significant variation in the rate and level of uptake of cancer drugs between countries. Among Western European countries, the UK has one of the lowest levels of medication usage, in particular of new medicines, and has a relatively long time to uptake (see Figure 18). The study finds that there are indications that NICE guidance has impacted on drug usage in some cases, but that there is no evidence of systematic impact of HTA on uptake of new drugs.[66]

65 "Extent and causes of international variations in drug usage", A report for the Secretary of State for Health by Professor Sir Mike Richards, July 2010

66 Wilking et al, "Comparator Report on Patient Access to Cancer Drugs in Europe", January 2009

Figure 18: Uptake of cancer drugs in the major European markets



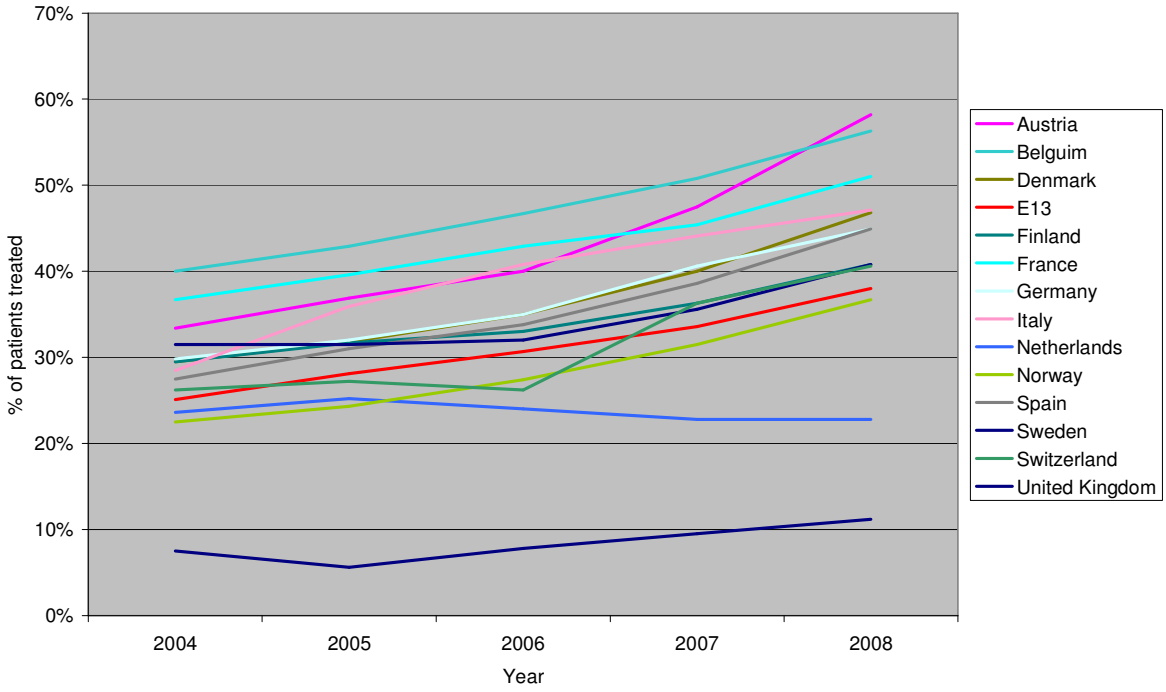
Source: Wilking et al. 2009

A survey of access to innovative rheumatoid arthritis treatments in Europe found that Norway, Belgium, Switzerland and Sweden have the highest proportions of rheumatoid arthritis patients treated with biologic drugs, while Austria, Italy, Germany and the UK have the lowest proportions. Variations in the assessment of cost-effectiveness of these drugs in the respective countries appears to have contributed to differences in usage, although this is only one of a number of factors that have an effect such as clinical guidelines and institutional budget limitations.[67] An associated survey of access to innovative treatments for multiple sclerosis (MS) in Europe found that cost-effectiveness assessment had significantly less impact on differences in usage across countries than was the case for rheumatoid arthritis drugs. The MS treatments investigated generally achieved reimbursement without many restrictions, except in the UK, where NICE's restrictive evaluation accounts for the lowest use of biologic disease modifying treatments among the EU13 countries assessed (see Figure 19). The authors suggest that in most countries, because of the limited number of MS patients, reimbursement decisions are based more on budget impact analysis than on cost-effectiveness analysis.[68] This suggests the influence of the HTA is also likely to vary by therapeutic area.

67 "Access to innovative treatments in rheumatoid arthritis in Europe", report prepared for EFPIA, October 2009

68 "Access to innovative treatments in multiple sclerosis in Europe", report prepared for EFPIA, October 2009

Figure 19: Proportion of multiple sclerosis patients treated with biologic disease modifying treatments in EU13



Source: Kobelt and Fasteng 2009

Packer et al. have analysed the diffusion of six health technologies, including four pharmaceutical technologies and two devices, across ten countries.[69] The aim of the study was to assess the factors driving differences in diffusion between the countries, by examining the relationship between diffusion and five potentially explanatory variables, one of which was "the presence of HTA or other guidance". The existence of HTA or other guidance was found to be associated with increased diffusion in five out of six cases, and with decreased diffusion in the remaining case (COX II inhibitors) (see Table 14). It was evident that in the five cases where the presence of HTA had a positive impact on diffusion, this was regardless of whether the guidance was supportive; although the nature of the HTA guidance in each case was not systematically assessed, there were cases where restrictive guidance was associated with increased diffusion. The authors suggest that this is because "all publicity is good publicity".[70]

Table 14: Impact of five variables on technology diffusion

Variable	Sildenafil	COX II Inhibitors	Verteporfin	Interferon beta	Drug-eluting stents	Deep brain stimulators

69 Australia, Canada, Denmark, France, The Netherlands, Norway, Spain, Sweden, Switzerland and the UK

70 Packer et al., "International diffusion of new health technologies: A ten country analysis of six health technologies", International Journal of Technology Assessment in Health Care, 2006

Early warning activity	No net effect	No net effect	Reduce	Reduce	Increase	Reduce
HTA or other guidance	*Increase*	*Reduce*	*Increase*	*Increase*	*Increase*	*Increase*
National coverage decision	*	Reduce	Reduce	Reduce	No net effect	No net effect
Health spend per capita above average	Increase	Increase	No net effect	No net effect	Increase	Increase
Health funding from taxation above average	No net effect	*	Reduce	Reduce	No net effect	No net effect
Percent variation explained	60%	79%	79%	74%	91%	62%

* Variable was not independent of the other variables and was therefore omitted

Source: Packer et al. 2006

However, even if the positive HTA decisions brings advantages in terms of diffusion, it does so at a cost. In England, NICE has been criticised for the delay between drug availability and publication of NICE guidance, leading to limited access prior to review ("NICE blight") as clinicians may prefer to wait for NICE's decision or may be forbidden from prescribing the medicine by their PCT. While this phenomenon is widely recognised, there is little systematic evidence of the frequency and degree to which this happens. [71] [72] [73]

3.5. CLINICAL PRACTICE

As discussed above, the existing literature on the impact of HTA on clinical practice has predominantly focused on the impact of academic HTA in its broadest sense[74] encompassing academic studies published in scientific journals and clinical guidelines.

Gerhardus et al. have conducted a systematic review of the literature from 1990-2007 that examines the impact of HTA reports on decision making. The majority of the studies identified in the review looked at the impact of NICE guidance on the dissemination of pharmaceuticals and procedures. Findings on the impact of NICE guidance varied between studies, with one showing that practice reflected the recommendations of the NICE appraisals evaluated, while a number of others found that only a proportion of guidance decisions had an impact.

71 House of Commons Health Committee Report on NICE, 2008

72 Drummond and Sorenson, "Nasty or Nice? A perspective on the Use of Health Technology Assessment in the UK", Value in Health, September 2009

73 OFT Review of NICE, SMC and AWSMG 2007

74 For example, the Euromet 2004 survey on the influence of economic evaluation studies on healthcare decision-making

In total, the authors identified 60 studies for inclusion in the review, the results of which were analysed according to a hierarchical framework of the levels of impact an HTA report may have (see above). The key results of the systematic review are shown in Table 15 below.[75]

Table 15: Summary of key results from a systematic review of literature on the impact of HTA

Impact Step	Number of studies reviewed	Key results from studies
Awareness of HTA findings among target groups	9	40-85% awareness; >60% in most studies. Whether respondents actually knew the guidance they claimed to know was not tested.
Acceptance: attitudes towards HTA reports	9	Broad variation: In two studies, recommendations were almost unanimously accepted but the report was perceived as stating the obvious and had limited impact on practice. Other studies showed heterogeneous acceptance. One study in the UK showed positive reaction from healthcare managers but a sceptical response from physicians.
Policy: impact on health policy process	5	HTA reports were often found to be controversial. One study showed two HTAs significantly changed implementation of technologies but had no impact on coverage decision
Policy: impact on health policy decisions	14	Majority of studies found at least 70% of HTAs to have impacted on policy. Some studies found the impact was variable depending on the professional groups and types of hospitals.
Policy: impact on clinical practice	17	Most studies investigated the impact of NICE guidance on dissemination of pharmaceuticals and procedures. Findings varied between studies. One concluded that practice basically reflected NICE recommendations. Other studies suggested that about half of guidance decisions had an impact. A high degree of regional variation in implementation of NICE guidance was demonstrated. A Swedish study found five out of seven reports had an impact.
Outcome: impact on health and economic parameters	4	One study analysing impact of eight reports on health status in Australia found probable impact for two, possible impact for one, and unknown impact or too early to assess for the remaining four. Three studies from Canada modelled hypothetical savings from HTA reports.

Source: Gerhardus et al. 2008

An earlier study conducted by Sheldon et al., included in the systematic review, is particularly informative in highlighting which types of guidance are most likely to have an impact on clinical practice and in which environments guidance is most likely to be implemented. The study looked at the impact of NICE guidance for procedures, pharmaceuticals and devices using prescribing data and hospital episodes statistics to assess the extent to which practice changed after the publication of guidance. Data from

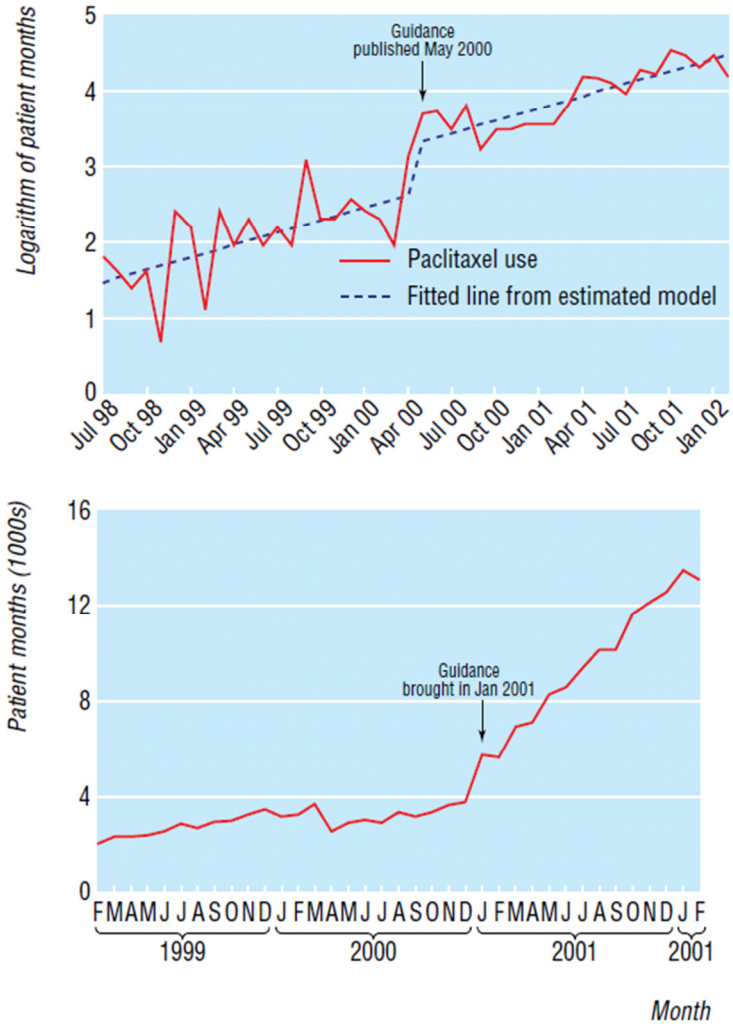
75 Gerhardus et al., "What are the effects of HTA reports on the health system? Evidence from the research literature" in Health Technology Assessment And Health Policy-Making In Europe: Current status, challenges and potential, European Observatory on Health Systems and Policies 2008

clinical audits was used to assess whether guidance was being implemented appropriately, and surveys and interviews with clinicians and managers revealed factors influencing likelihood of implementation.

In general, NICE guidance on pharmaceuticals was found to have a greater impact on practice than guidance for procedures and devices, although the data was mixed. Use of orlistat (for obesity) and taxanes (for ovarian and breast cancer), for example, increased rapidly following the publication of NICE guidance, while use of Alzheimer's drugs also increased but the trend started before the publication of guidance (see Figure 20). Similarly, other guidance such as that regarding wisdom teeth extraction was shown to have been adopted in accordance with NICE guidance but in continuation of a trend which was set prior to the guidance publication. In some cases, clinical audit showed that practice was compliant with the indications for treatment specified in the guidance, for example the use of taxanes in breast cancer, while compliance was low in other cases, for example for orlistat. Overall, the study concludes that guidance is more likely to be implemented where there is strong professional support, clear demonstrated value with a strong evidence base and adequate funding.[76]

76 Sheldon et al., "What's the evidence that NICE guidance has been implemented?", British Medical Journal, October 2004

Figure 20: Use of paclitaxel (top) and Alzheimer's drugs before and after positive NICE guidance



Source: Sheldon et al. 2004

The impact of negative or restricting guidance in particular has been examined in a study looking at prescribing prior to and following the publication of such guidance by NICE. The analysis of prescription volume of 31 medicines reviewed by NICE between 2000 and 2004 found no measurable decline in prescribing of these drugs following the publication of the guidance. The author suggests that the apparent lack of negative impact on prescribing rates is due to the lack of sanctions on physicians for noncompliance with guidance and the degree of restrictiveness that is really imposed in "restrictive" guidance.[77]

A UK survey examining the views and experiences of clinical professionals with regard to NICE guidance found that the majority were supportive of the existence of NICE in

77 Dietrich, "Effects of the National Institute for Health and Clinical Excellence's technology appraisals on prescribing and net ingredient costs of drugs in the National Health Service in England", International Journal of Technology Assessment in Health Care, 2009

principle. GPs in particular found NICE guidance valuable in assisting their decision making, although it was noted that guidance was less likely to be implemented where it did not conform to physicians' personal interpretations of the evidence. Only one of the twelve professionals interviewed commented that NICE acted as a constraint on autonomous decision-making but noted that it was usually possible to get around rationing decisions seen as inappropriate.[78]

There is therefore some evidence that HTA affects clinical decisions, however, the magnitude of this affect and how this varies by type of HTA is an area requiring additional research.

3.6. INCENTIVES TO INNOVATE

The next impact we consider is on the incentive to invest in R&D for innovation. It is argued that while HTA should identify and reward products that are of high medical value, but there are concerns that HTA does not take the process of innovation into account adequately. Failing to reward innovation for a given technology not only adversely impacts diffusion of that technology but also compromises future follow-on developments that would be of benefit to patients.[79]

There is limited empirical evidence on the impact of HTA on incentives to innovate, but Jena and Philipson argue from a theoretical perspective that cost effectiveness thresholds effectively act as price controls, and as such can have similar negative effects on economic efficiency. Cost effectiveness assessment is based on a comparison of patient benefits from a technology with spending on that technology and is therefore focused on maximising the static consumer surplus. This is at the expense of profits to innovators and therefore of dynamic efficiency.[80]

Camejo et al. also argue that decision making based on cost effectiveness can act as a barrier to investment in R&D, focusing on the shortcomings of a uniform cost effectiveness threshold applied across disease areas. Within a disease area, the clinical effectiveness of standard care tends to increase over time with successive introduction of new drugs and clinical experience. Hence the clinical effectiveness of comparators used in cost effectiveness analysis increases over time, while prices decrease due to market competition. At the same time the cost of R&D increases over time (as has been the case over the last decades). As these trends occur at different rates across disease areas, the authors argue that a general cost effectiveness threshold applied uniformly may prevent investment in efficient R&D, resulting in a loss of affordable, clinically effective technologies.[81]

There are indications that the requirements of HTA are having an impact on the decisions pharmaceutical manufacturers make regarding R&D investment. For example, there is

78 Owen-Smith et al., "The usefulness of NICE guidance in practice: Different perspectives of managers, clinicians and patients", International Journal of technology Assessment in Health Care, 2010

79 Sussex, "Innovation in Medicines: Can we Value Progress?", Office of Health Economics, 2010

80 Jena and Philipson, "Cost-effectiveness analysis and innovation", Journal of Health Economics 2008

81 Camejo et al., "A dynamic perspective on pharmaceutical competition, drug development and cost effectiveness", Health Policy, 2010

real world evidence that pharmaceutical companies discontinued development of particular candidates (for example, the osteoporosis candidate arzoxifene) despite having demonstrated its effectiveness in a phase III trial, as there was no evidence of an advantage over existing therapies.[82]

However, we are unaware of any empirical evidence demonstrating the relationship between HTA and incentives to innovate.

3.7. THE COST-BENEFIT ASSOCIATED WITH HTA

Finally, the overall impact of the HTA could be assessed by comparing the cost to the benefits. From a government health system perspective, who are the main funders of HTA agencies, the obvious question to address after a 5-10 years period of experience is, 'Can we quantify areas where we have improved the efficiency of allocating our scarce resources by following the recommendations of our HTA agencies?'

There are few studies that have looked at this question. Basu and Philipson have simulated the impact on health outcomes and medical spending of health payers implementing policies which reflect comparative effectiveness research. The analysis is focused on the US antipsychotic medicines market and the effects of the CATIE comparative effectiveness study, which found that more costly second generation drugs had equal effectiveness to first generation drugs. The authors model the impact of Medicaid responding to this study by restricting coverage to a single drug from the second generation class. They conclude that this would lead to a reduction in spending on medication, but this would be outweighed by a negative impact on the overall health of the covered schizophrenia population and increased spending on psychiatric service utilisation. This is a result of the fact that the most effective treatment choice will be different for different patients, and hence some patients will relapse because of the unavailability of alternative treatments. Monetising the cost of a QALY at $100,000, the authors calculate that a restrictive policy on the coverage of second generation drugs would produce a loss of $0.1bn for Medicaid programmes compared with an open policy.[83]

We have not, however, found any overall estimates of the actual benefits of HTA. In particular there does not appear to be a comparison of the expenditure that would have happened without the HTA and the allocation of resource with the HTA.

Equally, an analysis of the cost-benefit associated with HTA would require an examination of the costs. The implementation of HTA can be costly (although the costs are small relative to overall healthcare costs). The cost of HTA can be looked at in terms of direct cost (of the agency that undertakes the HTA), the cost on the industry of preparing the HTA submission (and the cost of delay could also be included) and other stakeholders notably patients and physicians. There is very little literature on the cost of

82 Berger and Grainger, "Comparative Effectiveness Research, The View from a Pharmaceutical Company", Pharmacoeconomics, 2010

83 Basu and Philipson, "The Impact of Comparative Effectiveness Research on Health and Health Care Spending", National Bureau of Economic Research 2010

undertaking an HTA. Table 16 reports the budgets of several HTA agencies in different countries that have been discussed in the literature.[84]

Table 16: Resources of HTA agencies in 5 countries

	Australia	Canada	Germany	Sweden	UK[85]
HTA agency	MSAC/PBAC	CADTH	IQWiG	LFN	NICE
Funding	$22.83m	$17.9m	$19.3m	$7.31m	$48.6m
Permanent staff	15/17	Over 100	92	30	270

Source: Perez Pugatsch (2009) and OFT (2007)

The literature suggests that given limited resources, most governments struggle to keep pace with the introduction of new health technologies. This is especially true in smaller countries, where resources for the evaluation of health technologies may be limited. Prioritizing topics for assessment has therefore become an important part of the HTA process.[86]

For countries with greater capacity constraints, it is important to consider the total available budget, available human capital (trained HTA evaluators), accessibility of data, and the capacity of the health care system to use the results. These factors often influence the number and range of assessments that can be conducted. Moreover, determining which technologies or interventions to assess is often influenced by the availability of data or published reports of economic analyses, known clinical relevance and the prospective budget impact.[87]

Therefore, even though HTA assesses the costs and benefits of particular healthcare technologies we have not found any attempt to apply the rigour of cost benefit analysis to HTA itself to show whether the overall impact is positive or negative.

3.8. OVERALL ASSESSMENT

In this chapter we have reviewed the existing literature on the impact of HTA. The results of this are summarised in Table 17 below. Although there is a significant literature comparing reimbursement decisions, diffusion and the impact on clinical practice, there is little on the impact on prices or the allocation of expenditures. Little of the literature examines whether the outcome of the HTA is consistent with the value of the medicine, the type of HTA or ultimately if this results in a superior allocation of scarce health resources. Even if this was the case, the limited data on the cost of HTA means we would still not be able to determine if HTA brought benefits to society.

84 Perez Pugatch (2009)

85 The funding and staff figures apply to all NICE's activities, not just technology appraisal. As set out in Table 26 only about €7 million is associated directly to HTA.

86 Sorenson et al. (2008)

87 Sorenson et al. (2008)

Table 17: The impact of HTA by stakeholder

Stakeholder	Impact	Potential measure	Existing evidence
Patients	Allocate resources on health services that offer greatest benefits	Distribution of expenditure	No analysis that directly relates HTA to impact on allocation of resources
	Speed of access to good value medicines	Impact of HTA review on time to market	HTA clearly increases time relative to markets where manufacturers are free to launch. However, no evidence that HTA increases time relative to countries with a traditional P&R approach Results in greater restriction being imposed on reimbursement of medicines but little assessment of detriment imposed
	Availability of good value medicines	Diffusion of medicines to patient population	Mixed evidence. HTA appears to slow diffusion but a positive assessment appears to increase diffusion
Physicians	Provide information regarding best clinical practice	Awareness of changes to best clinical practice	Physician appear to value information but awareness varies considerably
	Affect clinical standards	Adoption of changes to best clinical practice, reduce variation in patterns of treatment	Mixed evidence but overall HTA is seen to have an impact on clinical standards if funding is available
Payers	Efficiency of health system	Cost savings achieved from assessing redundant or inferior technologies	No analysis that directly relates HTA to impact on allocation of resources
	Imposes a direct cost	Cost of the HTA	Broad estimates but no attempt to determine how cost vary by type of HTA
Pharmaceutical industry	Affect return to innovative medicines	Allocation of resources to products and speed of assessment	Very limited information on the relationship between HTA and price. Analysis of the French system shows HTA can associate price to value and even incorporate information over time Theoretical argument that HTA favour static efficiency over dynamic efficiency and hence lower returns to innovation
	Predictability of rewards for future	Consistency between HTA assessment and P&R decisions	Regional systems show markedly less relationship between the HTA and the ultimate P&R decision

Source: CRA analysis

4. THE ASSESSMENT

In this chapter we use the information collected in the literature review, review of HTA documents, the input from our interviews with HTA agency representatives and analysis of case studies to compare the role and impact of HTA in different countries. We start with a comparison of the role of HTA in the policy context and then review how these systems compare against the best practice principles described in chapter 2.

It is clear from the overview presented in Table 18 that the agencies responsible for HTA vary significantly in terms of the number of reviews completed in 2009 and the number of our case studies where a review has been undertaken.[88]

Table 18: HTA in the selected markets

Country	Principle HTA agency	Other HTA agencies/ programme	# in 2009	Coverage of case studies
Australia	PBAC	N/A	228 (73 major submissions)	7
Brazil	CITEC	REBRATS	14	1
Canada	CADTH	JODR	28	4
England	NICE	NCCHTA	17	6
France	HAS (transparency commission)	HAS (CEESP)	657	12
Germany	IQWiG	DIMDI	6	0
Italy	AIFA	N/A	Unknown	N/A
Netherlands	CVZ	Gezondheisraad	41	9
New Zealand	PHARMAC	N/A	58	4
Poland	AOTM	N/A	66	4
Scotland	SMC	SIGN	82	12
South Korea	HIRA	NHTA	53	1
Spain	CAHIAQ (Catalan HTA Agency)	Other regional agencies; National Instituto Superior Carlos III	6	0

88 Given the methodology it is unsurprising that we find the greatest number are in France and Scotland. In some markets the number is low as not all products undergo HTA. This is the case in the UK and Germany for example. In other markets, this reflects the fact that products will only be reviewed in the future. In two countries, Italy and Turkey, the assessments are not published and therefore we have not been able to review the case studies.

Sweden	TLV	SBU	30	6
Turkey	SSK	N/A	Unknown	N/A

Source: CRA analysis

4.1. THE ROLE OF THE HTA IN THE POLICY PROCESS

The first issue to establish is the role of the HTA process in the health system. The simplest method is to look at the formal objectives of the HTA process. Table 19 sets out our assessment of the objectives of each of the HTA processes.[89] As expected all HTA processes are undertaken to assess clinical benefits of the medicine, however, the role in terms of value for money and budget impact vary significantly. Only a small number of HTA processes aim to reduce regional disparities.

Table 19: Stated objective of the HTA process

Country	Assessment of Therapeutic Value	Assessment of Value for Money	Assessment of Budget Impact	Avoid Regional Disparities
Australia	✓	✓	✓	
Brazil	✓	✓	✓	
Canada	✓	✓		✓
England	✓	✓		✓
France	✓			
Germany	✓	✓		
Italy	✓	✓ (reg.)	✓ (reg.)	
Netherlands	✓	✓	✓	
New Zealand	✓	✓	✓	
Poland	✓	✓	✓	
Scotland	✓	✓		✓
South Korea	✓	✓	✓	
Spain	✓	✓		
Sweden	✓	✓		
Turkey	✓	✓	✓	

Source: CRA analysis

89 The first principle of the International groups principles reflect whether HTA has an explicit objective. Based on an early review it seems clear that all HTA systems have explicit objectives.

In Table 20 we summarise the role of the HTA in terms of whether it is a formal part of the P&R process (defined as the requirement to undertake an HTA to achieve a P&R decision) and the primary influence of the HTA in terms of pricing, the reimbursement category or its role in determining access (in terms of restriction imposed on the product). As can be seen 11 of the 15 HTA processes reviewed are a formal part of the P&R process.

Table 20: The role of HTA in the pricing, reimbursement and market access decision

Country	HTA Separate/Part of P&R Process	Influence on Price, Reimbursement and Market Access
Australia	Part	Price and access
Brazil	Part	Access only
Canada	Part	Access only
England	Separate	Access only
France	Part	Price, reimbursement and access
Germany	Separate	Reimbursement and access
Italy	Part	Price and reimbursement (limited influence)
Netherlands	Part	Price, reimbursement and access
New Zealand	Part	Price and access
Poland	Part	Price and access
Scotland	Separate	Access only
South Korea	Part	Price and access
Spain	Part (regional reim-bursement)	Access only
Sweden	Part	Reimbursement and access; some influence on price [90]
Turkey	Part	Price and access (limited influence)

Source: CRA analysis

The UK's NICE and SMC and Germany standout as a separate process that is not required to determine price and reimbursement (although they clearly are a significant

90 There are no negotiations on price in Sweden; reimbursement is rejected if the price is deemed too high and the company can re-apply with a lower price

impact on usage). The German and UK assessment will clearly change following upcoming reforms.[91]

An additional dimension of the role of HTA in the price and reimbursement process is the timing of the review. Using the models described in the introduction we have assessed whether the role of the HTA is ex ante - prior to the launch (and P&R decision) – or occurs after the medicine has been launched on the market. This is summarised in Table 21 (and presented in detail in the appendix).

Table 21: Models of HTA

Model of HTA	Countries
Ex ante relative effectiveness	France (old), Italy
Ex ante cost effectiveness	Australia, Brazil, Canada, England (new), Italy (regional), Netherlands, New Zealand, Poland, Scotland, South Korea, Spain, Sweden, Turkey
Ex post relative effectiveness	US (not included in the study)
Ex post cost effectiveness	England (old), Germany (old)
Ex ante relative effectiveness & ex post cost effectiveness	France (new), Germany (new)

Source: CRA analysis

As can be seen from Table 21 the great majority of systems we have assessed are ex ante systems based on cost effectiveness. It is also apparent that many markets are still evolving with the English (as the system moves from assessing multiple medicines to focusing on single technology assessments much closer to launch)[92], French (through the incorporation of the economic assessments undertaken by the CEESP) and German system (through the AMNOG reforms) possibly changing categories in the near future.

Given the role of the HTA process, the next step is to assess first the scope and prioritisation by which individual assessments are undertaken, then the methodologies adopted, the process for taking into account information and different stakeholder interests and finally the impact of the HTA process.

91 Under the AMNOG reforms in Germany there will be an assessment of added therapeutic value of the medicine within one year, this will determine if the product enters into the reference pricing system or there is a negotiation with the manufacturers regarding a rebate. A system of Value Based Pricing in which HTA will have an important role in price-setting is expected to be introduced in the UK by 2014. As discussed in "A new value-based approach to the pricing of branded medicines A consultation" December 2010.

92 The English system is likely to evolve further with the proposed development of value based pricing.

4.2. SCOPE AND PRIORITISATION

4.2.1. Principle 1: HTA should be an unbiased and transparent exercise

The first principle focuses on whether the HTA process is absent of bias and transparent. In the majority of assessed countries, HTA is conducted independently of groups that have a vested interest in the outcome. For example, in Canada, the CADTH is an independent advisory body to the provincial payers, and in the Netherlands, a separate committee (the CFH) is responsible for conducting the HTA which provides the basis for CVZ's recommendations on pricing and coverage in the basic health insurance package. Countries scoring amber are those where although HTA is conducted by an independent body, there have been instances where its decisions appear to have been influenced by political interests. For example, NICE's decision to review and recommend Herceptin (trastuzumab) for early stage breast cancer has come under criticism for being influenced by governmental pressure[93]. In Italy, New Zealand and Turkey, the HTA process is considered to be undertaken by parties that have a clear vested interest in the outcome. New Zealand's PHARMAC has a clear remit to manage the pharmaceutical budget; in Italy, HTA at regional level is conducted by regional payers, and in Turkey, HTA is conducted by the government Department of Labour and Social Security.

Table 22: Assessment of bias and transparency[94]

Country	HTA is conducted independently of parties with a vested interest in the outcome	HTA is conducted separately from market authorisation	The rationale for HTA decisions/ recommendations is clearly stated	Scientific advice is available to manufacturers during development stage to enable the availability of evidence required for HTA
Australia	●	●	●	◑
Brazil	●	●	○	○
Canada	●	●	●	◑
England	◑	●	●	●
France	●	●	◑	○
Germany	◑	●	●	○
Italy	○	◑	○	○
Netherlands	●	●	●	●

93 House of Commons Health Committee Report on NICE, 2007

94 We apply the traffic light system described in the introduction. The colour coding works as follows: Green - Meets the best practice principle in terms of the HTA guidelines and evidence that it is followed in reality; Amber - Meets principle in guidelines and no evidence to assess situation in reality (or evidence that the system is moving towards best practice principle); Red - Guidelines are not consistent with best practice principles or evidence that it is not followed in practice.

New Zea-land	○	●	●	◑
Poland	●	●	●	○
Scotland	◑	●	●	○
South Korea	●	●	●	○
Spain	●	●	●	○
Sweden	●	●	◑	●
Turkey	○	◑	○	○

Source: CRA analysis

In all the countries covered in this report, HTA is conducted as a separate process from market authorisation, although in Italy (at a national level) and Turkey, market authorisation is by the same body as that conducting HTA.

Most of the assessed countries publish reports summarising the key points of the HTA and the rationale for the recommendation/decision. NICE provides particularly detailed reports with information about the evidence included in the manufacturer's submission and NICE's consideration of the evidence. In France, the Transparency Commission describes its rationale for decisions in general terms but does not provide any detail in its reports describing the procedure and criteria for assigning SMR and ASMR scores[95] from its assessment of the clinical evidence. Similarly, the TLV in Sweden publishes only brief reports and the rationale for decisions is not always transparent. However, Brazil, Italy (AIFA) and Turkey do not publish any rationale of their recommendations (with the result that detailed assessment in later principles is impossible).

Only three countries (England, Netherlands and Sweden) offer a formal scientific advice service to manufacturers during the development stage to assist manufacturers anticipate the evidence required for HTA, but others do offer this advice to manufacturers on a more informal basis (those scoring amber). It should be noted however that the HTA agencies in many of the countries are relatively small and their markets represent only a small proportion of the global pharmaceutical market. As such, those HTA agencies believe that pharmaceutical manufacturers are unlikely to prioritise complying with specific HTA requirements in those countries when designing clinical trials and hence it is reasonable that the capacity to provide a scientific advice service will be limited.

4.2.2. Principle 2: HTA should include all relevant technologies

Principle 2 considers whether the HTA process encompasses different types of technology (so allowing resources to be allocated efficiently in the health system) and whether it is applied to new and existing technologies. In the majority of assessed countries, some form of HTA is conducted for non-pharmaceutical technologies including devices, interventional procedures and diagnostics, often through a different HTA agency or programme than that responsible for reviewing pharmaceuticals.

95 SMR: medical benefit provided; ASMR: added medical benefit provided

Table 23: Inclusion of different technologies

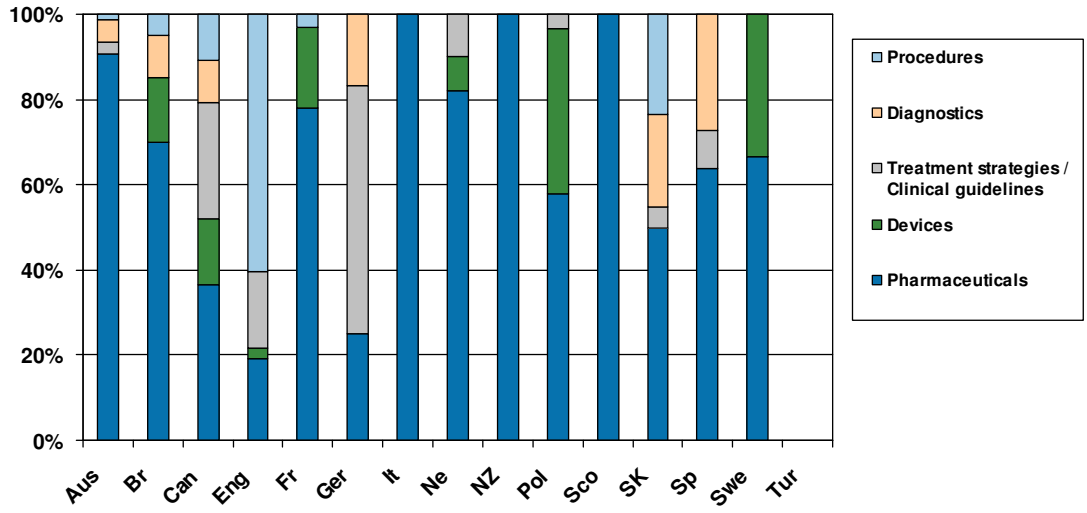
Country	HTA is conducted for pharmaceuticals, devices, procedures, diagnostics and treatment strategies	Proportion of HTAs conducted for each of pharmaceuticals, devices, procedures, diagnostics and treatment strategies	HTA is conducted for old as well as new technologies	Proportion of HTAs conducted for old technologies
Australia	◑	●	◑	◑
Brazil	●	●	◑	◑
Canada	●	●	●	●
England	●	●	●	◑
France	●	●	●	●
Germany	●	●	●	●
Italy	◑	◑	○	○
Netherlands	●	●	○	○
New Zea-land	○	○	◑	◑
Poland	●	●	●	●
Scotland	○	○	○	○
South Korea	●	●	◑	◑
Spain	●	●	○	○
Sweden	●	●	●	◑
Turkey	◑	Not available	○	○

Source: CRA analysis

However, in some cases, the standards required for other technologies are not as stringent as those required for pharmaceuticals; for example, in Australia, no cost-effectiveness analysis is conducted as part of evaluation for devices.

Figure 21 presents an assessment of the proportion of HTAs conducted for pharmaceuticals versus other technologies. This confirms that HTAs for other technologies are being conducted in appreciable numbers in all countries where there are processes in place. The exceptions would appear to be in Scotland and New Zealand, where HTA is only conducted for pharmaceuticals. In Italy, HTA at a national level (by AIFA) is only conducted for pharmaceuticals, but HTA processes for other technologies are in place in some regions.

Figure 21: Distribution of reviews by type of technology, 2009[96]



Source: CRA analysis

HTA systems in Canada, France, England, Germany, Poland and Sweden allow for the systematic evaluation of existing technologies as well as new drugs. In some cases, this may happen through a separate process to the evaluation of new drugs; in Canada for example, new drugs are evaluated through the Common Drug Review (CDR) programme while older technologies are evaluated in CADTH's HTA programme. Countries scoring amber are those where processes exist to evaluate existing technologies, but where this is not done on a routine basis. In Australia for example, most reviews of on-market drugs occur at the instigation of the manufacturer, requesting a change in the reimbursement conditions for the drug. While the Catalan HTA agency in Spain plans to conduct HTA for existing technologies in the future, it is currently focused on assessing new drugs.

Looking at the proportion of HTAs conducted for older pharmaceutical technologies indicates that while NICE has processes in place to routinely review older technologies, in practice, this happens infrequently. According to the director of technology appraisals at NICE, this is because of commitments to review new drugs in a timely fashion and due to constraints on the number of reviews that can be undertaken in a given year, which mean that evaluation of new drugs tends to be prioritised.[97] In France, the Transparency Commission revises its recommendations every five years and a significant proportion of all of the Transparency Commission's output (85% of opinions in 2009) are re-evaluations of older pharmaceuticals.

96 In Australia, number of assessment of devices done by the Prosthetics and Devices committee in 2009 was not available. No information was available for Turkey.

97 Interview with Director of Technology Appraisals at NICE, November 2010.

4.2.3. Principle 3: A clear system for setting priorities for HTA should exist and the costs of HTA should be proportionate

Even if all technologies are included in the HTA process, there is a question as to whether they are prioritised. This is the focus of Principle 3. Clear and publicly available criteria for selecting and prioritising topics for HTA review exist in most assessed countries, some of which simply review all new drugs in the order in which submissions are received, such as the SMC in Scotland and the CDR programme in Canada. In Sweden, the TLV reviews all new drugs and is also systematically conducting reviews of all drugs reimbursed prior to the establishment of the current system by therapeutic group, in order of sales value for each group. In Poland, all new drugs are reviewed, but the AOTM also conducts reviews of other technologies at the request of the Ministry of Health and National Health Fund, the selection process for which is not explicit. In Germany, IQWiG is commissioned by the G-BA or Ministry of Health to conduct specific HTAs and can also select topics independently but the rationale used for these decisions is not transparent. In Italy, at the national level, AIFA reviews all new drugs but at the regional level, selection of topics for HTA is less clear.

Table 24: Prioritisation and proportionality

Country	The process and rationale for selecting and prioritising topics is clearly defined and publicly available	Selected topics reflect stated priorities	Total annual cost of conducting HTA	HTA includes input from / references other national or international agencies on the same or closely related projects
Australia	●	●	○	●
Brazil	◑	◑	○	◑
Canada	●	●	●	●
England	●	◑	●	◑
France	●	●	○	○
Germany	○	○	●	●
Italy	● (natl) / ◑ (reg)	● (natl) / ◑ (reg)	○	● (natl) / ● (reg)
Netherlands	●	●	●	◑
New Zea-land	●	●	●	●
Poland	◑	◑	○	●
Scotland	●	●	●	●
South Korea	●	Unavailable	●	●
Spain	○	○	○	●
Sweden	●	●	●	●

Turkey	○	Unavailable	○	◑

Source: CRA analysis

Where criteria exist, selected topics generally appear to reflect the priorities. There is a concern that pharmaceuticals selected for review by NICE however tend to be new, expensive secondary care drugs, which does not necessarily reflect the stated selection criteria; the reasons for this are likely to be similar to those stated above for why there is less emphasis on reviewing older technologies.

In terms of the number of reviews or the justification for reviewing particular medicines we found no account is explicitly taken of the cost of the HTA process (either directly on the HTA agency or indirectly on other stakeholders), although this was mentioned as a factor in decision-making in an interview with a representative from NICE. Some countries do make the cost of conducting HTA publicly available, for example through annual reports, while in others, no information could be identified and based on interviews it would appear that the cost of some HTA processes is currently unknown.

Table 25: The cost of HTA

Country	Annual Costs of HTA
Australia	No evidence available
Brazil	No evidence available
Canada	€18m (CADTH), of which €4m on CDR
England	€71m (NICE) of which €7m on health technology evaluation
France	No evidence available
Germany	€23m
Italy	No evidence available
Netherlands	€53m (Includes all CVZ programmes, not only HTA)
New Zealand	€13m (Includes all PHARMAC activities, not only HTA)
Poland	€2.7m
Scotland	€1m
South Korea	€100m (Includes all HIRA activities, not only HTA)
Spain	€1.8m (Catalan agency)
Sweden	€10.6m
Turkey	No evidence available

Source: INAHTA, others are from the agencies' documentation or interviews

One way to reduce duplicative cost is to draw on information that has already been collected and assessed. A review of HTAs on the same or similar topics that have been conducted by other agencies is standard practice for many agencies. The SMC in Scotland reviews such information where it is available, although as it is frequently one of

the first HTA agencies internationally to assess a drug, this is often not possible. Countries scoring amber are those where there is some evidence that information produced by other agencies is reviewed, but this does not appear to be done on a systematic basis. NICE for example does not systematically look at the output of other HTA agencies but occasionally references such information in its reports. In Turkey, evidence from an industry interview suggests that a review of NICE's appraisal is often influential although this is not stated in any formal guidelines. France and Italy (at a national level) do not appear to take account of such information at all. The assessment of this principle has been undertaken at a relatively high level, to comply with best practice the HTA should draw only on information that is applicable to their markets. Decisions which are dependent on the context and reflect local circumstances and priorities should not be directly used while underlying data and evidence may be of value.

4.3. METHODOLOGY

4.3.1. Principle 4: HTA should incorporate appropriate methods depending on its goal

Although in this report we have chosen to not focus on the merits and demerits of particular HTA methodologies (as there is a vast existing literature on this topic), we have looked at whether the methodology is explicitly stated and whether there are criticisms of the methodology in the academic literature. The results of this are presented in Table 26 below.

Table 26: Appropriate methods

Country	The approach used in HTA is clearly stated	Methods are deemed appropriate by experts (from literature)
Australia	●	●
Brazil	◑	◑
Canada	●	●
England	●	◑
France	●	●
Germany	●	◑
Italy	◑	◑
Netherlands	●	●
New Zealand	●	◑
Poland	●	●
Scotland	●	●
South Korea	●	◑
Spain	○	●

Sweden	●	●
Turkey	◑	○

Source: CRA analysis

Most HTA agencies make the methods and approach they use in assessments publicly available in guideline documents such as NICE's "Guide to the Methods of Technology Appraisal" and the Polish AOTM's "Guidelines for conducting Health Technology Assessment (HTA)". Others provide some documentation but are not specific about the approach adopted. For example, while Brazil's CITEC publishes the methodologies it uses on its website, the precise approach used is somewhat unclear. AIFA's algorithm for determining relative clinical efficacy and innovation is clear and publicly available[98], but at the regional level in Italy, HTA approaches are not always clearly stated. There are exceptions, in particular, no publicly available documents outlining the evaluation process used in Catalan's CAHIAQ were identified (although other sources are available identifying the elements of assessment, defined in the table below).

Table 27: Summary of methods used in different HTA systems[99]

Country	Relative effectiveness	Budget impact	Cost-effectiveness	Cost/QALY	Cost/QALY with threshold
Australia	✓	✓	✓	✓	
Brazil	✓	✓	✓		
Canada	✓		✓	✓	
England	✓		✓	✓	✓
France	✓				
Germany	✓		✓		

98 However, we understand the algorithm is currently under review and there is a debate as to how the algorithm will be developed in the future.

99 For the purposes of this project we did not collect data on elements of value such as the severity of the disease or the extent of unmet need or how these were weighted. This is clearly a significant issue given the publication of Belgium presidency report entitled "A call to make valuable innovative medicines accessible in the European Union". The recent report developed for the ministerial conference on valuing innovation, noted the importance of assessing the magnitude of innovation and the extent of medical need. They defined a valuable innovative medicine as one offering added therapeutic value and filling a medical need. They note that the assessment of medical need depends on severity of the condition; Ethical; and Social considerations. They suggested a medicine is only 'truly innovative' if and only if it offers additional clinical efficacy an/or effectiveness as compared to current care. If in addition, these medicines fill an unmet medical need, they propose calling them valuable. This is also part of the UK debate on value based pricing. This should be reflected in how this research is developed in the future.

Italy	✓				
Nether-lands	✓	✓	✓	✓	
New Zealand	✓	✓	✓	✓	
Poland	✓	✓	✓	✓	
Scotland	✓		✓	✓	✓
South Ko-rea	✓	✓	✓	✓	✓
Spain	✓		✓		
Sweden	✓		✓	✓	
Turkey	✓	✓	✓		

Source: CRA analysis

In general, the HTA systems assessed are using well-established and broadly accepted methods. Specific criticisms over methodology from the published literature were identified for NICE, Germany, New Zealand and South Korea, which were primarily directed at these agencies' emphasis on the financial implications for the healthcare system of new technologies. IQWiG's efficiency frontier methodology in particular is viewed by some as inappropriate for a number of reasons, including problems in assessing different interventions with different measures of value in the same framework[100], and in comparing decisions across therapeutic areas. However, we accept that there is more likely to be criticism for HTA systems that have been in place for a longer period of time and where there is a larger academic literature.

4.3.2. Principle 5: HTA should consider a wide range of evidence and outcomes

Principle 5 is focused on the inclusion of a wide range of evidence and outcomes in HTA, including unpublished clinical trial data and use of a broader evidence base than randomised controlled trials (RCTs) alone.

Table 28: Use of a wide range of evidence and outcomes

Country	HTA considers unpublished trial data	HTA considers data not from RCTs
Australia	●	●
Brazil	No evidence available	●
Canada	●	●

100 It is currently unclear how the efficiency frontier approach will be incorporated into the system following the AMNOG Bill.

England	◑	●
France	●	●
Germany	●	◑
Italy	No evidence available	●
Netherlands	●	●
New Zealand	◑	●
Poland	●	●
Scotland	◑	●
South Korea	No evidence available	●
Spain	●	○
Sweden	●	●
Turkey	◑	●

In all countries where information was identified on this issue, unpublished trial data is considered in HTA, although some agencies are more restrictive than others. In countries scoring green, the inclusion of unpublished data in manufacturer submissions is considered to be acceptable. NICE allows the use of unpublished data and in its methods guide states that it is important that attempts are made to identify evidence that is not in the public domain; however, only under exceptional circumstances will NICE guarantee to manufacturers that confidential commercial information will remain unpublished, which can be a barrier to manufacturer supplying all relevant data. The TLV states in its advice on economic evaluations that unpublished pharmacoeconomic studies can be used but that they will be subject to greater demands on quality control and transparency than published studies. In New Zealand and Scotland, guidelines clearly state that published trials are preferred to unpublished trials. In Turkey, only trial data that has been published or that is used in the regulatory submission can be included in the pharmacoeconomic evaluation section of the manufacturer's submission.

With respect to data from trials which are not RCTs, HTA agencies in all countries regard RCTs as the "gold standard", but most recognise that there is a place for non-RCT data in HTA. Typically, agencies employ a hierarchy of evidence to determine the scientific merit of a study, with RCTs at the top and other types of studies deemed to provide a lower level of evidence. For example, guidance from the SMC in Scotland on evidence for clinical efficacy states that, *"If active-controlled studies are not available, details of placebo-controlled or uncontrolled studies should be included. Placebo-controlled and uncontrolled studies can also be included if they provide evidence of relevant clinical benefits not demonstrated in active-controlled studies."* [101] In Italy, data generated from

101 Scottish Medicines Consortium Guidance to Manufacturers for Completion of New Product Assessment Form (NPAF) (Revised June 2010)

patient registries is central to decision making for drugs entered into risk-sharing agreements. The CDR programme in Canada has recently launched a pilot project in response to calls from industry under which resubmissions following rejection on the basis of safety and efficacy can use non-RCT data. For IQWiG, data generated by study designs other than the RCT are only taken into account if there is no alternative, and the agency has come under criticism for taking a particularly restrictive line on this. The regional Catalan HTA Agency in Spain only uses data from RCTs.

4.3.3. Principle 6: A full societal perspective should be considered when undertaking HTAs

Principle 6 focuses on the inclusion of societal costs. This is clearly a controversial principle as some agencies responsible for the HTA believe that these are not part of their objectives and should be accounted for elsewhere.

Table 29: Inclusion of a societal perspective

Country	HTA takes into account: cost on public purse; non-healthcare and indirect costs and benefits to patients and society	Proportion including information on societal benefits
Australia	◑	○
Brazil	◑	Unavailable
Canada	◑	○
England	○	○
France	N/A	N/ A
Germany	◑	○
Italy	National: N/A / Regional: ◑	○
Netherlands	●	◑
New Zealand	○	○
Poland	◑	○
Scotland	◑	○
South Korea	○	○
Spain	○	○
Sweden	●	◑
Turkey	○	Unavailable

Source: CRA analysis

Of the countries assessed, only the Netherlands and Sweden consistently uses a societal perspective for cost-effectiveness analysis. None of the other countries assessed systematically look at non-healthcare costs/benefits as part of HTA, but some take these into consideration to varying degrees. Countries scoring amber have provisions to take non-healthcare costs/benefits into consideration in some situations. For example in Poland, HTA guidelines state that the first line perspective of the analysis is that of the healthcare system, but analysis adopting a social perspective may be justified in some cases such as where the health effects of a particular technology affect members of society other than the patient. Other systems may take these types of considerations into account in a more qualitative way in decision-making. For example, in Australia, PBAC asks that manufacturer submissions include cost offsets such as productivity gains in the sensitivity analysis; consideration of these benefits may contribute to a positive recommendation for a product with a higher ICER than would usually be acceptable. Countries scoring red are those that take only the perspective of the healthcare system into account in assessment. NICE for example clearly states that it takes into account only the impact of a technology on NHS and Social Services resources (although this is likely to change following the Value-based Pricing proposals). This metric is considered not to apply for France and Italy (at a national level) as their evaluation systems are focused only on clinical effectiveness and not on costs.

A review of the published assessments for the case studies across all countries reveals few examples where there is evidence that non-healthcare costs or benefits has been taken into consideration in the evaluation. In the Netherlands and Sweden, where a societal perspective is used, documentation outlining the rationale for decisions do not elaborate on the societal benefits or costs included in the evaluation.

4.3.4. Principle 7: HTAs should explicitly characterise uncertainty surrounding estimates

Principle 7 is concerned with the recognition that there is uncertainty regarding the assessment and ultimately regarding the outcome of the HTA process and whether there are mechanisms to deal with this uncertainty.

Table 30: Characterisation of uncertainty

Country	Uncertainty regarding decisions is explicit	Existence of conditional reimbursement to facilitate access (risk-sharing/access with evidence development)	Schemes are used in practice
Australia	●	●	◑
Brazil	○	○	○
Canada	◑	◑	◑
England	●	●	◑
France	○	◑	○
Germany	○	◑	◑

Italy	○	●	●
Netherlands	●	●	●
New Zealand	◑	●	◑
Poland	●	●	●
Scotland	●	●	●
South Korea	◑	●	Unavailable
Spain	○	○	○
Sweden	●	●	●
Turkey	Unavailable	○	Unavailable

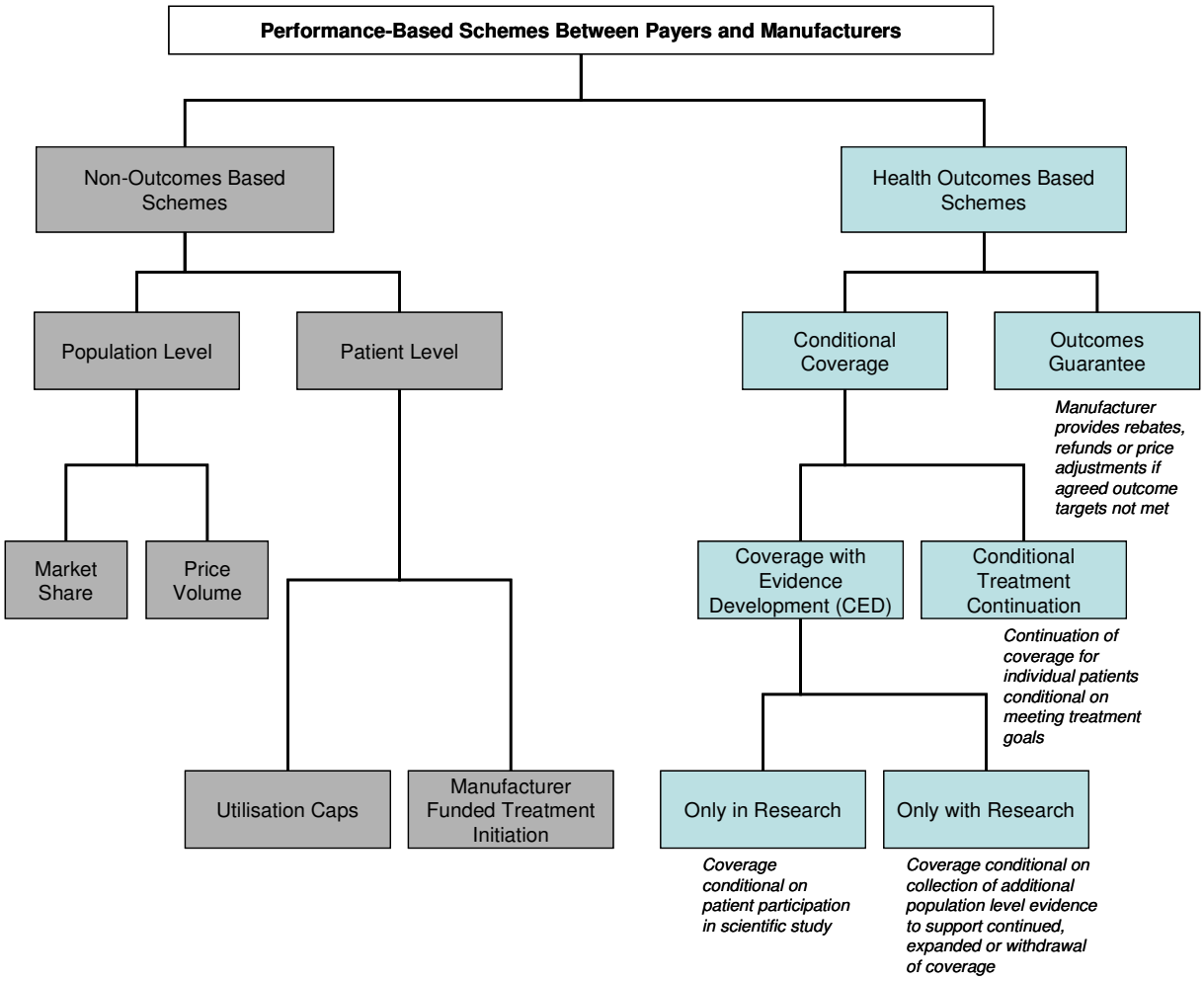
Source: CRA analysis

As shown in Table 31 the degree to which uncertainty around decisions is made explicit varies across countries. In countries using cost/QALY methodology, results of sensitivity analysis around the ICER is often reported, giving an indication of the uncertainty related to whether cost effectiveness is within reasonable bounds. For example, in Scotland, the SMC requires the manufacturer to demonstrate through sensitivity analysis under which circumstances the ICER exceeds the key thresholds of £20,000 and £30,000 per QALY, and these results are included in the agency's reports. There is no evidence of the uncertainty around decisions for Brazil, France, Germany and Italy. A technical assessor at CITEC in Brazil explained that while sensitivity analysis is not currently used to quantify uncertainty in decision-making, there are plans to do this in the future.[102]

Many of the countries have processes in place that allow access for drugs in cases where the benefits are uncertain. There are a number of different types of agreements, as illustrated in Figure 22.

Figure 22: Taxonomy of performance-based outcome schemes

102 Interview with Technical Assessor at CITEC, September 2010



Note: Only outcomes based schemes are considered to be mechanisms for dealing with uncertainty in HTA evaluation

Source: Adapted from Carlson et al. 2010

Examples of these schemes include conditional coverage in the Netherlands for high cost hospital drugs while additional evidence is generated, and risk sharing schemes in Italy where drugs are granted temporary price and reimbursement conditions, with all patients using the drugs being entered into a registry. In Sweden, in cases where cost-effectiveness is uncertain, the TLV uses a mechanism under which reimbursement is provided on the condition that cost-effectiveness in clinical practice can be demonstrated within an agreed timeframe. In Canada, France and Germany, similar types of arrangements exist, but they do not relate to the HTA process; rather they are conducted between payer bodies (provinces in Canada, Krankenkassen in Germany) or the Ministry of Health (CEPS in France) and manufacturers. A full description of the different types of agreements used in different countries is shown in Table 31.

Table 31: Use of outcomes based schemes

Country	CED – Only in Research	CED – Only with Research	Conditional Treatment Continuation	Outcomes Guarantee

Australia			✓	✓
Brazil				
Canada				
England	✓		✓	✓
France				
Italy		✓	✓	✓
Germany				
Netherlands		✓		
New Zealand	No information publicly available			
Poland			✓	✓
Scotland	✓		✓	✓
South Korea		✓		
Spain				
Sweden		✓		
Turkey				

Source: CRA analysis

In many countries where frameworks exist for schemes that allow access in cases of uncertainty, in practice these are rarely used for this purpose. In Australia for instance there is a framework for risk-sharing agreements, which can be used to address uncertainty in health outcomes but it appears that it is most often used in cases where there is a risk of use of the medicine beyond the subgroup for which it is recommended. The agreement provides for rebates from the manufacturer once an agreed volume cap is reached.[103]

The degree to which these schemes are socially beneficial is still uncertain. It is interesting to note that the value of patient access schemes in the UK have been questioned in the recent Government consultation. The cost of applying Patient Access Schemes is described as excessive due to the administrative burden. It is therefore likely that the cost of applying such a system would only be justifiable for the most expensive products.

103 A memorandum of understanding was signed in May 2010 between the pharmaceutical industry and government in laying out plans for "Managed Entry Schemes" which would provide for conditional reimbursement for drugs with uncertain clinical benefits

4.4. PROCESS

4.4.1. Principle 8: Those conducting HTAs should actively engage all key stakeholder groups

In terms of process, an important principle is that different stakeholders should be engaged in the process. This has been assessed by looking at whether they are included, their role through the process and whether there is an opportunity to appeal (if particular stakeholders do not agree with the assessment).

Table 32: Inclusion of stakeholder groups

Country	A number of relevant stakeholders are invited to contribute to the HTA process	Stakeholders are involved throughout the HTA process with opportunity for: contribution to assessment methodology, submission of evidence, review of recommendations	Existence of an appeal process	Number of appeals against HTA decisions
Australia	●	●	●	○
Brazil	○	○	○	○
Canada	●	●	○	○
England	●	◑	◑	●
France	○	○	◑	Unavailable
Germany	●	●	○	○
Italy	○	○	○	○
Nether-lands	●	◑	◑	◑
New Zea-land	●	◑	○	○
Poland	◑	◑	◑	Unavailable
Scotland	●	●	●	○
South Ko-rea	◑	●	○/● in future	○
Spain	◑	◑	○	○
Sweden	◑	◑	●	○
Turkey	○	○	○	Unavailable

Source: CRA analysis

NICE appears to have one of the highest levels of stakeholder participation in terms of the number of groups it actively seeks to engage, inviting input from patient and carer groups, health professional bodies, manufacturers both of the technology in question and of comparator products, and research groups working in the relevant area. NICE also

consults a "Citizens Council" made up of members of the public which provides advice on issues facing NICE from the public's perspective. By contrast, the Transparency Commission in France only invites the manufacturer to participate in the evaluation process with no other stakeholders formally invited to participate. Clinical experts may be consulted for specific advice but no general participation of physicians is facilitated.

Markets which invite relevant stakeholder groups to participate may not always allow contribution at key stages of the evaluation process. Taking the example of NICE, there is concern that manufacturers are given few opportunities to interact with the independent Evidence Review Group which is commissioned by NICE to conduct a critical analysis of the manufacturer submission. In contrast, the Australian system allows manufacturers to work closely with PBAC during the evaluation process, with pre- and post-submission meetings and opportunity to comment on the critique of their submission prior to the PBAC meeting.

Some agencies have mechanisms in place through which stakeholders can appeal against decisions. In Australia, a formal independent review process exists, although the review outcome has to go back to PBAC for a final decision. This process was not used in 2009, although since the mechanism has been in place, it has been used three times, and the original decision was upheld in each case. Scotland has a formal appeal process conducted by an independent body, which did not appear to be used in 2009. There were three appeals in Sweden in 2009; two of these appeals were rejected and no information was identified on the third. NICE and HAS in France have appeal processes but handled by the agencies internally and not by outside, independent bodies, leading to concerns over impartiality. However, over NICE's history, appeals against NICE's recommendations have been upheld in a significant proportion of cases; 23 of 58 as of November 2008. South Korea is expected to have an appeal process in place in the future when the USA-South Korea Free Trade Agreement is implemented.

4.4.2. Principle 9: HTA findings need to be communicated appropriately to different decision makers

Principle 9 is concerned with how the results of the HTA process is communicated once the assessment has taken place, first, in terms of whether it is published and then how it is communicated to different stakeholders.

Table 33: Communication of decisions

Country	Outcomes are published on a publicly accessible website	Decisions are explained in several levels of clinical/technical detail so that all relevant audiences may understand the decision (manufacturers, health plans, general population, patient groups)
Australia	●	◑
Brazil	●	○
Canada	●	◑
England	●	●

France	●	◑
Germany	◑	●
Italy	○	○
Netherlands	●	●
New Zealand	●	●
Poland	●	◑
Scotland	●	●
South Korea	●	●
Spain	●	●
Sweden	●	◑
Turkey	○	○

Source: CRA analysis

With the exception of Italy and Turkey, HTA outcomes in all countries are published on a publicly accessible website. IQWiG in Germany publishes most of its reports on its website, but there has been criticism that not all assessments are published and disseminated.

Many agencies ensure that reports detailing decisions/recommendations can be understood by all relevant audiences and some publish different versions of outcome reports tailored to different groups. In Scotland, for example, the SMC publishes a Drug Advice document with full details of the assessment, and press statements and briefing notes giving plain language summaries. While CITEC in Brazil publishes the top-line outcome of its assessments (i.e. simply whether a product is recommended for reimbursement or not), no further details on decisions are available.

4.4.3. Principle 10: Evaluations should allow new data to be considered

Principle 10 looks at whether new information can be taken into account in the assessment after the first assessment has been completed. There is clearly a difficult assessment as to whether re-evaluations integrate new information or simply reflect improved commercial terms.

Table 34: Allowance of new data

Country	There is a process for re-evaluation (input from manufacturers, patients to decision)	Proportion of assessments which are re-evaluations
Australia	●	◑
Brazil	○	○
Canada	●	◑

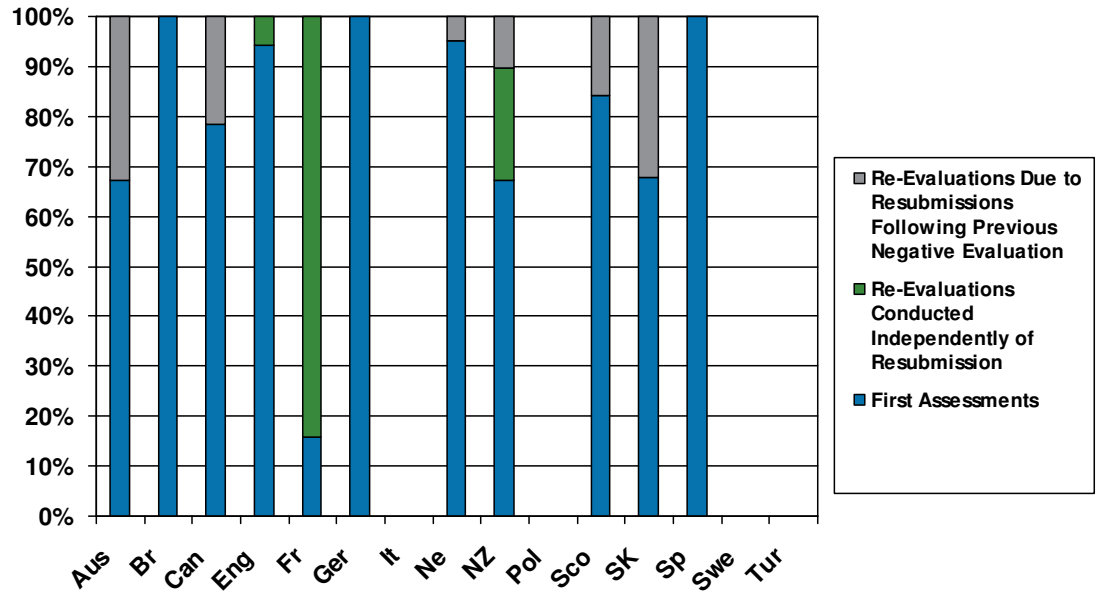
England	●	◑
France	◑	◑
Germany	◑	○
Italy	○	○
Netherlands	●	◑
New Zealand	●	◑
Poland	●	Unavailable
Scotland	●	◑
South Korea	◑	◑
Spain	Too early	Too early
Sweden	●	Unavailable
Turkey	●	Unavailable

Source: CRA analysis

In the majority of countries, manufacturers or other stakeholders can instigate a re-evaluation of a previously reviewed product, particularly in cases where new data is available. A distinction should be made with resubmission, where manufacturers request reconsideration of a negative recommendation within a short timeframe. This is usually based on a new submission which may include additional analyses or improved commercial terms but does not generally include new clinical data.

In France, re-evaluation takes place on a regular basis rather than at the request of the manufacturer or other stakeholder, but this review can include additional data generated at the request of HAS since the initial evaluation. In Germany there is evidence that assessments have been updated with new evidence but the process by which the manufacturer can submit this is unclear. HIRA in South Korea allows resubmissions but does not appear to have a process for re-evaluations. CAHIAQ in Spain has plans to develop a re-evaluation process in the future but this has not yet happened within the short period (since 2008) that the agency has been reviewing pharmaceuticals. In no countries where a re-evaluation process exists was a significant number of re-evaluations conducted in 2009 (see Figure 23).

Figure 23: Distribution of pharmaceutical reviews, first assessment versus re-assessment, 2009



Note: No data available for Italy, Poland, Sweden or Turkey

Source: CRA analysis

4.4.4. Principle 11: HTA should identify areas in which the evidence base on an intervention could most usefully be developed in the future

The final principle associated to the process of the HTA focuses on whether the assessment itself identifies where new information could be useful or would be valued in future re-assessments. The results of this are presented in Table 35.

Table 35: Identification of evidence required

Country	Proportion of assessments identifying the value of additional evidence
Australia	●
Brazil	Unavailable
Canada	●
England	●
France	●
Germany	○
Italy	Unavailable
Netherlands	◑

New Zealand	●
Poland	◑
Scotland	○
South Korea	●
Spain	◑
Sweden	●
Turkey	Unavailable

Source: CRA analysis

In a number of countries, HTA reports routinely identify evidence that was lacking for the assessment that would be valuable. For instance, the majority of NICE's reports include a section on "Recommendations for further research" outlining clinical trials or other studies that would generate useful additional evidence. Reports in Poland and the Netherlands discuss where evidence is lacking but are less explicit about the kind of additional data that would be valuable, while those in Germany and Scotland do not include this type of information.

4.5. THE IMPACT OF THE HTA

4.5.1. Principle 12: HTA should be timely

Principle 12 focuses on the timeliness of the HTA and whether this delays access to patients. We look at this by first assessing whether there is a time-specified for the HTA process, the average length of time and whether this prevents patient access.

Table 36: Timeliness

Country	Stated goal for duration of review	Length of time taken for reviews[104]	Length of time from approval to decision/ recommendation	Review can begin before product is approved	Product is accessible/ reimbursed prior to decision
Australia	●	●	●	○ (to ● in future)	○
Brazil	○	○	○	○	◑

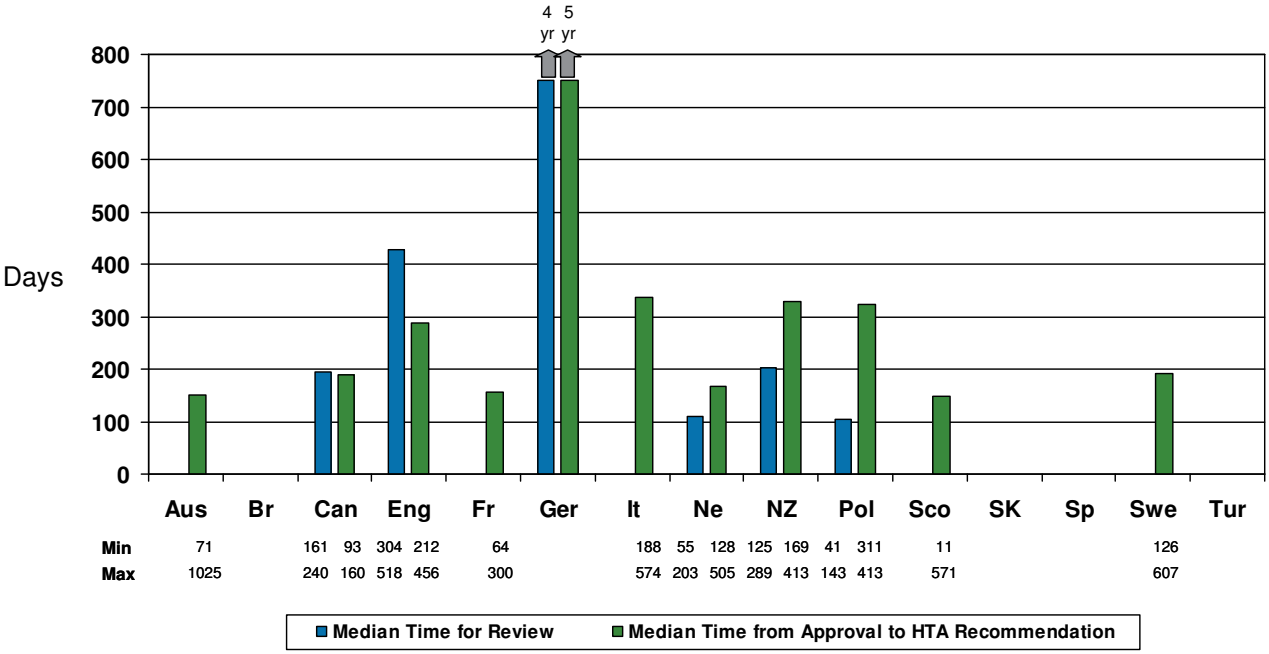
104 Australia: Median time for review not available from case studies, but evidence that all reviews completed within 17 weeks; Brazil: No information available from case studies, reviews take from several months to several years; France: Median time for review not available from case studies but HAS data shows it takes 54-94 days; Scotland: Median time for review not available from case studies, review is completed within 18 weeks in >95% of cases; Sweden: Median time for review not available from case studies, review was completed within 101 days on average in 2009; Turkey: No information available from case studies but in 2008 average time for reimbursement review was 16.5 months.

Canada	●	◑	●	●	○
England	●	○	◑	●	
France	○	●	○	●	◑
Germa-ny	○	○	○	Not applica-ble	○
Italy	○	○ (natl) / ● (reg)	◑	○	●
Nether-lands	○	●	●	○	○
New Zealand	○	◑	◑	◑	○
Poland	○ (to ● in fu-ture)	●	◑	No infor-mation	○
Scotland	●	●	●	●	○
South Korea	●	●	●	○	◑
Spain	●	No infor-mation	No infor-mation	○	○
Sweden	●	●	◑	●	○
Turkey	●	○	○	○	○

Approximately half of the countries do not have a stated goal for duration of reviews. In New Zealand, this is a reflection of the prioritisation process. PHARMAC aims to prioritise applications within 12 months of receipt, and in doing so makes explicit decisions as to their priority and the timeframe in which they will be processed. In South Korea and Turkey, although a stated goal for duration of review exists, the goal is lengthy (one year and 270 days respectively). While Poland currently has no stated goal, from 2011 under a new law relating to the pricing and reimbursement of pharmaceuticals, the AOTM will be obliged to give recommendations within 60 days of receipt of applications.

Scoring of countries on length of time taken for reviews and for the delay between product approval and HTA decision/recommendation is based on whether this length of time is less than six months (green), between six and 12 months (amber) or over 12 months (red). Where the information is available, this is based on case studies, but for many countries this is based on reported average numbers. In Australia, for example, time for review was not available for the case studies, but there is evidence that all reviews are completed within the goal of 17 weeks. Figure 24 shows the data available from case studies.

Figure 24: Median Duration of Review and Time from Regulatory Approval to HTA Recommendation, Based on Case Studies



Note: Germany numbers based on assessments for pharmaceuticals in 2009 as no case studies were covered in Germany

Source: CRA Analysis

The assessment above is based on available data regarding the length of the review process and assessment of the case studies. However, the case studies vary from country to country so we have attempted to allow for this using a simple regression analysis. This looks at the relationship between the length of the time between marketing authorisation and the announcement of the decision and whether this varies by country (after allowing for the systematic differences by product). This supports that agencies in Scotland, France, Australia and the Netherlands are systematically faster than those in other countries.

We also tested whether the speed of the review was associated to the characteristics of the product. Only in the case of Scotland (based on a small number of observations) is there a relationship between the therapeutic value of the medicine (as proxied by the ASMR in France[105]) and the speed of the review, with higher value products progressing more quickly through the review. In other countries there is no relationship between the proxy for the assessment of therapeutic value and speed – given many markets are based on order of application this perhaps should not be surprising.

Practice varies between countries as to whether reviews can begin before regulatory product approval is granted. In Sweden, this is routinely possible. In Australia, this will be

105 This result clearly needs to be treated with caution. ASMR is only an imperfect measure of therapeutic value. It takes into account the added therapeutic benefits but does not take into account wider aspects such as severity or burden of disease. This result is also clearly based on a relatively small number of case studies.

possible from 2011. In Canada and France, review can begin before approval for products designated as innovative and approved for priority review processes. In New Zealand, whether PHARMAC will start reviewing products before approval is at PHARMAC's discretion, but the PTAC review stage cannot start until approval is granted. The trend in England appears to be for NICE to start more assessments before product approval in order that a recommendation can be made within three to six months of market authorisation. A limitation is that the Appraisal Committee meeting at which preliminary recommendations are formulated cannot take place until after the CHMP of the EMA has issued an opinion on the product.

Only in Germany are products routinely available prior to HTA, although it remains to be seen if the situation will change when all products are reviewed within one year under the new AMNOG laws. In Scotland and England, in theory products can be prescribed and reimbursed prior to review by NICE/SMC, but in practice, local decision-makers (PCTs/Health Boards) usually restrict usage until a recommendation has been issued. As in Germany, policy changes in England including the phasing out of PCTs and the introduction of value-based pricing, may lead to changes in the future. In Brazil, it is possible for individuals to gain access to drugs not on the positive reimbursement list (either because review has not yet happened or because reimbursement has been rejected) through a legal process at the state level.

4.5.2. Principle 13: Pricing, reimbursement and market access decisions should reflect the HTA assessment in a transparent, clearly defined way and be implemented as intended

Principle 13 is one of the most difficult principles to assess. This focuses on whether the way the HTA is used in the price and reimbursement process is as it is intended to be.

Table 37: The impact of the HTA

Country	Relationship between HTA and pricing and reimbursement	Relationship between HTA and reimbursement restrictions	Impact on diffusion	Explicit treatment of innovation
Australia	◑	●	●	○
Brazil	NA	○	Unknown	◑
Canada	○	○	◑	◑
England	NA	◑	◑	◑
France	●	◑	NA	◑
Germany	NA (currently)	Unknown	Still untested	○
Italy	●	●*	NA	◑
Nether-lands	●	●*	Unknown	●
New Zea-land	○	●	○	○
Poland	Unknown	◑	Unknown	○

Scotland	NA	◑	◑	◑
South Korea	Unknown	○ (one product)	Unknown	○
Spain	NA	Unknown	●	○
Sweden	●	◑	◑	○
Turkey	NA	Unknown	Unknown	○

Source: CRA analysis

To the extent that the HTA feeds into pricing and reimbursement, there should be a positive relationship between a favourable assessment of the benefits of the medicine and the value associated to this by the HTA. There are number of ways to assess this. Firstly, the relationship between the HTA assessment and the Price and Reimbursement decision may be determined formulaically. For example, in the French or the Italian system, the assessment of added therapeutic value feeds directly into the negotiation regarding price. There is support in the literature that higher price is possible with a better assessment of clinical attributes of the product.

Equally, a threshold based cost effectiveness system is a partial method for associating the assessment of value to price. Where there is a cost effectiveness system if the price of the product is such that the product is not assessed as cost effective then it is more likely that the product will be rejected. In these cases, the onus is often on the manufacturer to provide further data demonstrating its value or to lower the price of the medicine. This therefore is a mechanism for encouraging the price to be associated with the value of the product as assessed in the cost effectiveness process. However, although this constrains the relationships between prices and the assessment of value, it does not ensure a positive relationship between value and rewards.

Secondly, where the HTA is not formally used in the pricing and reimbursement process, the introduction of HTA should not change the absolute level of prices. We have investigated this using our case study analysis. Looking at the relative price of products that were assessed by NICE in England versus those products that did not go through a NICE review. We can only use evidence from NICE as it is the only country where the case studies include products that were and were not assessed by the HTA process. If the application of the HTA process results in a lower price and reimbursement we would expect products that did not go through the NICE process to have a higher relative price. Based on the small number of case studies examined for this project we do not find any such relationship. There are a number of reasons to be cautious about this result. This could be because: (1) the impact of HTA does not directly affect price; (2) the price effect is embedded in arrangements such as risk-sharing schemes that cannot be fully observed; (3) the impact on prices affect all products, as the manufacturers do not know if the product will be assessed; (4) the sample is too small and this should be investigated further with a larger data set. Given the small sample size, this clearly requires more investigation with a larger database but represents a valuable methodology.

Thirdly, HTA could improve the relationship between the rewards a medicine receives and the therapeutic value. To test this we looked at the price premium of the medicine (relative to a market where HTA is not used – in this case Switzerland) and whether this was related to the therapeutic value of the medicine (as proxied by the ASMR awarded

the product in France with the limitations discussed above). We did not find this was the case systematically for any of the countries examined in this sample.

Fourthly, we have assessed whether there is a relationship between the price premium on different products and the type of HTA models used (using the categorisation described in the introduction). Here we find the HTA based on ex ante cost effectiveness is correlated with lower relative prices. In particular, ex ante cost effectiveness lowers the price by 15% compared to other models. However, this in itself does not tell us whether HTA makes rewards more closely related to the value of the medicine.

The second dimension we have looked at is whether the HTA results in restrictions being imposed on the medicine. While we cannot measure directly the impact of HTA on health outcomes, if restricted access leads to poorer health outcomes then the impact of HTA on access gives an indirect indication of the impact of HTA on health outcomes. There is evidence of the link between access and outcomes in cancer, where access to new medicines has been shown to have a positive impact on survival. Jonsson and Wilking conducted an analysis of the impact of new oncology products using data from the United States, Germany, UK, Spain, France and Germany, focusing on one and five year survival statistics. They find a positive relationship between the number of new products and the increase in survival rates, finding that 44% of the increase in survival in the US is due to the introduction of new products, whilst around 20% of difference between countries is due to new product introductions.[106]

Our assessment of the impact of HTA on access is based on the methodology developed by Raftery (2006) as set out in Table 38 below.

106 "The effect of cancer drug vintage on cancer survival and mortality" Annals of Oncology 18 (Supplement 3): iii67–iii77, 2007 doi:10.1093/annonc/mdm102

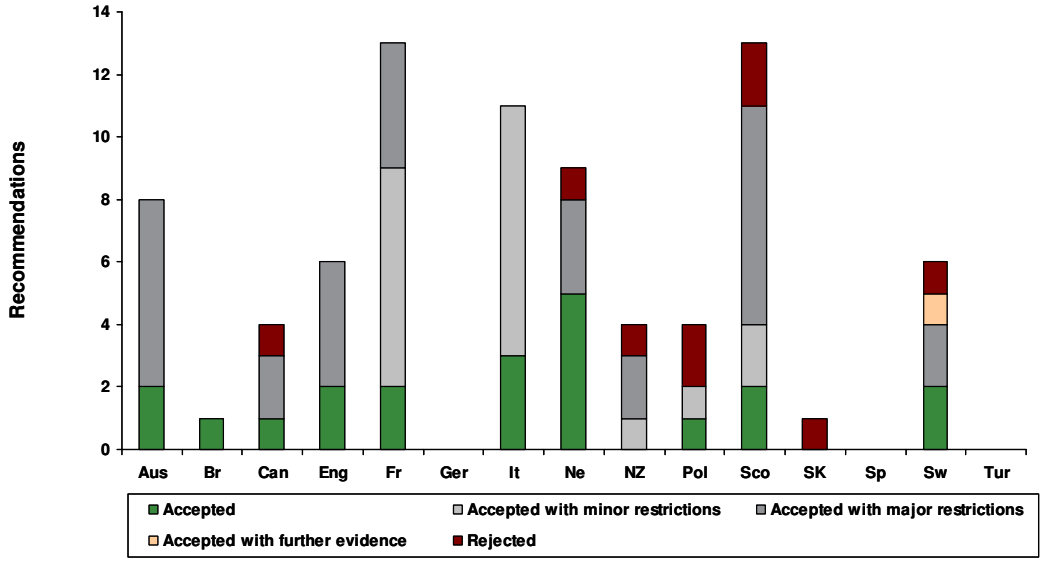
Table 38: Categorisation of restrictions

Category	Criteria
Accepted	Should be used routinely
	Can be considered as an option
Accepted with major restrictions	Use only as second or subsequent line treatment
	Use only if intolerant to other treatment
	Must show response within specified time
	Restricted to sub-groups within licensed indications
Accepted with minor restrictions	Use the least costly option
	Monitoring required
	Use by specialist only
Accepted with further evidence	Can be considered in the interim provided further evidence is provided in the future
Rejected	Insufficient evidence for use
	Do not use because of poor cost effectiveness

Source: Adapted from Raftery 2006

Figure 25 show that there is considerable variation in the degree to which restrictions are imposed by the agencies in the different countries even when comparing the same set of products, although it should be noted that there is variation in the specific set of case studies available in each country.

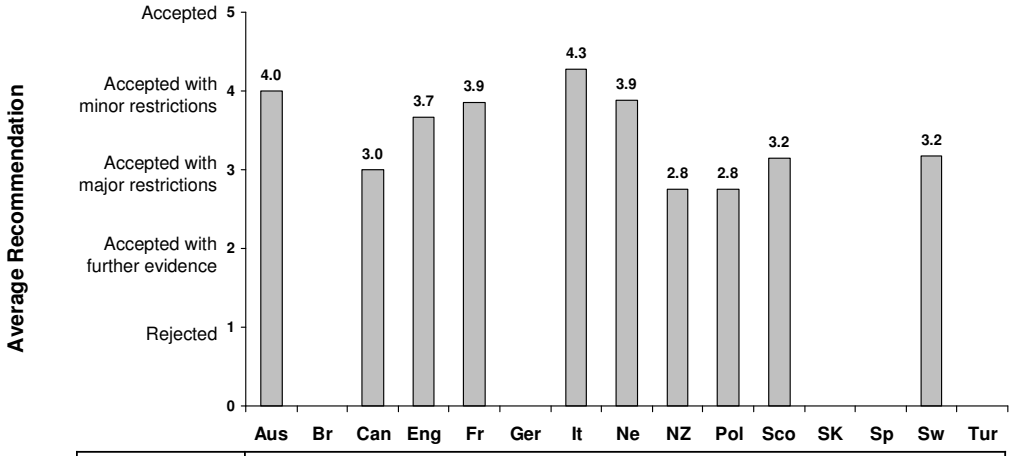
Figure 25: Distribution of recommendations for case studies by country



Source: CRA analysis. Note that Scotland and France has 13 observations as one product has two indications.

To compare across countries we have scored the restrictions between 1 (rejected) and 5 (accepted without restriction) and calculated averaged for each country. The results are shown in Figure 26. Based on this analysis, Italy appears to be the least restrictive in its recommendations (although this is based only on the national assessment), and Poland and New Zealand to be the most restrictive.

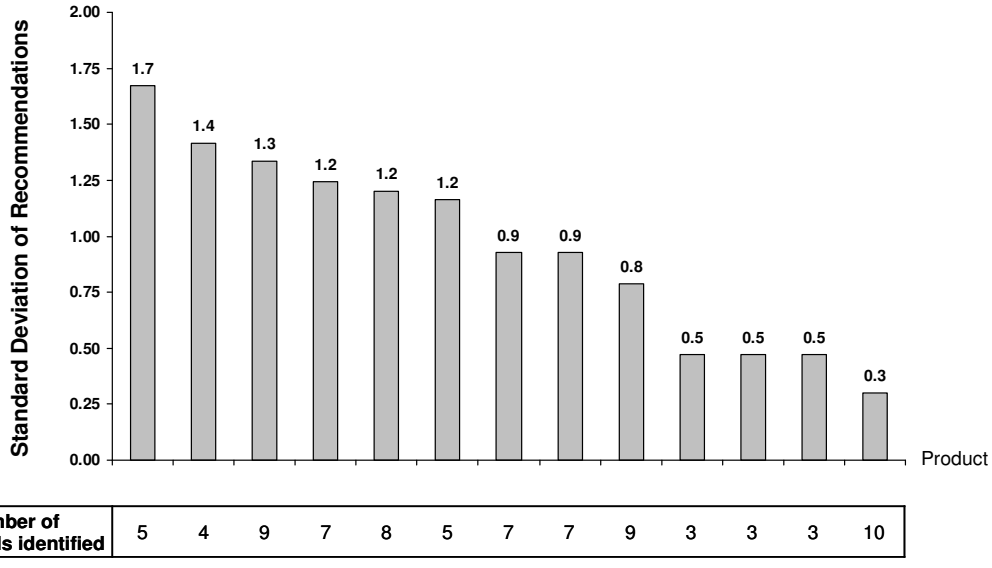
Figure 26: Average recommendations for case studies, by country



Source: CRA analysis. Note that Scotland and France has 13 observations as one product has two indications.

Figure 27 illustrates the variation in the level of recommendation for each case study product. For some case study products there is wide variation, with recommendations distributed across the full range from "accepted" to "rejected", while for others there is a greater degree of consensus between countries. This is consistent with the findings of Kanavos (2010) who finds wide variation in the recommendations for particular products.

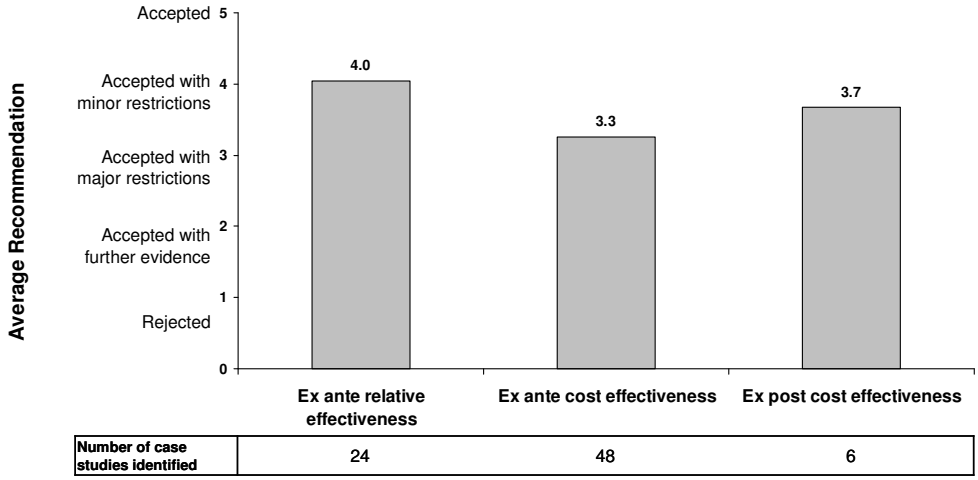
Figure 27: Variance in case study recommendations, by product



We have also looked at the average level of restriction for the case studies by model of HTA, ex ante relative effectiveness, ex ante cost effectiveness or ex post cost

effectiveness (see Figure 28). HTA based on ex ante relative effectiveness (as used in France and Italy) appears to be the least restrictive based on the available data. However, this is clearly based on a relatively small number of observations and should be treated with caution.

Figure 28: Average recommendations for case studies, by model of HTA



Source: CRA analysis

It is possible that the differences in restrictions reflect the assessment of clinical benefits associated to the product in different markets. However, one of the accusations regarding the role of HTA in price and reimbursement is that it aims to constrain costs rather than reflect the value of the medicine. To test this we have looked at if there is a relationship between the restrictions imposed on the medicines and the price of the medicine. If the restriction were imposed only in terms of clinical value of the medicine we might expect there to be little relationship between price and restriction. However, if restrictions are imposed to manage costs, if the price of the products is adjudged to be high we might expect more significant restrictions. Indeed, this is what we find in practice. We have therefore made our assessment of the relationship between HTA and reimbursement on a comparison of whether the countries imposed more or less restrictions for our set of case studies.

The third criterion for the assessment was based on diffusion of the medicines into the market. Where we have a favourable HTA we might expect this to result in more rapid usage than where the product is assessed unfavourably. Given the choice of case studies it is too early to assess the impact of diffusion but this should be part of the future research. We have therefore based our assessment on the literature review regarding the role of HTA in diffusion. This evidence suggests that ex post HTA does reduce diffusion until the assessment is made. Therefore ex post assessment systems with a significant delay until the publication of recommendations are scored negatively.

It is also possible that even after the HTA assessment determines the value of the medicine and feeds into the national reimbursement decision that the product is not reimbursed by the regional payers. There appears to be concerns on this in some of the markets considered in our study, in particular, Canada, Sweden and the UK. For Canada, we undertook a comparison of the CDR recommendations made in 2009 with the

provincial formulary decisions made in Saskatchewan and Ontario. Ontario followed recommendations for nine drugs, but decided not to list six that were recommended for coverage by CDR. Saskatchewan followed eleven recommendations and did not follow four, not listing when the CDR recommendation was to provide coverage. A similar analysis in Scotland looked at three Local Health Board (LHB) formulary decisions for the twelve case study drugs. This found that the coverage status of a number of drugs was still undecided in some LHBs several months after SMC guidance had been issued, and there were two cases where LHBs had recommended against SMC recommended products.

Finally, we consider the impact on incentives to innovate. In practice, it is very difficult to observe the impact on the incentives to innovate. Investments are often global decisions and changes in R&D take many years to be observed. Therefore we can only look at possible proxies for the impact on incentives to innovate. There are a number of possible elements that can be assessed with respect to the incentives to innovate. Firstly, where there is a clear relationship between value of medicine in terms of therapeutic impact and the rewards to the originator this itself should incentivise innovation (however, this is simply the first measure discussed in this section). Secondly, where originators can communicate with the HTA agency through the development of the medicine this should assist innovation as it adds to the certainty regarding how the product will be assessed. Thirdly, whether the value assessment is predictable (because the assessment mechanism is transparent for example). Finally, there is question as to whether innovation is itself recognised in the value assessment (beyond the direct impact on health outcomes). Our assessment of each of these is presented in Table 39 below.

Table 39: Allowance for innovation

Country	Early dialogue with the originator	Transparency regarding the assessment process	Assessment of Innovation
Australia	Possible		No explicit consideration of the level of innovation
Brazil			Level of innovation considered in CMED's pricing decision but not in CITEC's evaluation for reimbursement decisions
Canada			Innovative products can be granted priority review status allowing CDR submission to be processed more quickly. Innovative products may also be allowed a higher ICER than would normally be acceptable. Level of innovation considered in PMPRB's maximum price decision.

England	Possible	●	Products perceived as clinically innovative may be allowed a higher cost/QALY than would otherwise be acceptable. Changes to the review process resulting from the Kennedy review should make the assessment of innovation and its impact on the decision more explicit.
France		●	Level of innovation accounted for in the ASMR rating of added clinical value.
Germany		●	No explicit consideration of the level of innovation
Italy		◑	Algorithm to determine level of therapeutic / pharmacologic / technological innovation is used as part of P&R decision-making.
Netherlands	Possible	●	Medicines deemed to be therapeutically unique (not substitutable) have more pricing freedom compared with medicines deemed to be substitutable, where the price is referenced to existing medicines.
New Zealand	Possible	●	No explicit consideration of the level of innovation
Poland		●	No explicit consideration of the level of innovation
Scotland		●	Products perceived as clinically innovative may be allowed a higher cost/QALY than would otherwise be acceptable.
South Korea		●	No explicit consideration of the level of innovation
Spain		○	No explicit consideration of the level of innovation
Sweden	Possible	○	No explicit consideration of the level of innovation
Turkey		○	No explicit consideration of the level of innovation

Source: CRA analysis

4.5.3. Principle 14: The impact of HTA findings and how they are used needs to be monitored

The final principle reflecting the impact of the HTA is whether there is a process for monitoring its impact, evaluating whether it meets its objectives and whether this

assessment feeds into the appraisal process. The results of these assessments are presented in Table 40 below.

Table 40: Monitoring of outcomes

Country	There is a body with responsibility for overseeing impact	There is measurement of the value of HTA to the healthcare system	Effects of HTA decisions are monitored and data is collected to evaluate clinical impact over time	This information is used to modify/revise HTA process/ methodology
Australia	●	○	●	●
Brazil	◑	○	○	○
Canada	●	○	○	●
England	●	○	●	●
France	○	○	○	○
Germany	◑	○	○	○
Italy	○	○	○	○
Nether-lands	○	◑	◑	◑
New Zea-land	●	◑	◑	●
Poland	○	○	○	○
Scotland	●	○	●	●
South Ko-rea	○	○	○	○
Spain	○	○	○	○
Sweden	○	●	○	○
Turkey	○	○	○	Too early

Source: CRA analysis

In some countries, there is a body which has responsibility for overseeing the impact of HTA on the healthcare system. This role may be fulfilled by the government, for example in Canada where the House of Commons reviews the CADTH. In other countries, specific programmes have been set up to monitor HTA. For example, NICE monitors implementation and uptake of recommendation through its Implementation Programme and a dedicated, publicly available database for "Evaluation and review of NICE implementation evidence" (ERNIE). In Germany, there does not appear to be a body with responsibility for overseeing the impact of IQWiG, although review of the G-BA's (Federal Joint Committee) decisions is undertaken by the government.

Sweden appears to be the only country which explicitly measures the value of HTA, making estimates of the savings that will be realised from its evaluations of therapeutic classes. In the Netherlands and New Zealand there is quantification of the savings made

as a result of pharmaceutical policies but this relates to a broader set of activities than just HTA.

Australia, England and Scotland monitor patterns of drug usage to evaluate the impacts of HTA decisions. Scotland, for example, has established the SMC Evaluation Programme to monitor use of medicines following SMC advice and to assess the impact of SMC guidance.

In all countries where the impact of HTA is monitored, there is evidence that the HTA process has been modified over time as a result. In Canada for example, the House of Commons review of CADTH in 2007 led to a number of recommendations which have been subsequently adopted, such as soliciting patient input.

5. FUTURE RESEARCH ON THE IMPACT OF HTA ON DIFFERENT STAKEHOLDERS

One of the objectives of the research was to set the foundation for a regular report that would allow consistent assessments of the impact of HTA to be efficiently captured over time, whilst taking into account the complexity of HTA organisations, their continuing development and the changes that are on-going in terms of co-ordination and possible harmonisation.

5.1. EVOLVING ROLE OF HTA

It is clear from the interviews conducted for this project that all systems of HTA are still developing. This involves changes in their processes but also their role in the pricing and reimbursement system. For example, there is on-going debate regarding the role of HTA in markets which have used HTA for many years – this is illustrated by the on-going debate in the UK, France, Italy and Germany.

In some of the markets the development of HTA is clearly at an early stage and it is likely that the processes will change in the coming years (this is the case in Turkey and Brazil in particular). This would support relatively high frequency re-assessments, for example, on an annual or bi-yearly basis. The number and mix of countries however appears to capture a range of different models while allowing detailed comparison. We would therefore not recommend expanding the number of countries significantly.

5.2. DATABASE ON ASSESSMENTS

The methodology developed was a compromise focusing on 15 countries, a time window of 2009 and 12 case studies. This approach allows the report to make like for like comparisons across a range of dimensions. In further research it will be useful to:

- Broaden the range of case studies. A larger sample is needed to apply quantitative approaches pioneered in this paper. Given the different products assessed by different agencies, increasing the number of case studies would add considerably to the exercise;
- Following the same case studies over time. By following the same case studies we will be able to examine the timings of re-assessment and most importantly the impact of diffusion rates.

There may also be a case for including a focus on particular types of product. For example, following the focus on oncology products and CNS products in the Kanavos study or focusing on different types of innovation, for example products that involve a cost transfer between hospital and pharmacy channels (an oral product introduced into a class of infusion based products for example) or different types of innovation (based on measures of severity/burden of diseases or technological innovation as discussed in the Belgium Presidency and the consultation on value based pricing in the UK). As set out in the literature there is already some evidence that the impact of HTA varies significantly between therapy areas (comparing the experience of rheumatoid arthritis to multiple sclerosis for example). This would allow us to provide a map of how different types of

innovation are valued in different markets and why. Ultimately it would be interesting to determine if this affects the medicines that introduced into different markets.

The database could be extended to include more detail on the justification behind the decision on different medicines. In particular, the degree to which this depends on the type of evidence assessed, the comparator chosen and the main reason cited for the particular decision drawing on the Kanavos categorisation. This could be further extended to include interview evidence on the importance of the formal assessment and the importance of negotiation that followed (although this would clearly need to be on an anonymous basis). As in the Kanavos study this is likely to only be possible for a subset of products.

Overall, the compromise approach appears appropriate given the number of objective of the study but this may be more focused in the future.

5.3. DEVELOPING METRICS ON IMPACT

The current report has focused on decisions resulting from HTA and the implications this has for the time taken for the assessment process and the ultimate decision in terms of pricing and reimbursement. It may be useful to widen this in some areas for example capturing the price premium over the comparator product used in the HTA. The time taken and restriction imposed clearly are significant factors from the patient perspective. The same metrics should be followed over time. Further focus should be put on the patient perspective, in terms of the impact on the number and different types of patients and the impact on their physicians in terms of prescribing freedom and how effectively the preferences of patients are taken into account in the weights included in the value assessment.

The report has identified the minimal degree to which re-assessments take place at the moment. It is clearly possible that the low number of re-assessments represent limited resources of HTA in the market today (and there is some evidence to support this being the case). Alternatively it may reflect that new information justifying a re-assessment is relatively rare. This is an area that requires considerable more research and comparison across countries.

Finally, this report has only provided a first assessment of the degree to which 'innovation' is taken into account in the assessment system. It is clear that this is only a component of a small number of HTA systems and rarely has been influential in the assessments. A comparison of case studies that are most likely to benefit from these rules could be worthwhile. The effectiveness of this component and the degree to which this is compatible with the innovative process deserves greater attention.

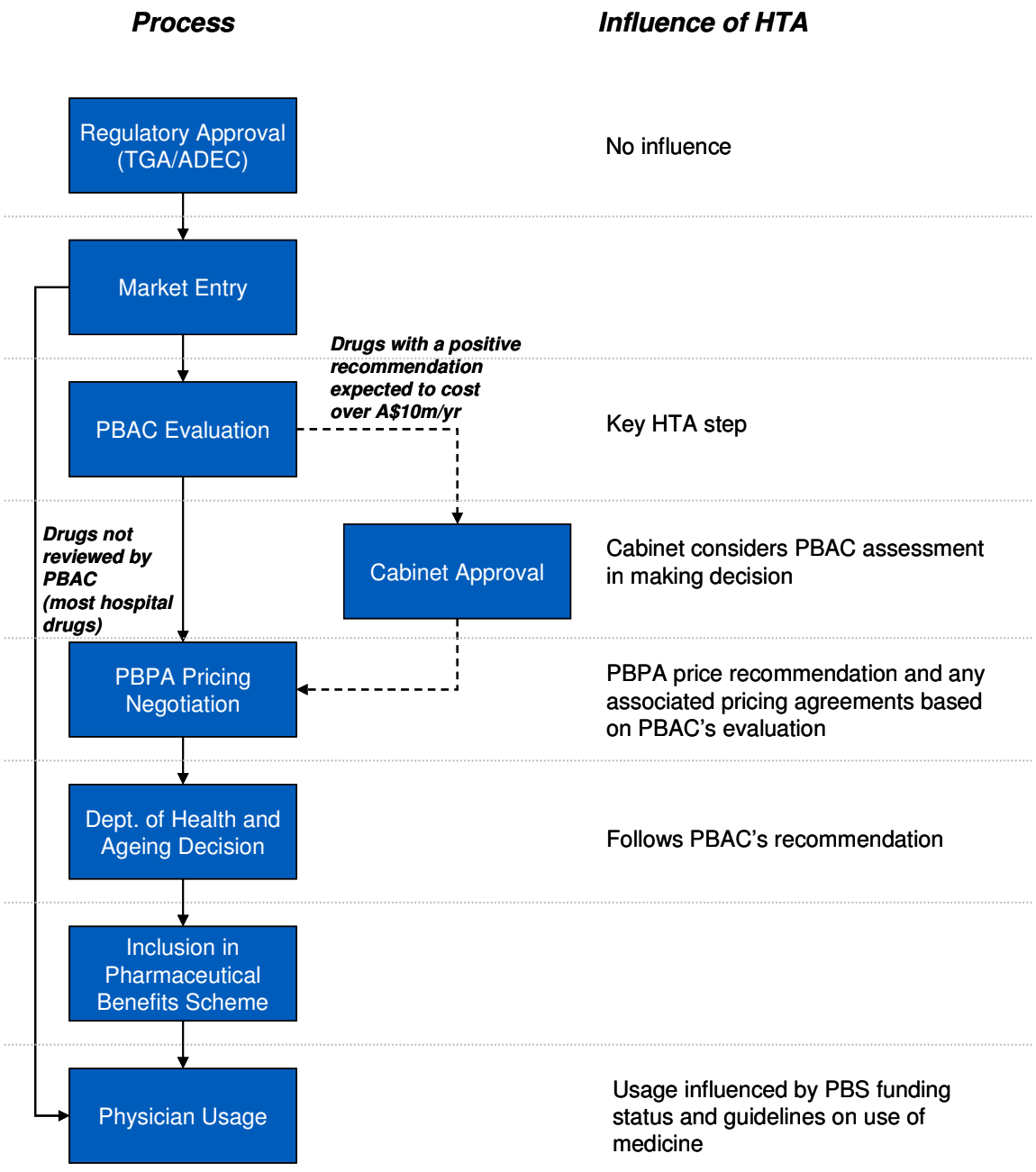
5.4. INTERVIEW PROGRAMME

The interviews undertaken for the project with the industry experts and HTA agencies were extremely useful to test how the systems work in practice, recent changes and on-going trends. The template was a useful medium to have this discussion and showed that there is considerable (although not universal) agreement regarding the best practice in the application of HTA. In future research the template should also be used to gather input from other stakeholders, for example, patients and physicians groups.

APPENDIX

Australia

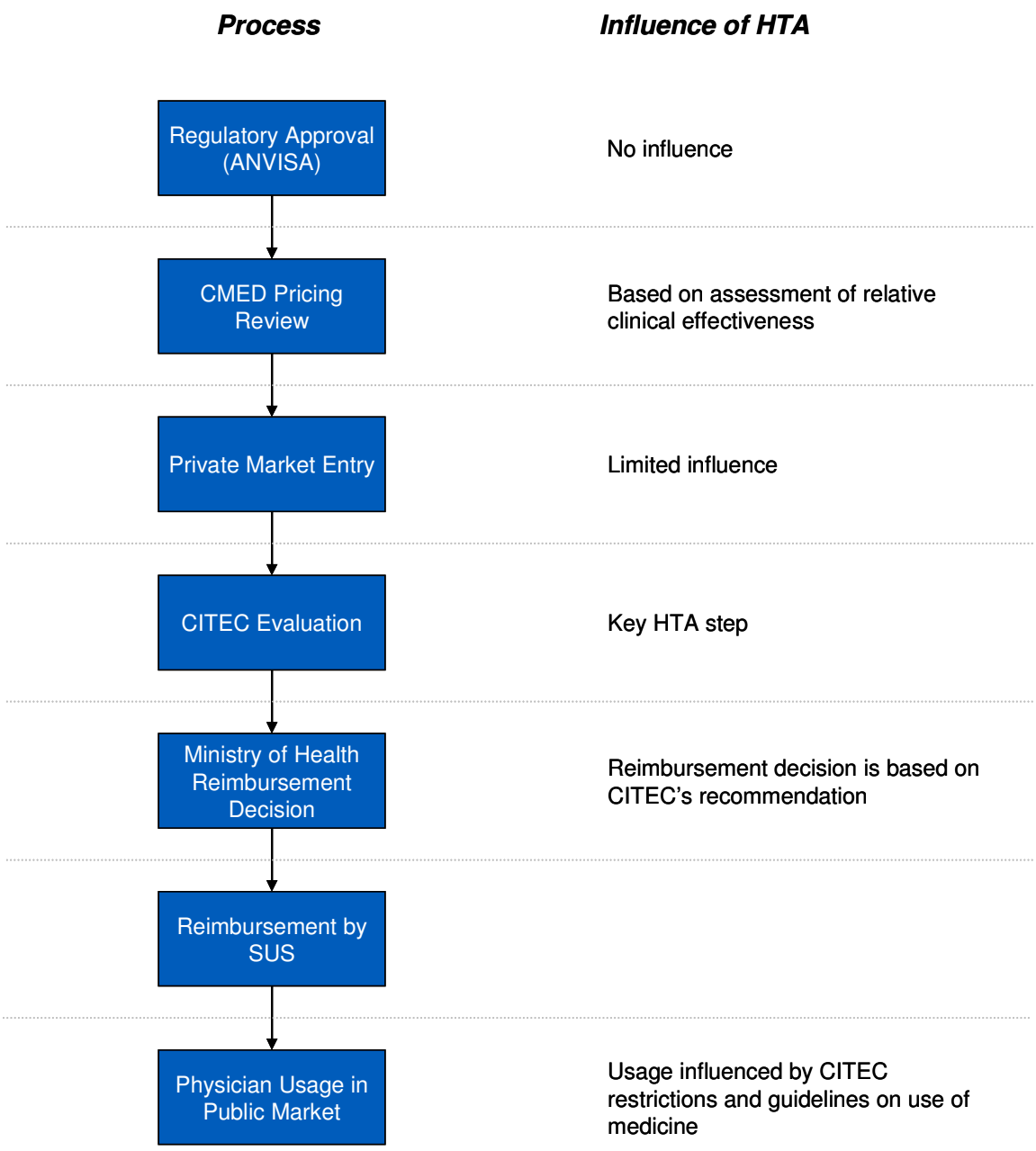
Figure 29: Impact of HTA on process from regulatory approval to physician usage of pharmaceuticals in Australia



TGA: Therapeutic Goods Administration; ADEC: Australian Drug Evaluation Committee; PBPA@ Pharmaceutical Benefits Pricing Authority

Brazil

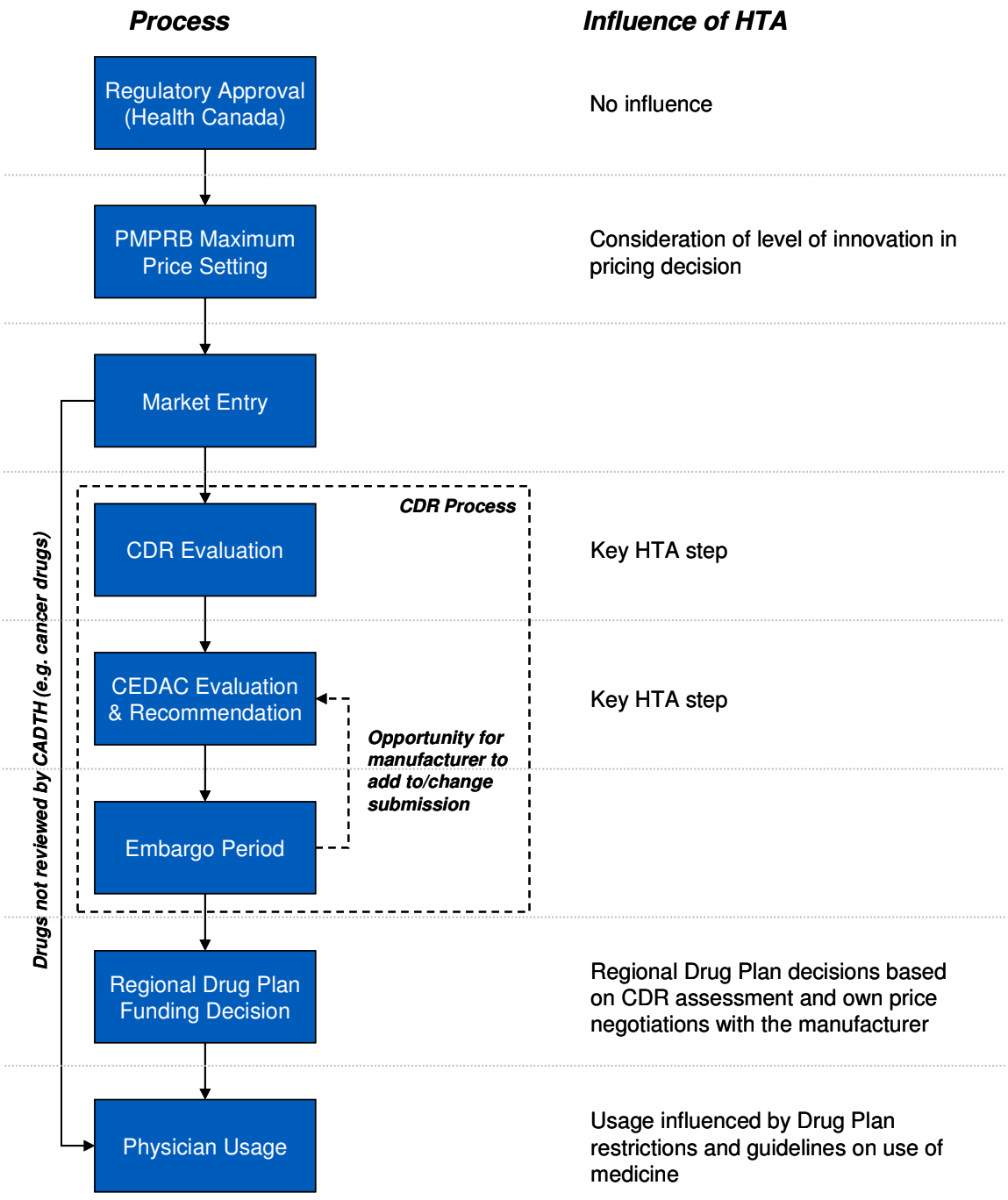
Figure 30: Impact of HTA on process from regulatory approval to physician usage of pharmaceuticals in Brazil



ANVISA: National Health Vigilance Agency; CMED: Medicines Market Regulation Chamber; CITEC: Commission on Health Technology Incorporation; SUS: Unified Health System

Canada

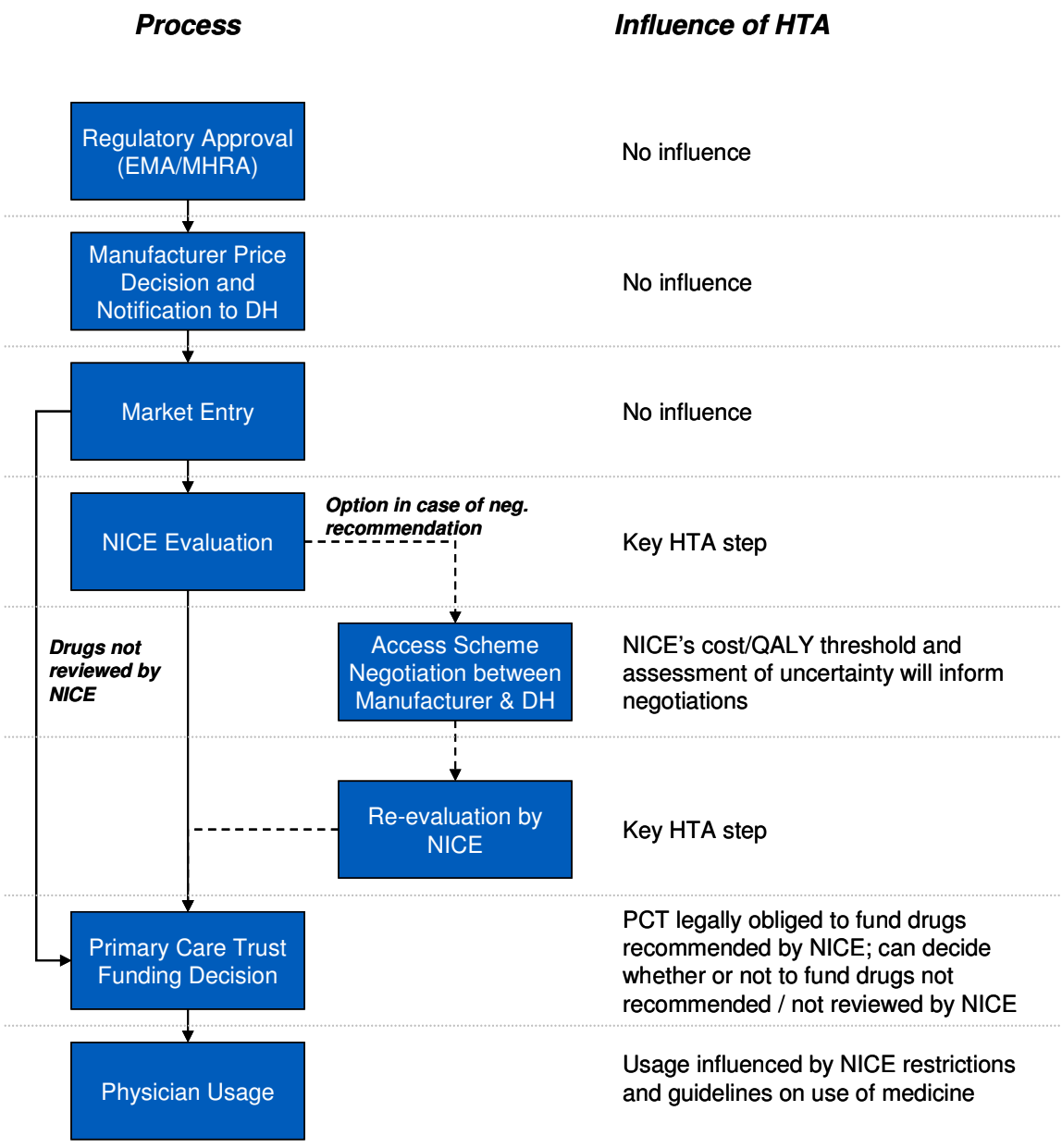
Figure 31: Impact of HTA on process from regulatory approval to physician usage of pharmaceuticals in Canada



PMPRB: Patented Medicines Pricing Review Board; CDR: Common Drug Review; CEDAC: Canadian Expert Drug Advisory Committee

England

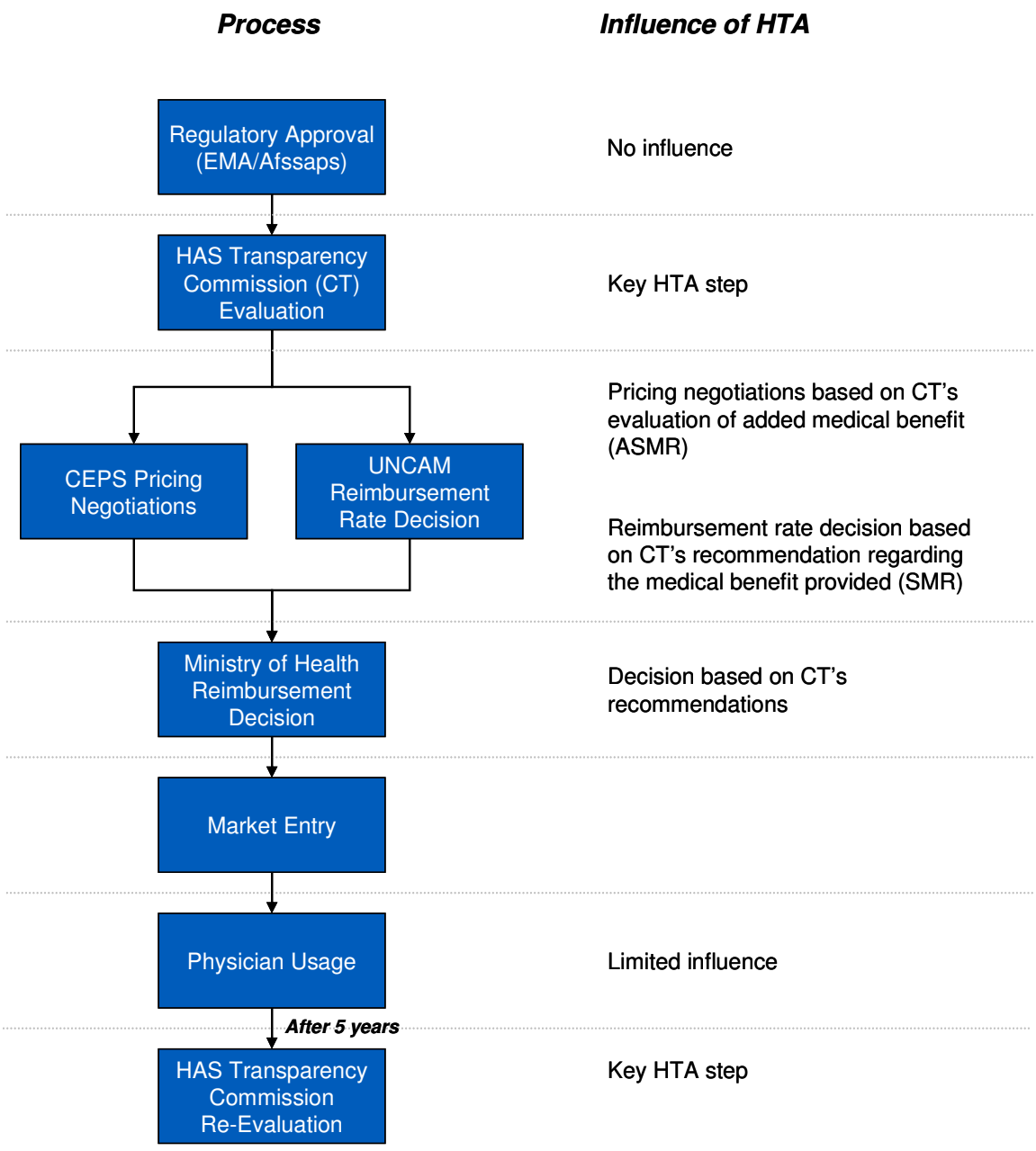
Figure 32: Impact of HTA on process from regulatory approval to physician usage of pharmaceuticals in England



EMA: European Medicines Agency; MHRA: Medicines and Healthcare Products Regulatory Agency; DH: Department of Health; NICE: National Institute of Health and Clinical Excellence

France

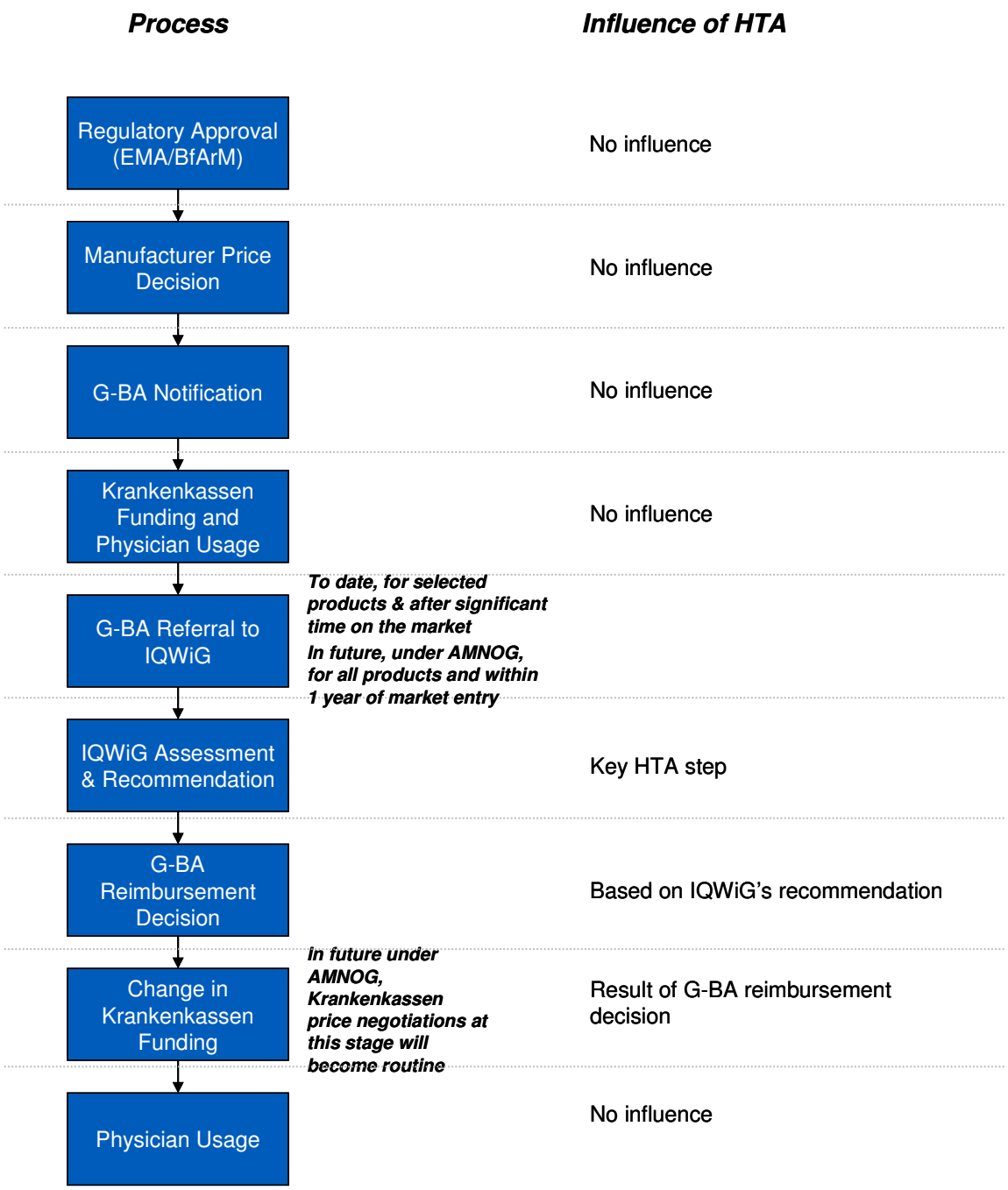
Figure 33: Impact of HTA on process from regulatory approval to physician usage of pharmaceuticals in France



EMA: European Medicines Agency; Afssaps: French Agency of Health Product Safety, HAS: National Health Authority; CT: Transparency Commission; CEPS: Health Products Economic Committee; UNCAM: National Union of Health Insurers

Germany

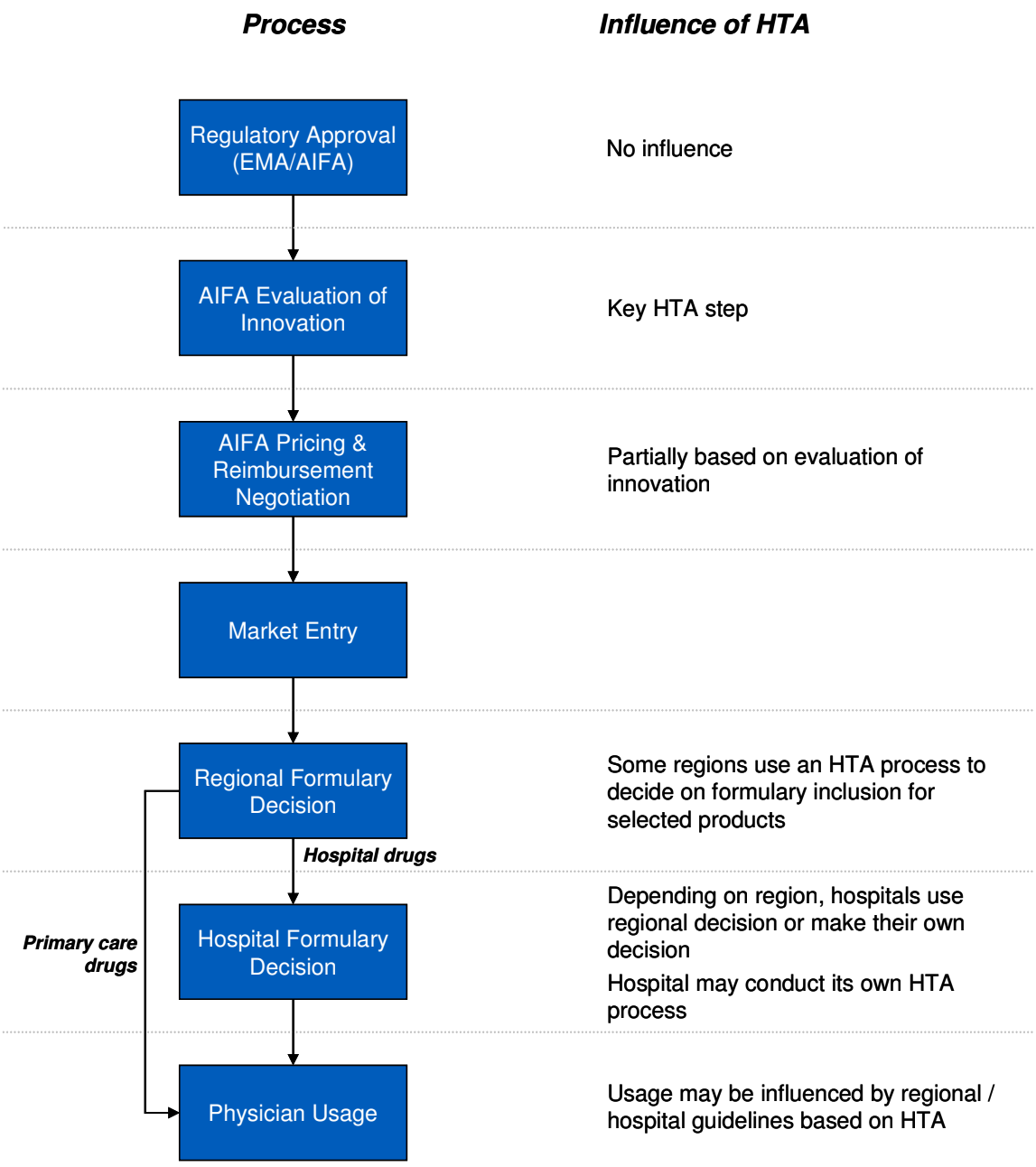
Figure 34: Impact of HTA on process from regulatory approval to physician usage of pharmaceuticals in Germany



EMA: European Medicines Agency; BfArM: Federal Institute for Drugs and Medical Devices; G-BA: Joint Federal Committee; IQWiG: Institute for Efficiency and Quality in Healthcare

Italy

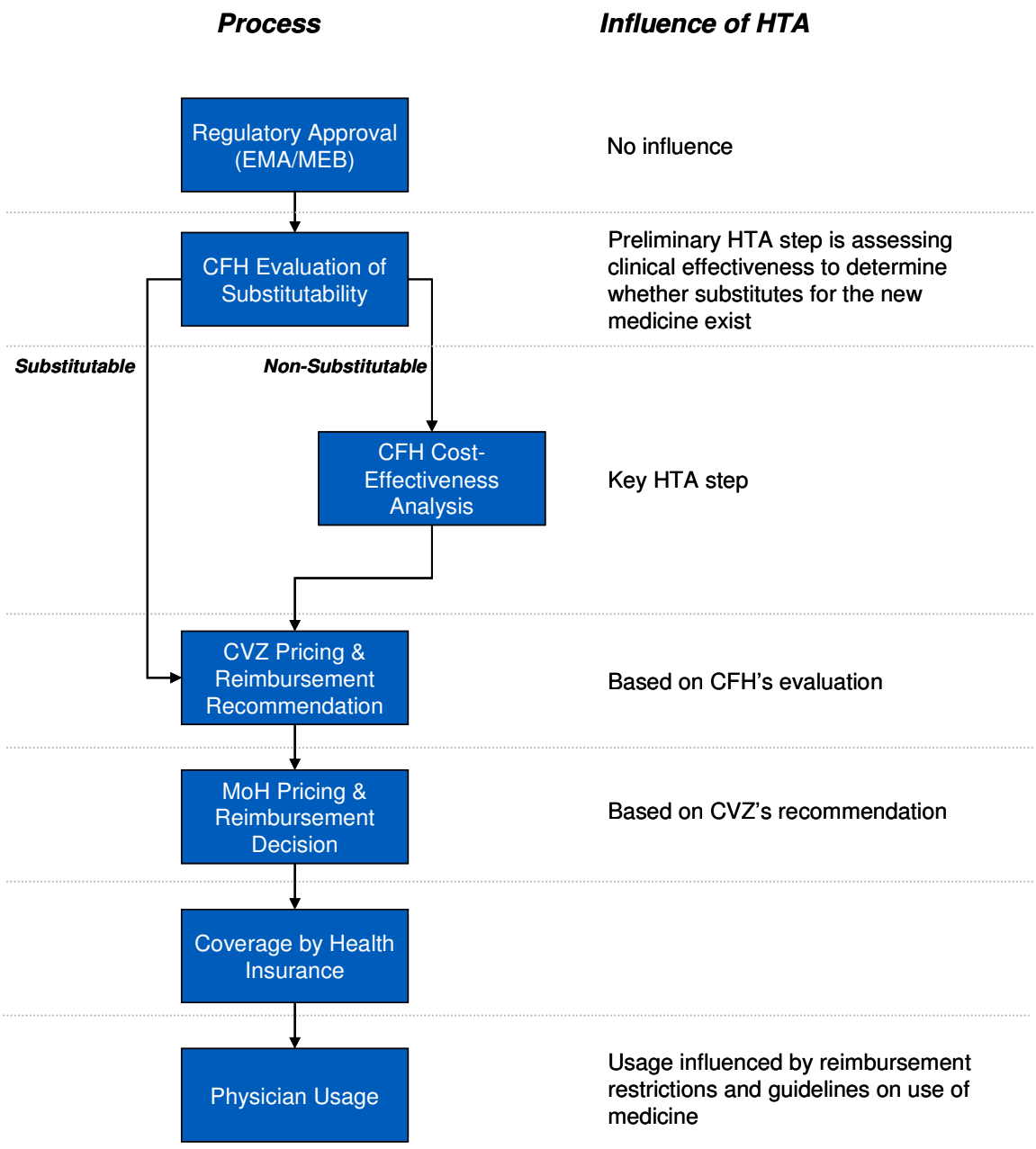
Figure 35: Impact of HTA on process from regulatory approval to physician usage of pharmaceuticals in Italy



EMA: European Medicines Agency; AIFA: Italian Medicines Agency

Netherlands

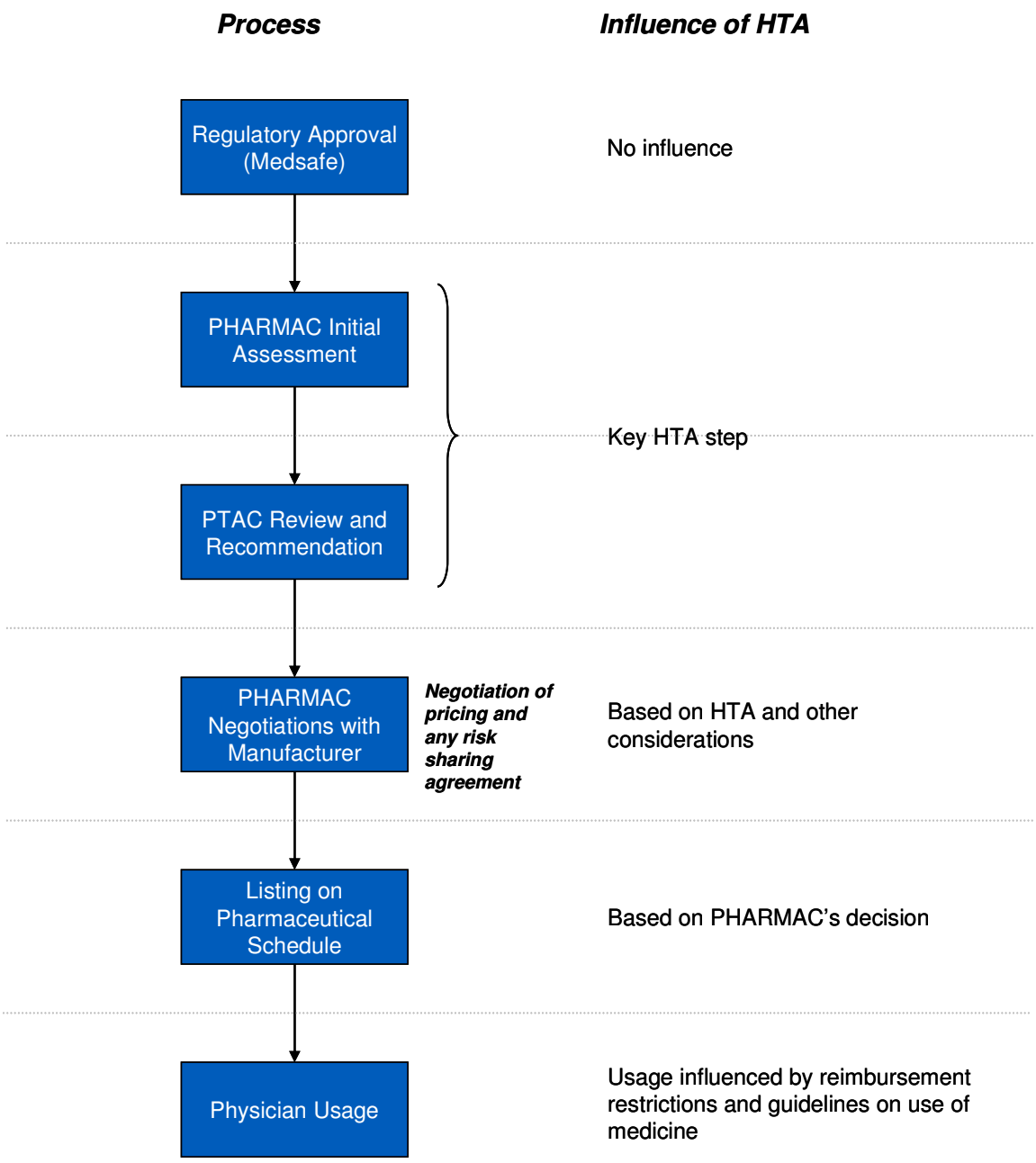
Figure 36: Impact of HTA on process from regulatory approval to physician usage of pharmaceuticals in Netherlands



EMA: European Medicines Agency; MEB: Medicines Evaluation Board; CFH: Committee for Medicinal Products; CVZ: health Care Insurance Board; MoH: Ministry of Health

New Zealand

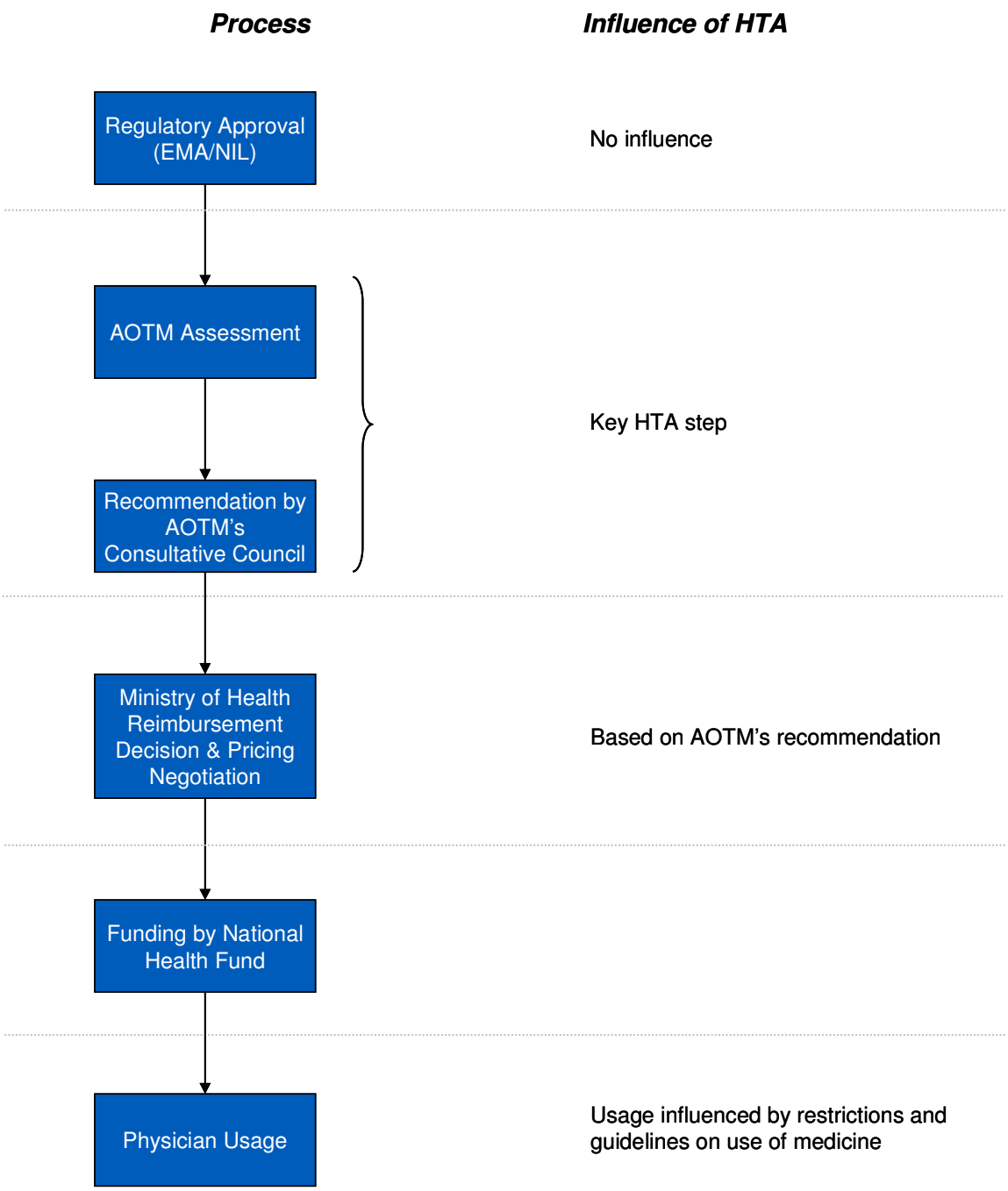
Figure 37: Impact of HTA on process from regulatory approval to physician usage of pharmaceuticals in New Zealand



PHARMAC: Pharmaceutical Management Agency; PTAC: Pharmacology and Therapeutics Advisory Committee

Poland

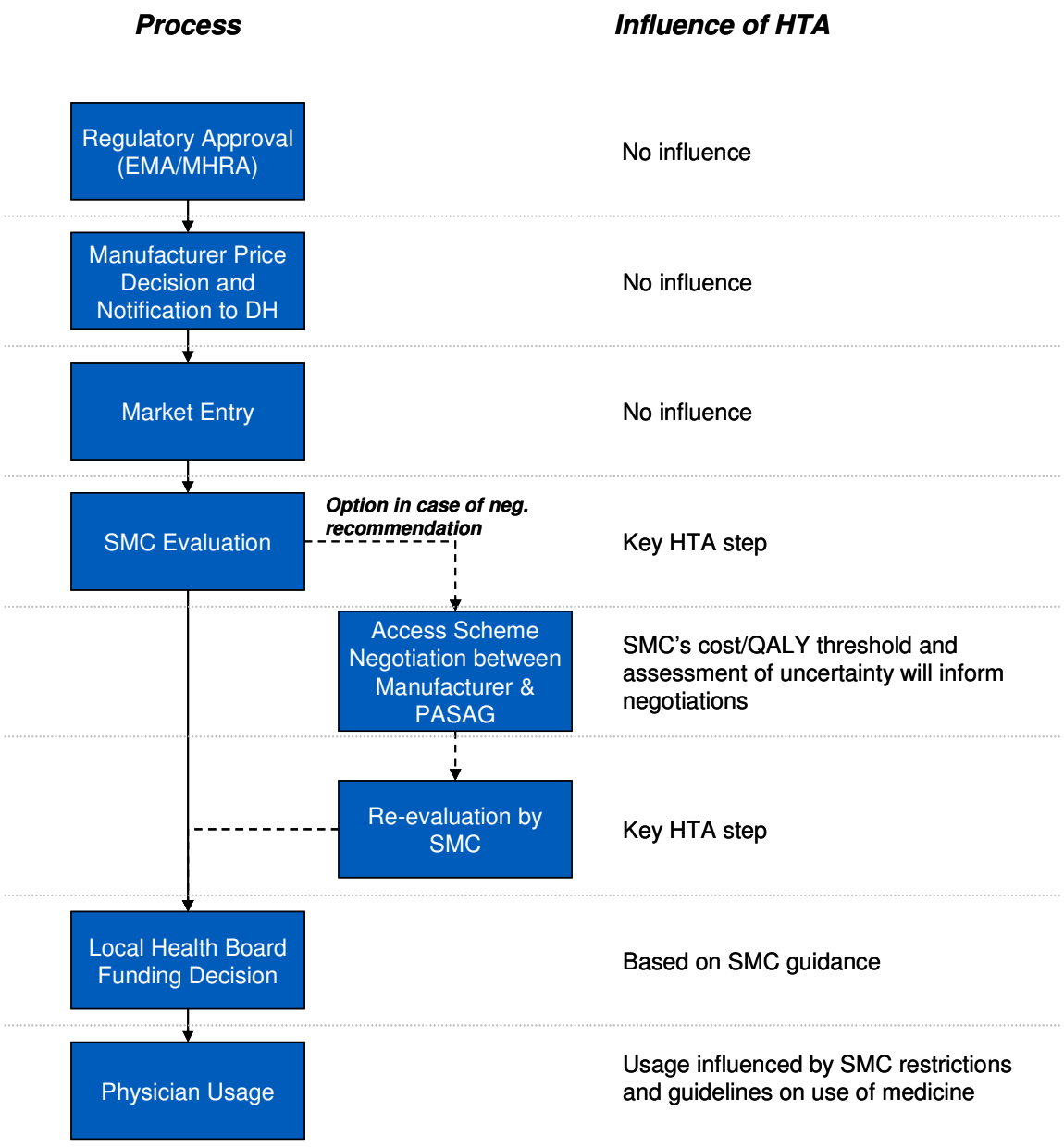
Figure 38: Impact of HTA on process from regulatory approval to physician usage of pharmaceuticals in Poland



EMA: European Medicines Agency; NIL: National Medicines Institute; AOTM: Health Technology Assessment Agency

Scotland

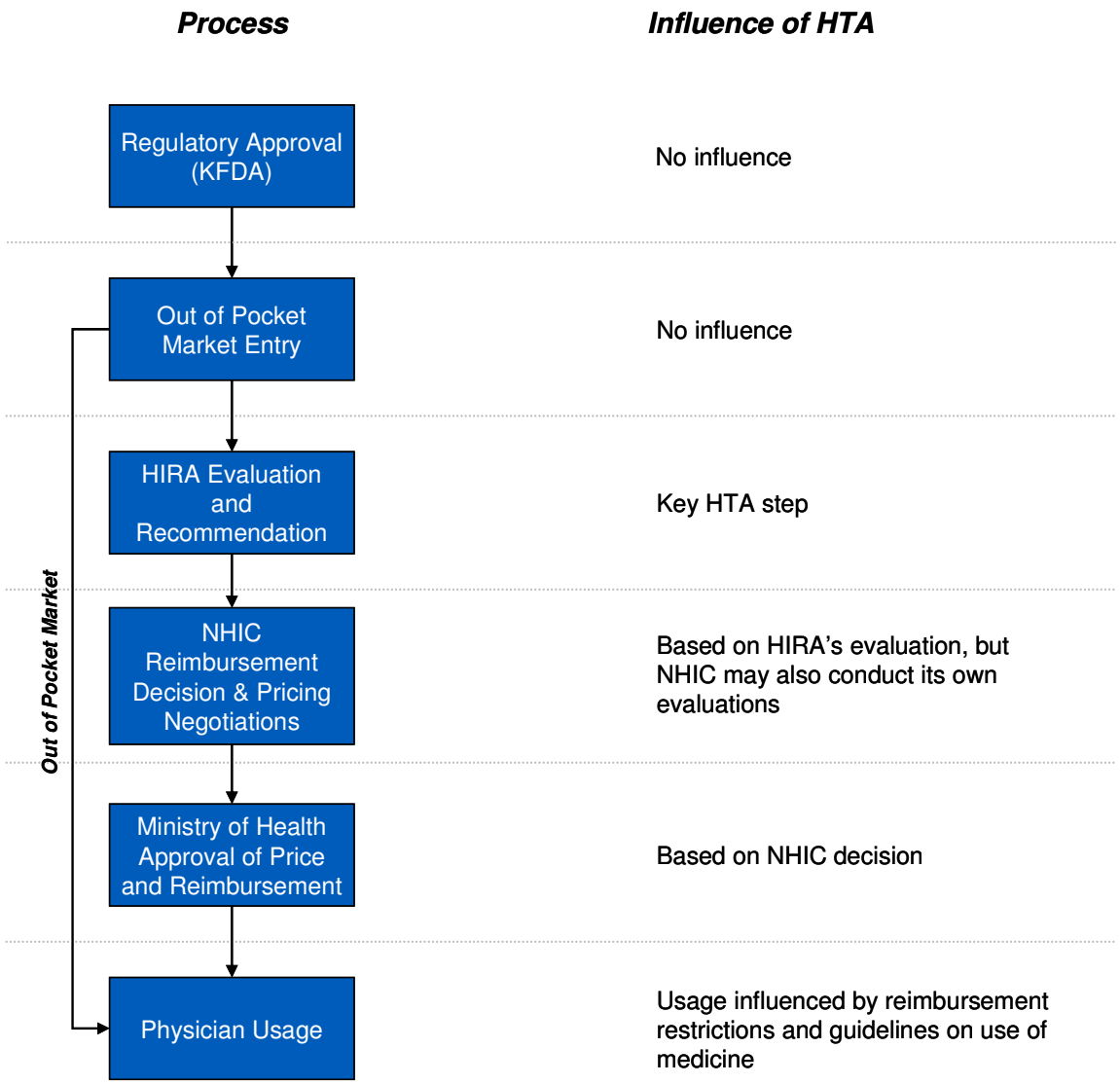
Figure 39: Impact of HTA on process from regulatory approval to physician usage of pharmaceuticals in Scotland



EMA: European Medicines Agency; MHRA: Medicines and Healthcare Products Regulatory Agency; DH: Department of Health; SMC: Scottish Medicines Consortium; PASAG: Patient Access Scheme Assessment Group

South Korea

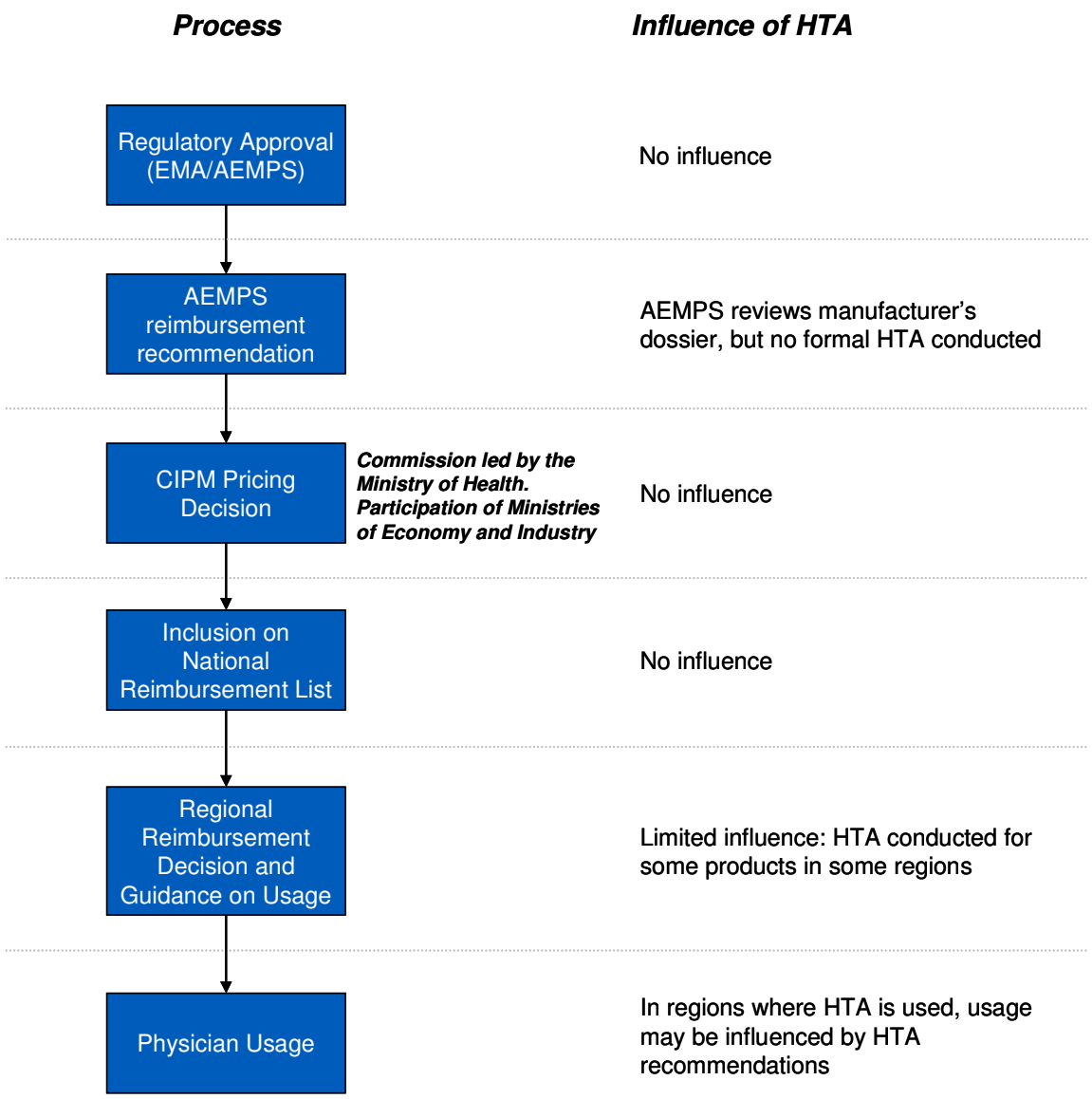
Figure 40: Impact of HTA on process from regulatory approval to physician usage of pharmaceuticals in South Korea



KFDA: Korea Food and Drug Administration; HIRA: Health Insurance Review Agency; NHIC: National health Insurance Corporation

Spain

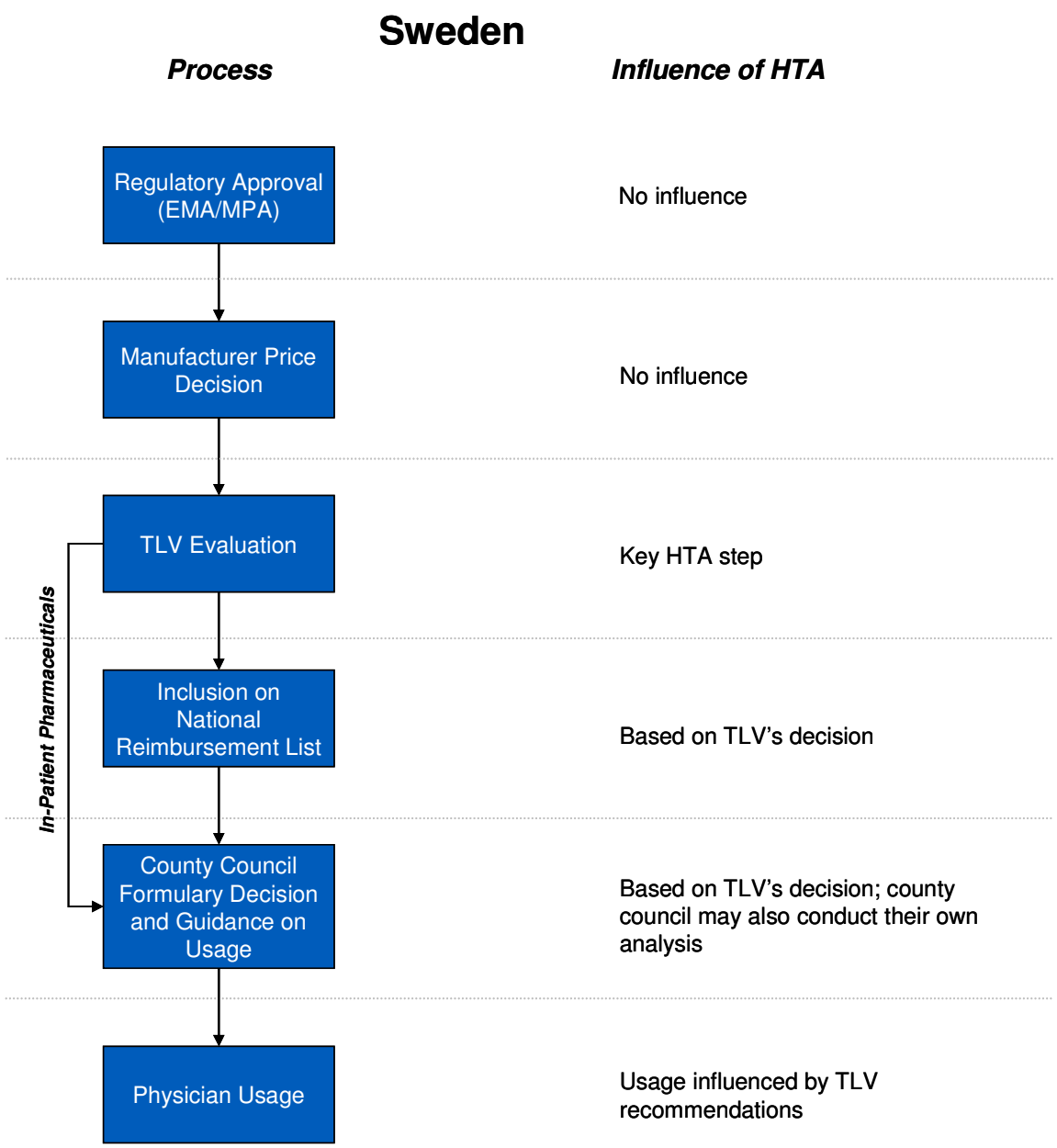
Figure 41: Impact of HTA on process from regulatory approval to physician usage of pharmaceuticals in Spain



EMA: European Medicines Agency; AEMPS: Spanish Agency for Medicines and Health Products; CIPM: Interministerial Pricing Commission

Sweden

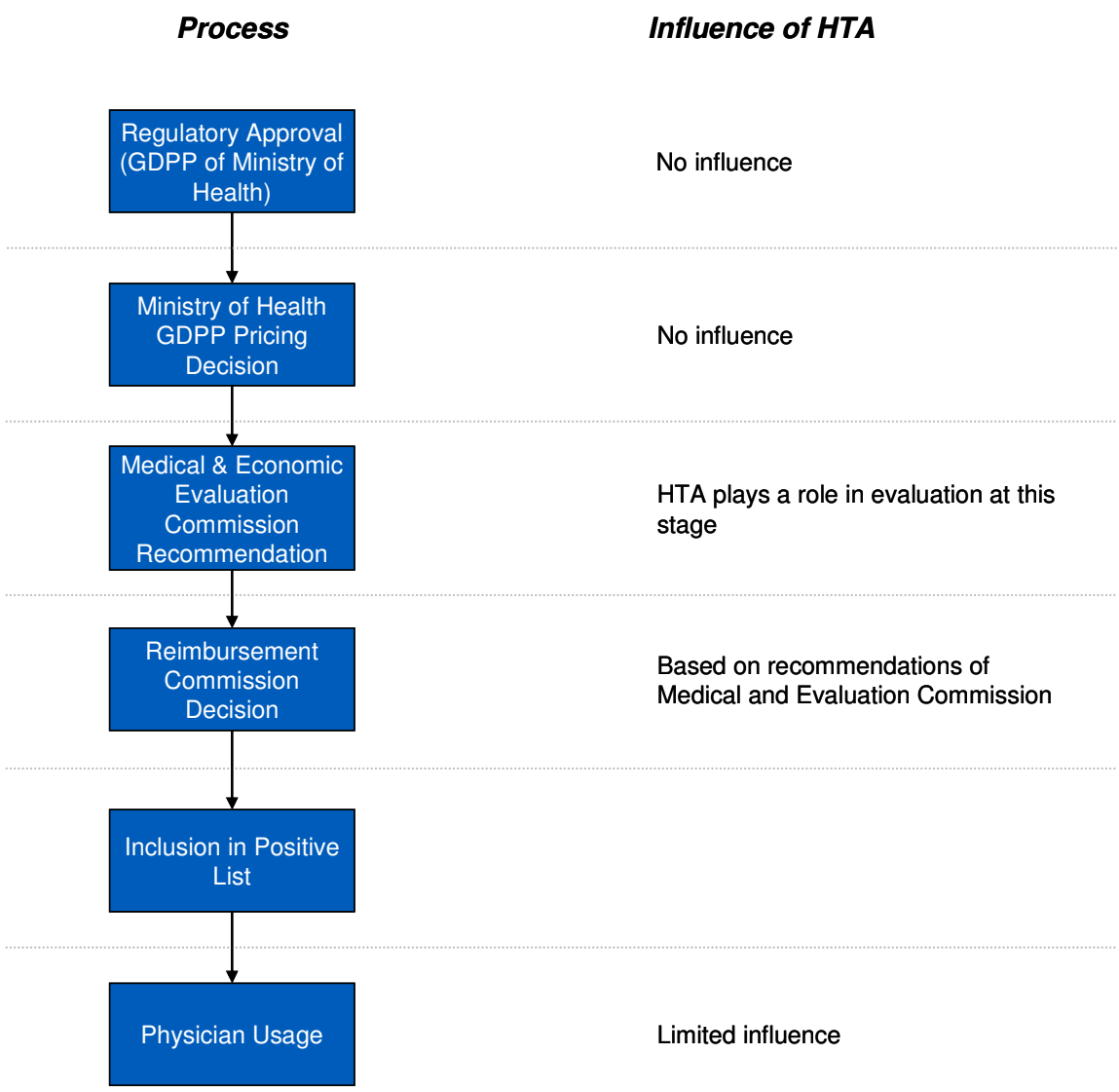
Figure 42: Impact of HTA on process from regulatory approval to physician usage of pharmaceuticals in Sweden



EMA: European Medicines Agency; MPA: Medical Products Agency; TLV: Pharmaceutical and Dental Benefits Board

Turkey

Figure 43: Impact of HTA on process from regulatory approval to physician usage of pharmaceuticals in Turkey



GDPP: General Directorate of Pharmaceuticals and Pharmacies

Principle 1: HTA should be an unbiased and transparent exercise

Table 41: Metrics for Principle 1

Metric	Red	Amber	Green
HTA is conducted independently of parties with a vested interest in the outcome	HTA strongly influenced by payers or other parties with a vested interest in the outcome	HTA sometimes influenced by payers or other parties with a vested interest in the outcome	HTA conducted independently of payers or other parties with a vested interest in the outcome
HTA is conducted separately from market authorisation	HTA is not conducted separately from market authorization with re-assessment of safety, efficacy and quality by HTA	HTA is conducted by same body that does market authorisation but in a separate process	HTA is conducted separately from market authorisation
The rationale for HTA decisions/recommendations is clearly stated	No rationale for HTA decisions / recommendations is available	Partial rationale for HTA decisions / recommendations is available	Full rationale for HTA decisions / recommendations is available
Scientific advice is available to manufacturers during development stage to enable the availability of evidence required for HTA	No scientific advice available	Informal scientific advice is available	Formal scientific advice service exists

Metrics relating to stated aims/processes
Metrics relating to actual activities/outputs

Principle 2: HTA should include all relevant technologies

Table 42: Metrics for Principle 2

Metric	Red	Amber	Green
HTA is conducted for pharmaceuticals, devices, procedures, diagnostics and treatment strategies	HTA conducted for pharmaceuticals only	HTA conducted for some other technologies but with less stringent standards than for pharmaceuticals	HTA conducted for most other technologies with similar standards as for pharmaceuticals
Proportion of HTAs conducted for each of pharmaceuticals, devices, procedures, diagnostics and treatment strategies	HTA conducted for pharmaceuticals only	Pharmaceuticals account for more than 80% of HTAs in 2009	Pharmaceuticals account for less than 80% of HTAs in 2009
HTA is conducted for old as well as new technologies	HTA only conducted for new pharmaceuticals / technologies	HTA occasionally conducted for old pharmaceuticals / technologies	HTA regularly conducted for old pharmaceuticals / technologies
Proportion of HTAs conducted for old technologies	HTA only conducted for new pharmaceuticals / technologies	New technologies account for more than 80% of HTAs in 2009	New technologies account for less than 80% of HTAs in 2009

Metrics relating to stated aims/processes
Metrics relating to actual activities/outputs

Principle 3: A clear system for setting priorities for HTA should exist and the costs of HTA should be proportionate

Table 43: Metrics for Principle 3

Metric	Red	Amber	Green
Selected topics reflect stated priorities	There is no clear, publicly available rationale for topic selection / Topics selected for HTA do not appear to reflect stated priorities	Process and rationale for selecting and prioritising topics somewhat non-transparent / Topics selected for HTA do not always reflect stated priorities	All new pharmaceuticals are reviewed / There are clear criteria for selecting and prioritising topics Topics selected for HTA reflect stated priorities
Total annual cost of conducting HTA as a proportion of healthcare spending	No information on cost of HTA available		Information on cost of HTA is available
HTA includes input from / references other national or international agencies on the same or closely related projects	Stated HTA process does not include looking at assessments by other agencies	Assessments from other agencies can be part of HTA process / Reference made to other national agencies	Looking at assessments from other international agencies is routine part of HTA process

Metrics relating to stated aims/processes
Metrics relating to actual activities/outputs

Principle 4: HTA should incorporate appropriate methods depending on its goal

Table 44: Metrics for Principle 4

Metric	Red	Amber	Green
The approach used in HTA is clearly stated	Approach used in HTA is unclear	Approach used in HTA is generally clear but there are aspects which are non-transparent or inconsistent between assessments	Approach used in HTA is clear
Methods are deemed appropriate by experts (from literature)	Methods deemed by experts to have major shortcomings	Some criticism of aspects of methods by experts	Methods deemed appropriate by experts

Metrics relating to stated aims/processes
Metrics relating to actual activities/outputs

Principle 5: HTAs should consider a wide range of evidence and outcomes

Table 45: Metrics for Principle 5

Metric	Red	Amber	Green
HTA considers unpublished trial data	No consideration of unpublished data	Consideration of unpublished data in limited circumstances	Routine consideration of unpublished data where appropriate
HTA considers data not from RCTs	No consideration of data not from RCTs	Consideration of non-RCT data in limited circumstances	Routine consideration of non-RCT data where appropriate

Metrics relating to stated aims/processes
Metrics relating to actual activities/outputs

Principle 6: A full societal perspective should be considered when undertaking HTAs

Table 46: Metrics for Principle 6

Metric	Red	Amber	Green
HTA takes into account: cost on public purse; non-healthcare and indirect costs and benefits to patients and society	HTA guidelines do not allow for consideration of non-healthcare costs such as productivity and carers	HTA guidelines allow for consideration of non-healthcare costs such as productivity and carers	HTA guidelines require consideration of non-healthcare costs such as productivity and carers
Proportion including information on societal benefits	No evidence of consideration of non-healthcare costs such as productivity and carers in case studies	Some evidence of consideration of non-healthcare costs such as productivity and carers in case studies	Evidence of consideration of non-healthcare costs such as productivity and carers in majority of case studies

Metrics relating to stated aims/processes
Metrics relating to actual activities/outputs

Principle 7: HTAs should explicitly characterise uncertainty surrounding estimates

Table 47: Metrics for Principle 7

Metric	Red	Amber	Green
Uncertainty regarding decisions is explicit	HTA process does not allow for consideration of uncertainty	HTA guidelines allow for consideration of uncertainty	HTA guidelines require consideration of uncertainty
Uncertainty regarding decisions is explicit	None of the case study reports include assessment of uncertainty	Some of the case study reports include assessment of uncertainty	Majority of the case study reports include assessment of uncertainty
Existence of conditional reimbursement to facilitate access (risk-sharing/access with evidence development)	No schemes exist for conditional reimbursement	No formal structure in place for conditional reimbursement but such schemes can be put into practice	Formal structure exists for conditional reimbursement
Schemes are used in practice	No schemes exist for conditional reimbursement	Similar schemes in place but without an explicit conditional reimbursement role	Evidence of conditional reimbursement schemes being used in practice

Metrics relating to stated aims/processes
Metrics relating to actual activities/outputs

Principle 8: Those conducting HTAs should actively engage all key stakeholder groups

Table 48: Metrics for Principle 8

Metric	Red	Amber	Green
# of relevant stakeholders are invited to contribute to the HTA process	No mechanism for stakeholders to provide input	Some stakeholder groups invited to contribute to HTA process	All main stakeholder groups invited to contribute to HTA process
Stakeholders are involved throughout the HTA process with opportunity for: contribution to assessment methodology, submission of evidence, review of recommendations	Stakeholder input during the HTA process is limited	Stakeholder input is sought at some stages of HTA process but influence is limited	Stakeholder input is sought throughout HTA process and can influence scope of assessment and outcome
Existence of an appeal process	No appeal process	Appeal process exists, conducted by HTA agency	Appeal process exists, conducted by independent body
Number of appeals against HTA decisions	None or too many failed ones	Few appeals	Some successful decisions

Metrics relating to stated aims/processes
Metrics relating to actual activities/outputs

Principle 9: HTA findings need to be communicated appropriately to different decision makers

Table 49: Metrics for Principle 9

Metric	Red	Amber	Green
Outcomes are published on a publicly accessible website	Outcomes of HTA assessment not on a publicly accessible website	Outcomes of HTA assessment sometimes published on a publicly accessible website	Outcomes of HTA assessment routinely published on a publicly accessible website
Decisions are explained in several levels of clinical/technical detail so that all relevant audiences may understand the decision (manufacturers, health plans, general population, patient groups)	Decision explained in only one level of detail	Decisions sometimes explained in multiple levels of detail	Decisions routinely explained in multiple levels of detail

Metrics relating to stated aims/processes
Metrics relating to actual activities/outputs

Principle 10: Evaluations should allow new data to be considered

Table 50: Metrics for Principle 10

Metric	Red	Amber	Green
There is a process for re-evaluation (input from manufacturers, patients to decision)	There is no process for re-evaluation	Re-evaluations can take place but only instigated by the HTA agency	Manufacturers / other stakeholders can request re-evaluation
Proportion of assessments which are re-evaluations	No re-evaluations	Few re-evaluations / Re-evaluations predominantly when there are resubmissions rather than new data	Number of re-evaluations happen in practice when there is new data

Metrics relating to stated aims/processes
Metrics relating to actual activities/outputs

Principle 11: HTA should identify areas in which the evidence base on an intervention could most usefully be developed in the future

Table 51: Metrics for Principle 11

Metric	Red	Amber	Green
Proportion of assessments identifying the value of additional evidence	No case study assessments identify areas where additional evidence would be valuable	Case study assessments identify areas where additional evidence would be valuable, but recommendations are non-specific	Case study assessments identify areas where additional evidence would be valuable, with specific recommendations

Metrics relating to stated aims/processes
Metrics relating to actual activities/outputs

Principle 12: HTA should be timely

Table 52: Metrics for Principle 12

Metric	Red	Amber	Green
Stated goal for duration of review	No stated goal		There is a stated goal
Length of time taken for reviews	>1 year	6 months – 1 year	<6 months
Length of time from approval to decision/ recommendation	>1 year	6 months – 1 year	<6 months
Review can begin before product is approved	Review cannot begin before product is approved	Review can begin before product is approved in some cases	Reviews can routinely begin before product is approved
Product is accessible/reimbursed prior to decision	Product is not accessible/ reimbursed prior to decision	Product has limited accessibility/ reimbursement prior to decision	Product has full accessibility/ reimbursement prior to decision

Metrics relating to stated aims/processes
Metrics relating to actual activities/outputs

Principle 13: Pricing, reimbursement and market access decisions should reflect the HTA assessment in a transparent, clearly defined way and be implemented as intended

Table 53: Metrics for Principle 13

Metric	Red	Amber	Green
Relationship between HTA and pricing and reimbursement	The relationship between HTA and P&R decisions is not clearly defined	The relationship between HTA and P&R decisions is somewhat defined	There is a formal and clearly defined relationship between HTA and P&R decisions
Relationship between HTA and reimbursement restrictions	Decisions for the case studies are restrictive relative to those of other assessed countries	Decisions for the case studies are average for the assessed countries	Decisions for the case studies are less restrictive than those of other assessed countries
Impact on diffusion	There is evidence that HTA has a negative impact on diffusion of medicines	There is evidence that HTA has had a negative impact on diffusion of medicines in some cases	There is no evidence of a negative impact of HTA on diffusion of medicines
Explicit treatment of innovation	Only one of: Possibility of early dialogue between manufacturers and HTA agencies Transparency regarding the assessment process Explicit consideration of innovation in assessment	Only two of: Possibility of early dialogue between manufacturers and HTA agencies Transparency regarding the assessment process Explicit consideration of innovation in assessment	All of: Possibility of early dialogue between manufacturers and HTA agencies Transparency regarding the assessment process Explicit consideration of innovation in assessment

Metrics relating to stated aims/processes
Metrics relating to actual activities/outputs

Principle 14: The impact of HTA findings and how they are used needs to be monitored

Table 54: Metrics for Principle 14

Metric	Red	Amber	Green
There is a body with responsibility for overseeing impact	No evidence of a body with responsibility for overseeing impact	HTA agency monitors its own impact	A body exists with responsibility for overseeing impact
There is measurement of the value of HTA to the healthcare system	No evidence of measurement of value to the healthcare system	Evidence of some measurement but not specifically for HTA	Systematic measurement of value to the healthcare system
Effects of HTA decisions are monitored and data is collected to evaluate clinical impact over time	No monitoring of effects of HTA decision	Some evidence of monitoring of effects but not on a systematic basis	Systematic monitoring of effects of HTA decisions
This information is used to modify/revise HTA process/methodology	No evidence that monitoring of effects has led to changes in the HTA process / methodology	Some evidence that monitoring of effects has led to changes in the HTA process / methodology	Results of monitoring studies have clearly led to changes in the HTA process / methodology

Metrics relating to stated aims/processes
Metrics relating to actual activities/outputs

Figure 44: Distribution of Decisions for Case Studies

Product	Indication	Aus	Br	Can	Eng	Fr	Ger	It	Ne	NZ	Pol	Sco	SK	Sp	Sw	Tur
Alitretinoin	eczema				◔	◕		◕	○			◕				
Cetuximab	colorectal cancer	◔			◔	◕		◕	◔			◔	○			
Degarelix	prostate cancer	◔				●			◔			○				
Doripenem	intra-abdominal infections / pneumonia					◔		◕				◔				
Lacosamide	epilepsy	◔				◔		●	●	◔	○	◔			◔	
Prasugrel	ACS	●			◔	◔		●	◔	○	○	◔			◔	
Rivaroxaban	venous thromboembolism	●		●	●	●		●	●	◕	●	●			●	
Romiplostim	Idiopathic thrombocytopenic purpura	◔		○		◕		◕	●			◔			◑	
Sapropterin	hyperphenylalaninaemia					◕		◕	●			○			○	
Sugammadex	anaesthesia					◕		◕				◔				
Tenofovir disoproxil	Hepatitis B	◔	●	◔	●	◕				◔		●				
Ustekinumab	psoriasis	◔		◔	◔	◕		◕	●		◕	◔			●	

● Accepted; ◕ Accepted with minor restrictions; ◑ Accepted with further evidence; ◔ Accepted with Major restrictions; ○ Rejected;

Blank: Product not assessed