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A comparative analysis of the role and impact of Health Technology Assessment: 2013

Final report

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The conclusions set forth herein are based on independent research and publicly available material. The views expressed herein are the views and opinions of the authors and do not reflect or represent the views of Charles River Associates or any of the organisations with which the authors and advisors are affiliated.

Executive Summary

Charles River Associates (“CRA”) was asked by EFPIA and PhRMA to update the Comparison report undertaken in 2010/11 (CRA 2011).¹ The overall purpose is to develop a neutral and objective description and comparison of health technology assessment (HTA), based on the stated methodologies that are used in systems, but also taking into account the actual behaviour of those involved and their observable impact. The goal of this update is:

- To describe any recent changes in the use of HTA;
- To widen the assessment by including emerging markets that have recently implemented HTA; and
- To further develop the analysis of the impact of HTA, particularly how HTA is used in decision-making and its impact over time on health system efficiency.

As in the initial Comparison report, the aim was to compare the application and use of HTA (rather than HTA agencies or units or health system decision-makers) across a diverse group of countries, covering different regions, including mature and evolving HTA processes. In this updated report, we have focused on 16 countries, including 12 of the original countries and four new countries.

The literature

Over the past three years, there have been a large number of publications focused on analysing the use of health technology assessment. Indeed, the debate on using best practice principles to audit or assess HTA has continued since the report. This has noted the methodological difficulties associated with such exercises, particularly the difficulty in establishing the counterfactual and a summary score that takes into account the various dimensions of comparison. However, the “best practice principles” developed in the initial report still represent the best framework for conducting a comparison of this kind.²

In terms of the HTA methodology, there has been a large debate on the merits of including wider societal factors (particularly around value based pricing or assessment), the role of managed entry agreements and on the need for harmonisation of the evidence requirements from a regulatory and health technology assessment perspective. However, these dimensions were already captured in the assessment template. We have added a number of

¹ “A Comparative analysis of the role and impact of Health Technology Assessment”, A report commissioned by EFPIA, PhRMA, Medicines Australia and EuropaBio. This is referred to as the initial Comparison report or CRA (2011) throughout, CRA, 2011. Available here: <http://www.phrma.org/node/741>.

² It should be noted that this report is not intended to be an endorsement of the increasing and concerning trend across a number of emerging markets to adopt HTA. On the contrary, too many markets are utilizing HTA as an overelaborate cost-containment tool. Rather this report simply seeks to analyze whether those countries that have adopted HTA systems are following best practice principles in the implementation of those systems.

new metrics to reflect the interest in how comparators are chosen and the relationship between HTA recommendations and clinical guidelines.

There have been more papers comparing the different recommendations given by HTA agencies for the same molecules across countries. Most of these papers focus on the continued divergence of these recommendations rather than determining the underlying factors that lead to the divergence. The differences in the recommendations for oncology products have received particular attention in the last two years (reflecting both the number of oncology products that are being assessed and that the application of HTA to oncology has been identified as having particular challenges). Finally, there are a number of papers examining the speed of the various HTA processes. However, the literature on the impact on prices or innovation remains sparse.

Our methodological approach

The update report has followed the same approach as used in the initial Comparison report. A template, based largely on that used for the 2011 study, capturing the HTA best practice principles through a range of quantitative and qualitative metrics was constructed to capture the key characteristics of the HTA system in each country (see technical appendix). In addition to adding a small number of metrics to the template, we have distinguished between metrics that reflect the design of the system and those that reflect the operation of the system.

We then used both primary and secondary sources to collect information on the approach to HTA in each country. This was supplemented with a review of 17 case study medicines (covering a wider range of therapeutic areas) listed in Table 1. This allowed us to review a total of 185 assessments of medicines across the countries studied (compared to 74 in 2011).

Table 1: Case study medicines used in the assessment by molecule name and indication

Abatacept (Rheumatoid arthritis in adults)	Ticagrelor (Acute Coronary Syndrome)
Boceprevir (Hepatitis C)	Trastuzumab (Initial breast cancer; Advanced breast cancer)
Certolimumab pegol (Rheumatoid arthritis in adults)	Abiraterone (Oncology)
Fingolimod (Multiple Sclerosis)	Apixaban (Venous thromboembolism)
Golimumab (Psoriatic Arthritis; Ankylosing spondylitis)	Cabazitaxel (Prostate cancer)
Rituximab (Non-Hodgkins linfoma follicular)	Eribulin (Breast cancer)
Roflumilast (COPD)	Ipilimumab (Advanced melanoma)

Retigabine (Epilepsy)	Vemurafenib (Metastatic melanoma)
Telaprevir (Hepatitis C)	

Source: CRA analysis

The draft populated template was then discussed with representatives of the HTA agencies (10 interviews were completed) and with the industry associations in each of the countries. Additional, targeted interviews with patient experts were undertaken to capture further insight on the patient perspective.

Changes in HTA system since the Initial Comparison report

Most of the HTA systems reviewed have undergone incremental change, with the majority of metrics assessed as performing at the same level as they did in the initial Comparison report. Indeed, almost 70% of the 43 metrics analysed in both 2011 and 2013 assessments received the same score within both years.

There are some exceptions where there has been significant change in HTA system over the last three years. In particular, we would highlight Brazil, Germany and Poland as having undergone a significant reform in the way HTA is conducted. In other cases, although change has occurred through a series of reforms, the overall result of this is that HTA process is significantly different to that of 2011; this would be the case in France and in South Korea. However, overall, our conclusion remains that, while there have been slight improvements in the assessed metrics, all systems have areas where they could improve significantly according to the identified best practice principles.

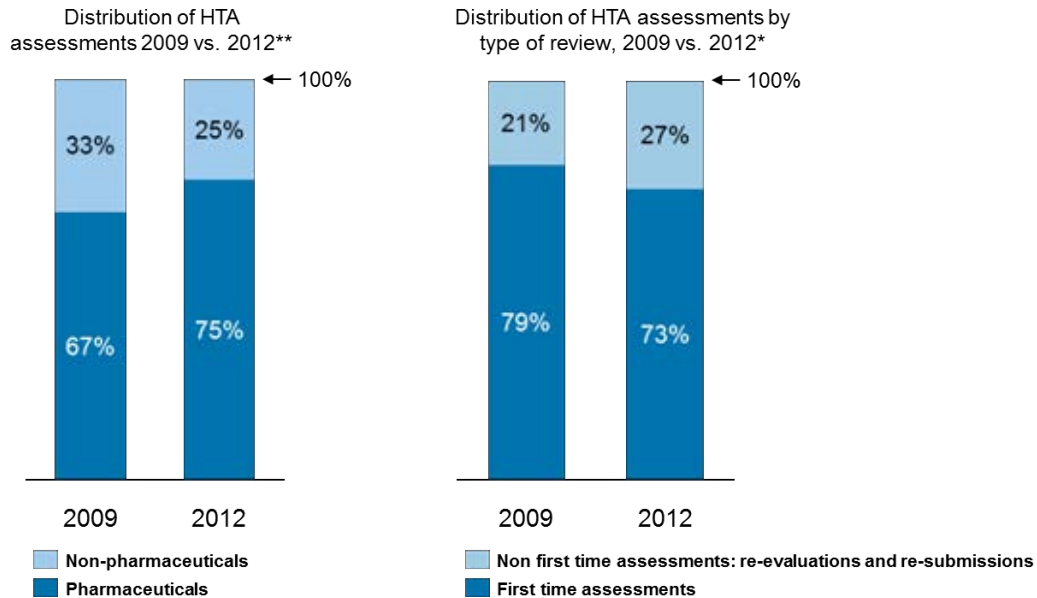
If we consider the overall trends by category:

Scope and prioritisation: In terms of scope and prioritisation of HTA systems, our assessment is quite similar to the initial Comparison report, with many metrics receiving the same scoring as previously. There is more transparency in the way that some countries choose to prioritise the technologies that are assessed (France, Germany³, South Korea, would be good example of this). However, in other markets the rationale for undertaking reviews remains unclear (Mexico, Brazil, or Poland are examples of this). In particular, most of the new countries that were included did not perform well on this metric. Finally, as illustrated in Figure 1, there has been an increase in the proportion of HTA focused on pharmaceutical products and a decrease in the proportion of first time reviews (compared to re-evaluations and re-submissions) since the last report.

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It should be noted that the German system changed considerably following the AMNOG reform. The significant structural changes make the comparison between the assessment in the two reports particularly challenging and care should be taken in drawing conclusions.

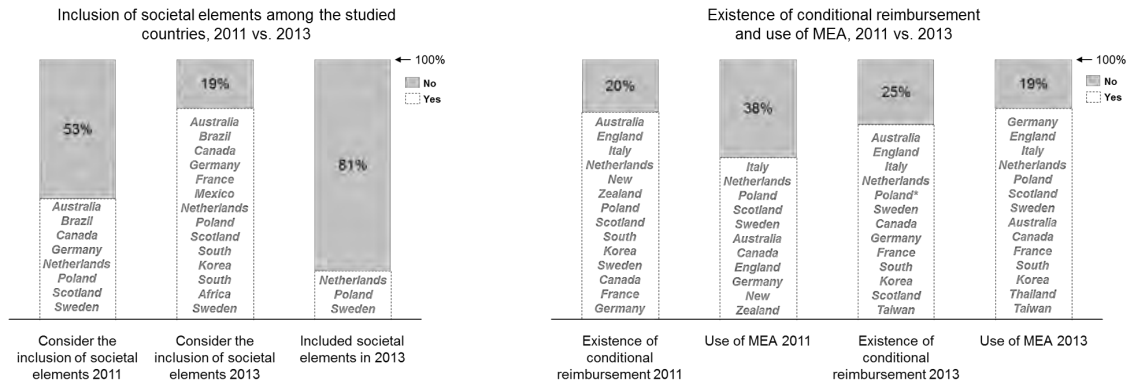
Figure 1: Distribution of HTA assessments by type of technology and type of review, 2009-2012



Source: CRA analysis; Note: The 2009-2012 comparison only includes those markets that were included in the 2011 report

Methodology: As in the initial Comparison report, we found that most of the studied countries provide guidelines for companies on how to submit evidence for the purposes of the HTA and on how the assessments will be undertaken. In terms of the methodology used, we found, at least on paper, an increase in the inclusion of societal elements (for example, in South Korea, Taiwan, Mexico societal elements can in principle be included in the assessment) as illustrated in Figure 2. However, the number of countries where we can find evidence that this is included in the assessment remains small. In fact we only have evidence in the Netherlands, Sweden and Poland of societal aspects actually being included in assessments. An increase in the use of managed entry agreements (MEAs) has been observed although in general, these appear to be used to deal with financial restrictions (England, Scotland or Australia) rather than managing uncertainty about outcomes. However, other markets are tailoring their approach to HTA, for example by offering immediate reimbursement to hospital medicines (Netherlands and Australia are good examples of these practices). Finally, we can observe a greater awareness on the cost of conducting HTA processes, key information if the HTA process itself is to be proportionate and efficient.

Figure 2: Countries including societal aspects and recognising uncertainty within their HTA assessments, 2011 vs 2013

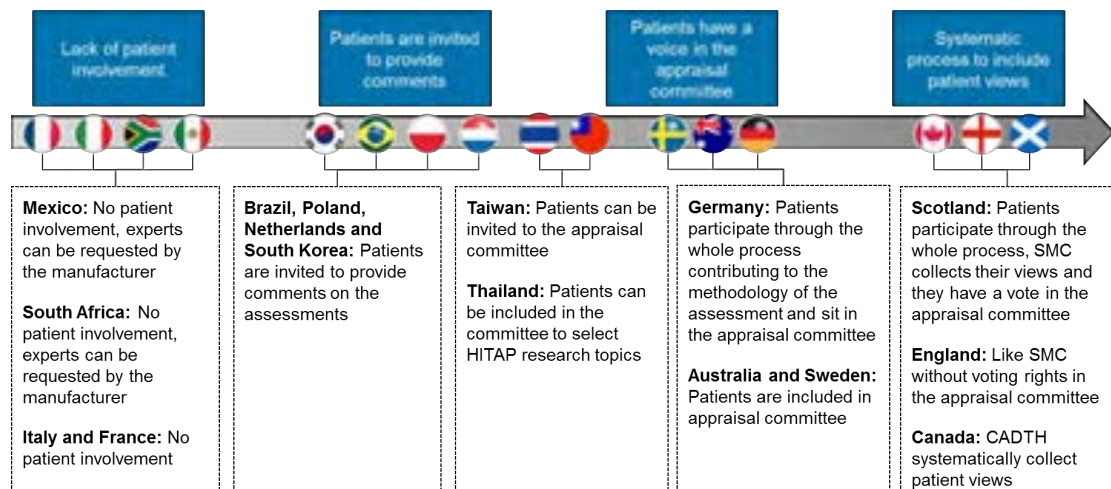


Source: CRA analysis

Based on a new metric for 2013, we found a concern regarding the choice of comparators in some countries. Although using the standard treatment as the choice in comparator is a common element across the studied countries, a preference for the lowest cost drug is observed (Canada, England, Germany, South Africa, Sweden or Thailand).

Process: Improvement has been observed in the metrics assessing HTA process among the reviewed countries. Most of the improvement has been linked to a more inclusive process. However, there continues to be significant variation across markets when looking at how stakeholders are invited to contribute. There are countries where a formal process is implemented (Canada, England or Scotland). In other markets, patients are invited to contribute to some extent (Germany, Taiwan, Thailand or Brazil), but no formal process exists. Finally, there are countries where different views are not included within the process (France and Italy). These differences are illustrated in Figure 3.

Figure 3: The role of patients within the HTA systems analysed

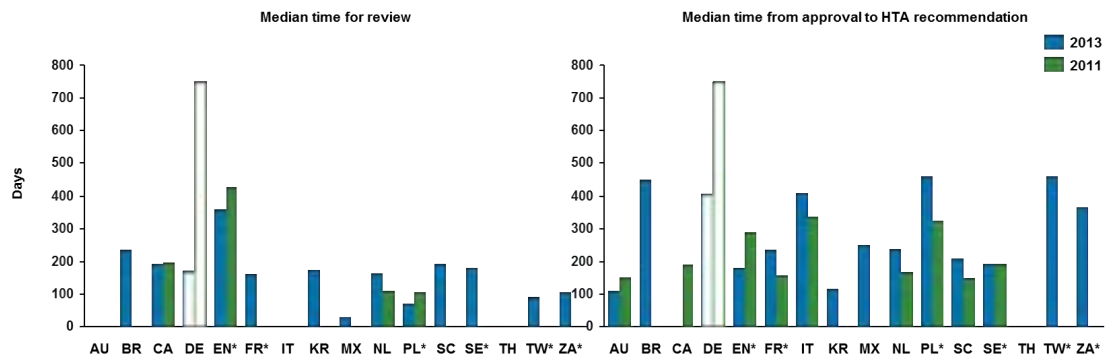


Source: CRA analysis

Some countries have become more transparent in the way results are communicated to the public. For example, the amount of information regarding the assessments undertaken in Brazil has improved significantly since the creation of CONITEC. This can also be illustrated by the much greater number of assessments that provided sufficient detail for us to be able to review in this update. However, there are still countries, such as Italy, where the rationale behind the conclusions remains opaque.

Impact: Some improvement has been observed in the metrics used to assess the impact of HTA. Much of this relates to more timely processes being implemented (for example, in Germany, France or Brazil). This is illustrated in Figure 4. However, comparisons across years need to be undertaken with care as access to medicines may be possible prior to the HTA recommendation. For example although the speed of the German system has increased, both before and after AMNOG medicines were available on the market during the period of the review, so the impact on patient access is not as significant as in other international markets where patient access is contingent on the recommendation from the HTA process.

Figure 4: Median duration of the HTA by length of the review and the time from regulatory approval to HTA recommendation, 2011 vs. 2013



Source: CRA analysis; Note: *Reflect numbers that have been collected through interviews with industry and HTA representatives as data was not always available. The German observation has no fill to reflect that effective patient access is possible prior to the recommendation.

On the other hand, there has also been a slight increase in the number of restrictive recommendations (restricting the use of medicines). The country with the least restrictions remains Italy, but it is now closely followed by the Netherlands, Scotland and Sweden. Poland, which was identified as one of the more restrictive markets in the initial Comparison report, is now slightly more flexible. Overall, HTA systems based on ex ante cost-effectiveness remain the most restrictive.

In 2013 report, we looked more deeply at the impact of HTA processes on the diffusion of medicines. We used IMS sales data to understand what happens after the HTA recommendation is published. First, we looked at the length of time it took following publication of the HTA recommendation for sales to be observable. We did not find that more innovative medicines were assessed more quickly or were available on the market more quickly following the assessment. Indeed, in some markets, the process for innovative products was significantly longer than for less innovative products. France was the exception

to this. Where we could observe sales before and after the publication of the HTA recommendations, we did not find a significant change in the growth of the sales following the publication. This, in part, is likely to reflect assessment being undertaken more quickly after launch than in the past. In terms of sales growth, perversely we found that products deemed to be less innovative grew more quickly than products that were assessed as more innovative. Finally, in terms of the relationship between the HTA recommendations and decisions on pricing and/or reimbursement, more systems are using a classification system based on added therapeutic value that is then used in the process for determining prices and/or reimbursement. However, the classification across countries is not consistent; this means that anticipating rewards remains a challenge for industry and, the impact on investment decisions is therefore likely to remain weak. The relationship between the HTA recommendations and price and reimbursement is even less clear within emerging HTA systems. We found that HTA is designed to determine the inclusion of health technologies within positive reimbursement; however, budget impact analysis also has a significant role in determining the decision. The result of this is that it is difficult to anticipate how a positive assessment of value will affect the negotiation. Mexico or Thailand would be the clearest examples. Taking all the above into consideration, the relationship between the HTA and the price and reimbursement decision remains opaque in a number markets.

A number of countries are considering how best to monitor the impact of HTA, however, in practice only a small number of countries have instituted a process by which this is undertaken (e.g. Canada or England).

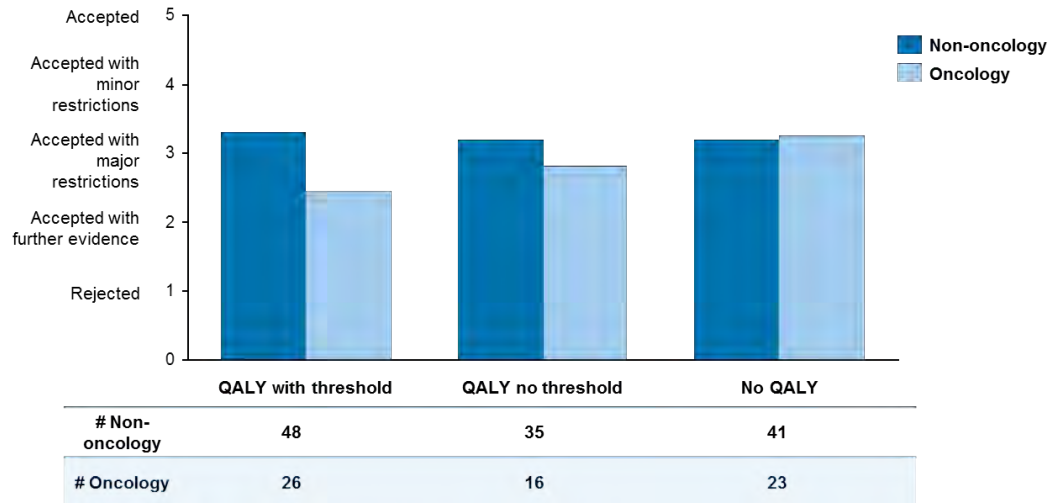
New countries included in 2013 analysis

In terms of the new countries included in the analysis, our assessment varied significantly across the countries, with strengths and weaknesses in each. There was limited inclusion of different stakeholders in all of the new countries (although in principle there is a process allowing their inclusion in Taiwan). Our assessment of metrics measuring the impact of HTA (for example, in terms of the timeline for completing the assessment or having a clear relationship between the assessment and the price and reimbursement process) was weakest for the new countries.

Therapy specific analysis

Given the focus on oncology in the academic literature since the last report and the number of oncology products included in our case studies, we have also looked in more detail at these assessments. We found that oncology drugs face more restrictive recommendations than other therapy areas. This is the case, even in those markets, like Canada, where oncology drugs are reviewed by a separate entity. Interestingly we found that oncology drugs receive more restrictive recommendations in markets that use some form of QALY with threshold to make HTA decisions as shown in Figure 5 below.

Figure 5: Average HTA recommendations by therapy area and model of HTA



Source: CRA analysis; QALY with threshold includes: AU, CA, EN, PL, KR, SC, TH; QALY no threshold includes: MX, NL, SW; No QALY includes BR, GR, FR, IT, TW and SA

Recommendations regarding future assessments

The way that HTA is used and impacts on the wider system continues to evolve. In addition to the significant changes noted above, further changes are expected in the future. The impact of these further changes was not captured in the case studies, so they are not yet fully incorporated in the 2013 assessment. Examples include:

- In England, value based assessment is expected to be introduced in the autumn of 2014. It is believed that this will incorporate a more formal assessment of wider societal value and unmet need within the HTA and associated processes.
- In France, a country where HTA has focused up to now on relative effectiveness, the CEESP, a commission created to conduct cost-effectiveness studies, has now been given a greater role and is tasked with supplying the CEPS with a product-by-product cost-effectiveness assessment. Although this is included in the system assessment above, this has not impacted on the case studies.
- The Netherlands has created a separate committee to assess societal benefits.

It will be important to monitor the impact of these and further developments in future assessments of HTA systems and performance. In addition, there are important debates that should be taken into account in future assessments, particularly, the increasing role of regional networks and the interaction between HTA and efforts to accelerate HTA processes and policies such as adaptive licensing.

1. Introduction

Charles River Associates (CRA) was asked by EFPIA and PhRMA to update the Comparison report undertaken in 2010/11 (CRA 2011).⁴ The overall purpose is to develop a neutral and objective comparison based on the stated methodologies that are used in different health technology assessment (HTA) processes, but which also takes into account the actual behaviour of the agencies and their observable impact. The goal of this update is:

- To describe any recent changes in the use of HTA;
- To widen the assessment by including emerging markets that have recently implemented HTA; and
- To further develop the analysis of the impact of HTA, particularly how HTA is used in decision-making and its impact over time on health system efficiency.

In this updated analysis we have incorporated the views of a wider set of stakeholders into the assessment. We have undertaken interviews with representatives from the agencies responsible for HTA and patient groups as well as industry associations in each of these markets.⁵

As with the previous report, the purpose is to examine the role of Health Technology Assessment in the health system. Therefore the paper is focused on the role of HTA in a country rather than the agencies that undertake them. This has a number of implications. Firstly, in some countries a number of different agencies will be included in the assessment because they are responsible for assessing different types of technology, for example. Secondly, we cover a wide range of countries including countries which do not have a dedicated HTA agency.

We have purposely focused on areas where there has been less analysis and debate. For example, we do not attempt to review or add to the vast literature on the pros and cons of different methodologies for undertaking HTA (for example using explicit ICER thresholds).⁶ Also, we do not directly address the issue of harmonisation of HTA models or practices, or its application to particular categories of product such as orphan medicines.

4 "A Comparative analysis of the role and impact of Health Technology Assessment", A report commissioned by EFPIA, PhRMA, Medicines Australia and EuropaBio. This is referred to as the initial Comparison report or CRA (2011) throughout this report. Available here: <http://www.phrma.org/node/741>.

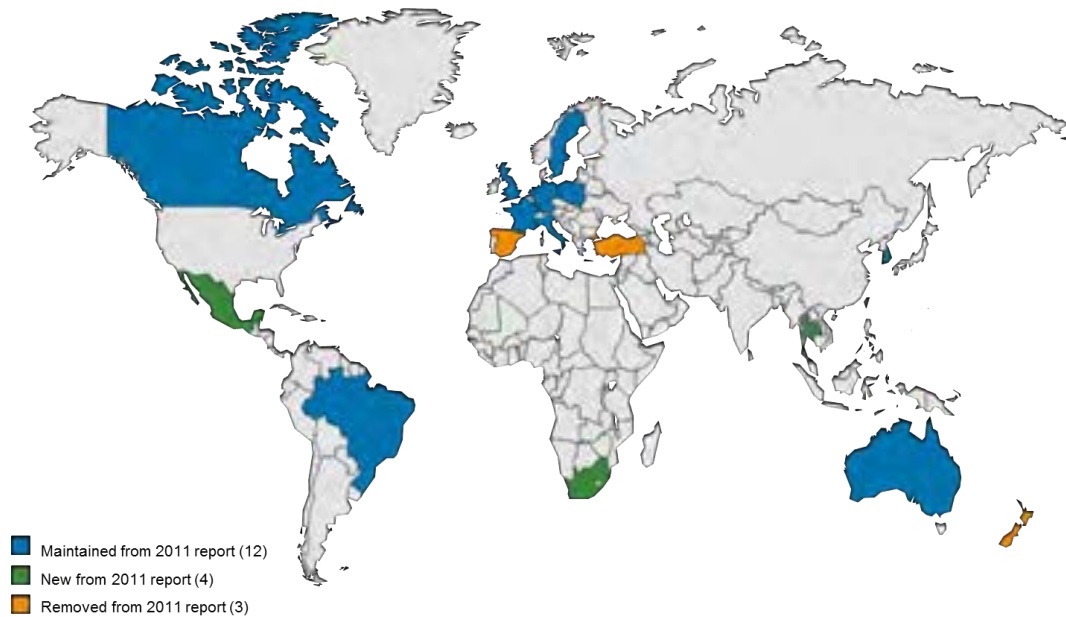
5 In addition to incorporating many valuable comments received from the academic review of the last report and comments from the HTA agencies following the publication of the first Comparison report, we have been advised throughout the update by Dr. Chris Henshall.

6 Incremental cost effectiveness thresholds (ICER).

1.1. Country selection

As in the first Comparison report, the aim is to compare the use of HTA across a diverse group of countries, covering different regions, including mature and evolving HTA processes. In order to understand how systems have changed since the last report, we included many of the countries from the first report. Twelve of the original countries are included in this updated analysis (out of the 15 countries included in CRA 2011).⁷ To account for the adoption of HTA in emerging economies, four new markets were included.⁸ Three of the original countries were excluded from the assessment.⁹ In total, 16 markets were included in the 2013 analysis, these are summarised in Figure 6.

Figure 6: Countries included in the CRA 2013 assessment compared to those included in the CRA 2011 assessment



Source: CRA analysis

1.2. Approach

The methodology builds on the approach undertaken in the original Comparison report and involved the following tasks:

- A review of the literature on the use of HTA published since CRA (2011);

⁷ Australia, Brazil, Canada, England, France, Germany, Italy, the Netherlands, Poland, Scotland, South Korea and Sweden.

⁸ Mexico, South Africa, Thailand and Taiwan.

⁹ Spain, New Zealand and Turkey.

- An update to the 2011 template that relates “best practice” principles of HTA to observable characteristics of the way HTA are undertaken and their impact. In particular we distinguished between how the HTA system is designed or how it is actually implemented;
- An interview programme including experts within the agencies responsible for the HTAs in different countries, representatives of patient associations and industry experts;
- An assessment of a selection of medicines (which we refer to as case studies) that have been through the HTA process in different markets during this period and the outcome of this process; and
- An analysis of what happened following the HTA of the case study medicines included in the 2011 report and the effect of HTA decisions.

1.2.1. Existing literature

The first task of this update was to review the literature published since CRA (2011). This update focuses on studies that have compared the approach to HTA used in different countries, best practice principles or the benchmarking methodology, or studies that have looked directly at the impact of HTA. This included a review of academic studies in Pubmed or Google Scholar, research undertaken by think tanks or published by governments. In total we reviewed 19 articles in detail.

1.2.2. Template

To provide a comprehensive update we have used the same assessment template that was used in the CRA (2011). The template was based on the existing literature setting out the principles of best practices and finding metrics that represent each principle.¹⁰ This includes an assessment of statements made by the HTA agencies about the process they are using, but also metrics based on real world evidence, so we capture actual activities or outputs. This is illustrated, using the example that HTA should include a range of technologies, in Figure 7 below.

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In particular, the best practice principles draw heavily on those produced by the International Group. Drummond et al., “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, 2010, pp. 71–78. Available here: <http://journals.cambridge.org/action/displayFulltext?type=1&pdfType=1&fid=7029668&jid=THC&volumeId=26&issueId=01&aid=7029660>.

Figure 7: 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 diagnosis and treatment strategies	Proportion of HTAs conducted for each of pharmaceuticals devices, procedures diagnosis and treatment strategies
	HTA is conducted for old as well as new technologies	Proportion of HTAs conducted for old technologies

Source: CRA analysis

In this updated report, we incorporated a number of new metrics to capture elements related to recent debates. In particular, we included:

- Two metrics related to the choice of comparator that is used in the HTA;
- Two metrics related to the use of HTAs to update clinical guidelines.

The templates were completed based on the guidelines set out by each of the agencies responsible for the HTA, assessments of the HTAs 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 following colour coding:

- Green: Meets the best practice principle in terms of the HTA own guidelines and there is evidence that this is followed in reality;
- Amber: Meets the principle in guidelines, but there is no evidence to assess what is happening in reality;
- Red: Guidelines are not consistent with best practice principles or evidence that it is not followed in practice;
- Non-applicable: The metric cannot be assessed.

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

1.2.3. Filtering exercise

There were two main criticisms of the reporting in the initial CRA report (2011). To capture the best practice principles, the template becomes relatively complicated (with 49 different metrics) and therefore difficult to digest. Secondly, some of the principles relate to the objective of the HTA process (the mandate of the HTA agency) and others relate to how the process is applied by the HTA agency. This made the interpretation of the results difficult. In some cases, it was argued that the HTA process was constrained by the role or objectives that the HTA agency was given.

To address these criticisms, we have classified the metrics into two levels:

- **System design (d):** This is intended to capture the role of HTA within the country, and the stated process for how HTA should be conducted. This would normally (but not always) be defined by either the Ministry of Health or the agency itself.
- **System operation (o):** Captures how the system is applied in practice by the agency and refers to elements that can be observed in reality.

The original categorisation of the best practice principles (where this division was not made explicit) and the associated metrics to assess these two different categories is not perfect. However, if this is found to be useful in the presentation of the updated report, we would recommend further refinements in future updates of the analysis.

1.2.4. Interviews

To complete and verify the assessment included in the templates, we undertook interviews with industry experts working in the markets, agencies undertaking the HTAs¹¹ and patient representatives.¹² We used the same process as in CRA (2011), sending a draft template prior to the interviews and then asking the interviewees to comment on this assessment.

Table 2: Interviews undertaken with HTA agencies

Country	Agency	Interviewee
Canada	CADTH	VP Strategic Initiatives and Chief Scientist for response
England	NICE	Programme Director Technology Appraisals
France	HAS	Member of the Appraisal Committee
Germany	G-BA	Head of Department of Methodological Consultancy
Italy	Commission for Reimbursement, Lazio Region	Member of Regional Reimbursement Commission

¹¹ Requests were made to all agencies responsible for HTA between September 2013 and November 2013.

¹² In addition to talking to the HTA about the role of patients, we also had discussions with a non-executive director at NHS Scotland who specialises in the patient role within the HTA processes, worked on developing international patient surveys and has been exposed to patient groups throughout the world. We also talked with the chair of Consumer Advocate Network who is also an ex-IAPO member.

Poland	AOTM	President CEESTAHC
Scotland	SMC	Ex-chair
South Africa	DPEE	Member of research Consortium, CMeRC HTA Unit
Taiwan	BNHI – CDE	Member of the Appraisal Committee
Thailand	HITAP	Programme leader and senior researcher

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 3 and chapter 4.

1.2.5. Comparison of actual health technology assessments

Following the methodology used in CRA (2011), when possible, we based the analysis on the health technology assessments published in 2012. For example, we looked at the number of assessments undertaken in each country and the pattern of acceptances and rejections. This has the advantage of representing recent assessments and hence allowing for the recent evolution of HTA in some markets.

However, to make meaningful comparisons between countries, we need to compare the same set of assessments (and these might not occur in the same year). As before, we have supplemented our assessment with a set of case studies to allow for comparable molecules. The case studies were chosen based on assessments undertaken by HAS, NICE, SMC, IQWiG and CONITEC between 2010 and 2012. We chose products which had been assessed by at least four agencies during this period.¹³

Table 3 provides a summary of the information reviewed.

13

This differs from the assessment in 2011 where the choice of molecules was based on NICE, SMC and HAS. Note that for CONITEC, only 2013 assessments were included as they previously were not publicly available.

Table 3: Agencies reviewed to select the case studies

HTA agency	Country	Years reviewed	Total number of assessments
HAS	France	2010, 2011, 2012	675
NICE	England	2010, 2011, 2012	119
SMC	Scotland	2010, 2011, 2012	281
IQWiG	Germany	2011, 2012	53
CONITEC	Brazil	2012, 2013	46

Source: CRA analysis

The case studies are important as they allow us to examine differences in the recommendation, the timing of the appraisal and the impact on reimbursement and prices on a meaningful basis. The case studies were chosen using an objective criterion and all of the data used in the report are publicly available information published on the HTA agency websites.¹⁴ This results in a group of 17 molecules with 19 indications covering a range of different therapy areas:

Table 4: Case study medicines used in the assessment by molecule name and indication

Abatacept (RA in adults)	Ticagrelor (Acute Coronary Syndrome)
Boceprevir (Hepatitis C)	Trastuzumab (Initial breast cancer; Advanced breast cancer)
Certolimumab pegol (RA in adults)	Abiraterone (Oncology)
Fingolimod (Multiple Sclerosis)	Apixaban (Venous thromboembolism)
Golimumab (Psoriatic Arthritis; Ankylosing spondylitis)	Cabazitaxel (Prostate cancer)

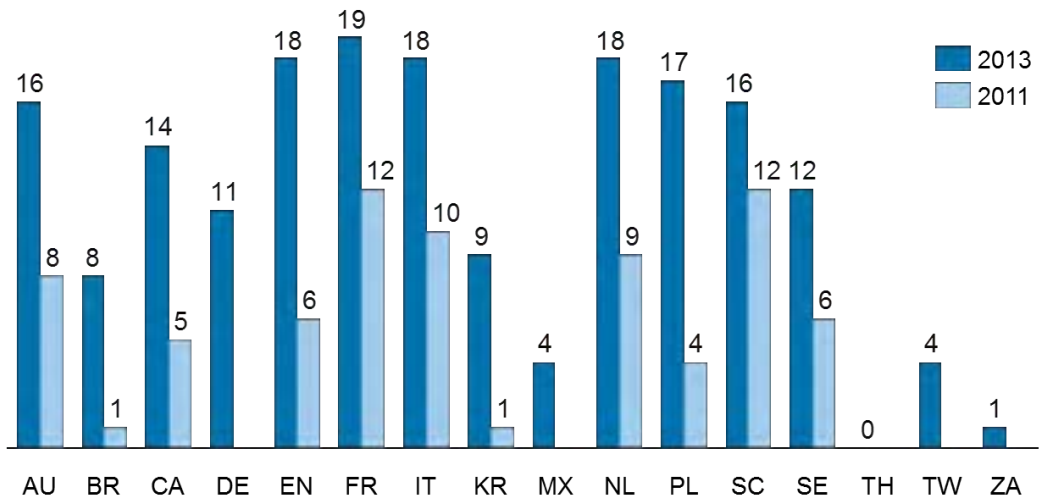
Rituximab (Non-Hodgkins Lymphoma follicular)	Eribulin (Breast cancer)
Roflumilast (COPD)	Ipilimumab (Advanced melanoma)
Retigabine (Epilepsy)	Vemurafenib (Metastatic melanoma)
Telaprevir (Hepatitis C)	

Source: CRA analysis

For these 19 indications, there are 185 assessments (compared to 74 in 2011). However, even after selecting the case studies in this way, the number of reviews assessed by each market can vary significantly. As Figure 8 demonstrates, some countries like France, have reviewed all 19 of the molecules, while others have not reviewed any or very few of the selected molecules. This is the case for Thailand or South Africa.

Even with this limitation, the number of assessments represents a significant improvement in coverage compared to the previous report. Where countries have only a small number of published assessments, this is indicative of the embryonic nature of the process or the current level of transparency in these countries.

Figure 8: Coverage of case studies by country, 2011 vs. 2013



Source: CRA analysis

1.2.6. Diffusion analysis

In CRA (2011) we did not have the opportunity to observe what happened after the HTA for the case study molecules. In the current report we have been able to examine what happened in terms of diffusion after the publication of our report and the impact of the HTA in the different markets.

The diffusion analysis is based on IMS sales data of 10 products¹⁵ (alitretinoin, degarelix, doripenem, lacosamide, prasugrel, rivaroxaban, romiplostim, sapropterin, sugammadex and ustekinumab) for 13 countries during 2008 to 2012.¹⁶ This analysis looks at:

- Time to market: The speed between the publication of the HTA results and when sales are actually observed on the market;
- Uptake: The speed of uptake of medicines following the review; and
- Impact of ex post reviews: Whether there is a change in the speed of uptake of medicines following the review for medicines that are already on the market.

It is important to keep in mind that the uptake of medicines may be affected by other factors that have not been captured in this analysis. Given the limited number of molecules in this analysis, we have only been able to undertake a bivariate analysis. Therefore, the current analysis identifies a correlation between diffusion and the HTA process and caution needs to be taken when drawing conclusions about causality.

1.3. The structure of the report and a road map for how it can be used by different readers

The report is structured as follows:

- Chapter 2 briefly updates the literature on the impact of HTA since the last report;
- Chapter 3 updates the assessment of the HTA process in different countries and how this has changed since the last report (for countries included in both assessments);
- Chapter 4 discusses the lessons learned from the assessments, literature and case studies; and
- Chapter 5 discusses ongoing trends and implications for future updates.

The report has information that is of interest to different readers depending on which type of information is needed. For those interested in how the HTA process in particular countries is assessed, then chapter 3 goes through the assessment on a country-by-country basis. For those more interested in the policy conclusions and the overall trends, chapter 4 goes through the assessment on a thematic basis.

We have also included a number of appendices: (1) the template and assessment criteria (i.e. the boundary conditions that determine whether we assess a particular country to be green,

15 We removed cetuximab and tenofovir from the analysis as they were already used for other indications prior to the assessment, meaning that we could not associate the observable sales in a meaningful way.

16 Note that IMS data is limited and not all molecules were provided across countries. Only France, Germany and the UK had information for all 12 requested molecules; Italy (11); Australia, Spain and Sweden (10); Poland (9); South Korea and the Netherlands (8); Canada and New Zealand (5); and Brazil (3). Additionally, information on hospital sales for the Netherlands was not provided.

amber or red on a particular metric), (2) a tool to understand the filtering exercise used to summarise the results, and (3) the complete CRA assessments by country at principle and metric level, (4) we have also included a glossary defining the terms used through the report.

2. Recent literature on the impact of HTA

In line with the previous report, we have focused specifically on reports analysing the impact of HTA, rather than the large volume of literature on advances in methodologies. The literature review can be grouped into two categories:

- Further consideration of best practice principles and approaches to benchmarking HTA processes; and
- Evidence on the impact of HTA from the perspective of different stakeholders.

2.1. Best practice principles and benchmarking

There has been continued academic interest in benchmarking HTA and several papers have been published on the strength and limitation of different approaches since the first Comparison report.

Drummond et al. (2012) discuss the conceptual and methodological challenges associated with benchmarking HTA and set out a list of audit questions that can be used to assess their 15 key principles for HTA.¹⁷ The authors highlight that the key question is whether HTA has improved healthcare provision. However, they recognise that assessing the improvement in healthcare provision is challenging because of:

- The difficulties in implementing the decisions made by reimbursement agencies, particularly where there are “mixed decisions” (a drug is recommended for a subset of patients);
- Little is known about real displacement when clinicians face budget constraints; and
- The challenge of specifying the counterfactual.

Indeed, they found that benchmarking is not currently straightforward because of the differences in the ways that HTA “systems” are set up (e.g. decisions are often made about the scope of HTA by those outside of the HTA agency itself) and the stage of development of HTA in a given jurisdiction. However, they concluded that benchmarking is still a useful exercise and further research needs to be done on alternative methods for weighting the various principles and for generating an overall score, or summary statement of adherence to the principles. They go on to note that any weighting system, if developed, would need to be explored in different jurisdictions to assess the extent to which the relative importance of the principles is perceived to different stakeholders. Hence, considerable challenges remain in how best to develop a single aggregate score to compare HTA processes.

¹⁷ Drummond, M et al., “Can we reliably benchmark health technology assessment organizations?”, *International Journal of Technology Assessment in Health Care*, 28 (2), 2012.

A more empirical approach was developed in Stephens et al. (2012).¹⁸ This used a survey of HTA agencies¹⁹ to explore whether HTA, as practised, is meeting the 15 principles for best practice established by Drummond et al. (2008).²⁰ Their assessment focuses on methods, but also explores principles that relate to the impact of HTA. They found that:

- Only 28% of respondents repeat or update the assessment at regular intervals. This is consistent with the findings in CRA (2011).
- Respondents representing European reimbursement agencies said that HTA reports received were excellent, with only one exception. Contrarily, US respondents said that HTA reports were either poor or fair approximately half of the time.
- More than 80% of respondents said that they partially rely on HTA findings to inform decision-making; a further 7% indicated complete reliance.

Other studies have focused on particular best practice principles. For example, that HTA should include the societal value of innovations and that could be achieved by including the views and benefits to patients, payers and manufacturers. Drummond et al. (2013)²¹ argued that HTA agencies should include views from different stakeholders if sustainable access to health wants to be maintained. Although several approaches are suggested, the authors recognised that reconciliation between different agencies is not an easy task.

Although most papers base their assessment on the International group's best practice principles, other best practice principles have been developed. A recent paper by Goodman (2012) sets out 17 international good HTA practices. These are represented at a higher level, but are similar to the best practices identified by Drummond (2012) including issues related to transparency, goals, priority setting, the involvement of stakeholders, reassessment, appeals and HTA impact assessment.²² A few additional practices have been mentioned that have not been accounted for in this report. These include issues such as training of staff and participation in international HTA networks. As these are focused on process rather than impact, we did not include these metrics in our updated assessment.

Interest in developing and applying best practice principles in HTA continues to move forward. However, there is a recognition of the challenges in applying these principles in an

18 Stephens, J M, et al., "International Survey of Methods Used in Health Technology Assessment (HTA): Does Practice Meet the Principles Proposed for Good Research?", *Comparative Effectiveness Research*, (2): 29-44, 2012.

19 30 respondents representing 16 countries in 5 major regions: Australia (n = 3), Canada (n = 2), Europe (n = 17), Latin America (n = 2), and the United States (n = 6).

20 Drummond et al., "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,

21 Drummond et al., "Assessing the added value of health technologies: Reconciling different perspectives", *Value in Health*, 16, S7-S13, 2013.

22 Goodman, "Toward international good practices in Health Technology Assessment", *International Journal of Technology Assessment in Health Care*, 28:2, 2012.

objective and measurable way. Therefore, the principles used in the CRA (2011) still appear to represent a reasonable framework for assessment.

2.2. Assessing the impact of HTA

There have also been a series of papers comparing the outcomes of different HTA processes. The papers have primarily focused on the decision and how these vary within different jurisdictions.

Fischer (2012) develops a systematic review that explores the drivers of coverage decision-making and highlights the diversity of approaches and variables that are likely to influence final decisions.²³

Another review by Nicod and Kanavos (2012) assessed 287 drug indications across five countries (England, Scotland, Sweden, Canada and Australia).²⁴ The authors found significant variability in HTA recommendations, as almost half of the drug-indication pairs received different recommendations. They found that this divergence reflects that HTA processes are influenced by different priorities in individual settings in terms of both perceptions of benefit and value, and tools used to assess the HTA appraisal process. They also found that the Dental and Pharmaceutical Benefits Board (TLV) in Sweden was more likely to issue a positive recommendation, and the Pharmaceutical Benefits Advisory Committee (PBAC) and National Institute for Health and Care Excellence (NICE) were more likely to issue a positive recommendation with restrictions, and CDR was more likely to issue a negative recommendation. One other finding is that agencies differ in terms of the relative importance they place on innovation (with CDR less minded to recommend follow-on products) and on uncertainty (with SMC less minded to recommend products where there is significant uncertainty).

Some studies have looked at particular types of review. Looking at the effects of rapid assessment processes, Kleijnen et al. (2011)²⁵ found that recommendations resulting from single/rapid assessment of pharmaceuticals were more often not binding by law (55% of respondents saying that it is always binding by law vs. 31% never binding by law and a further 14% sometimes). The countries where the recommendations resulting from single/rapid assessments were always binding include: Czech Republic, Denmark, Finland, Italy, Latvia, Luxembourg, Malta, Slovenia and Sweden. The recommendations resulting from full assessment of pharmaceuticals were even less likely to be binding in law (24% of

23 Fischer, KA, "A Systematic Review of Coverage Decision-Making on Technologies – Evidence from the Real World", *Health Policy*, 107:218-230, 2012.

24 Nicod and Kanavos, "Commonalities and differences in HTA outcomes: A comparative analysis of five countries and implications for coverage decisions", *Health Policy*, 108, 167-177, 2012.

25 Kleijnen, S et al., "Relative Effectiveness Assessment (REA) of Pharmaceuticals: Background Review". EUnetHTA JA WP5, July 2011 (Version 5B).

respondents saying that it is always binding by law vs. 71% never binding and 6% saying sometimes).

The same study by Kleijnen et al. (2011) found that single/rapid assessments have less impact on pricing (55% of respondents) compared to reimbursement decisions (97% of respondents). On the influence of HTA on price, Drummond (2012) focuses on the development of “economics-based assessments” and concludes that economic evaluations have increasingly assisted price negotiations, but also resulted in lower prices accepted by manufacturers.²⁶ This is more evident in Australia and the UK, through the use of managed entry agreements (or patient access schemes as they are known in the UK).

There has been further research on diffusion, which has produced mixed evidence. Focusing on recent developments in England, the “innovation scorecard” was introduced to explore and encourage diffusion of innovative technologies. Evidence from the latest report in 2013 illustrates variations in volumes across seven areas, where three areas displayed a lower than expected usage and four areas where usage was greater than expectations, but there is no elaboration on the factors of such variations.²⁷⁻²⁸ However in Austria, Zechmeister and Schumacher (2012) found evidence to be uniform across all studied areas.²⁹ Their results suggest that HTA can lead to reduced use as observed in six out of seven studied areas, with the remaining showing no impact.

Finally, an area where there has been considerable academic interest is the impact of HTA on cancer products. This has primarily focused on developed markets, for which HTA is more mature and more data is available. Canada has received particular attention, as it is the only one with a dedicated oncology-specific agency for providing recommendations regarding reimbursement. The pan-Canadian Oncology Drug Review (pCODR) has an Independent Expert Review Committee which reviews clinical and cost-effectiveness of new oncology medicines and provides recommendation to provinces. A study by Samjoo and Grima (2013) assesses the trends in recommendations in Canada, compared to Australia, Sweden and the UK.³⁰ Final pCODR recommendation since its establishment to end of 2012 were identified and compared to the respective decision issued by agencies in the other three countries.

26 Drummond, M et al. “Can we reliably benchmark health technology assessment organizations?”, *International Journal of Technology Assessment in Health Care*, 28 (2), 2012.

27 “NICE Technology Appraisals in the NHS in England – 2012, Experimental Statistics, Innovation Scorecard”, HSCIC, 2013.

28 Please note that a more recent report has been published in March 2014, Available here: <http://www.hscic.gov.uk/catalogue/PUB13669>.

29 Zechmeister and Schumacher, “The Impact of Health Technology Assessments Reports on Decision Making in Austria”, *International Journal of Technology Assessment in Health Care*, 28(1), 2012.

30 Samjoo and Grima, “Comparison of Cancer Therapy Reimbursement Recommendations Made in Canada to Australia, Sweden and the United Kingdom”. Cornerstone Research Group. ISPOR 18th Annual International Meeting, 2013.

Significant agreement was observed between all four agencies but in cases of different decisions taken, pCODR issued a positive recommendation as opposed to rejections in the other agencies. This was mainly attributed to process and options applied in pCODR such as recommendations of clinically beneficial technologies subject to improved cost-effectiveness and modification of cost-effectiveness analysis by the agency to reflect alternative data and input.

However, an analysis by Chabot and Rocchi (2010) concluded that oncology decision makers in Canada recommended medicines with high cost-effectiveness ratios, compared to what is considered acceptable in other therapeutic areas, even prior to the establishment of pCODR.³¹ The case study analysis focused on one indication (Sunitinib), which despite a high ICER equal to \$144K/QALY was recommended on the basis of substantial free progression gains and few alternative treatment options. This, they concluded, demonstrates the flexibility of the system in decision making where therapeutic benefit has been observed.

There have been a number of other international comparisons. Shah et al. (2013)³² compared decisions made by Australia's PBAC, Canada's CDE, England's NICE, France's HAS, and Scotland's SMC for pharmaceuticals to treat breast and colorectal cancer. They find differences in the recommendations made by the agencies for the same products. Whilst they recognise that classifying the reasons for recommendations is subjective, they highlight differences to reflect the ways in which (i) agencies interpret data on surrogate end points; (ii) differences in the extent to which agencies consider "patient voice"; and (iii) differences in what is considered an appropriate comparator technology.

Further studies have aimed to identify the disparity in practice and factors of influence. Cheema et al. (2012) established a relationship between the application of cost-effectiveness in the assessments and rate of reimbursement.³³ Based on 49 oncology indications in 13 countries/regions,³⁴ the authors observed the lowest percentages of reimbursed technologies in countries where cost-effectiveness is strictly applied, namely Canada (54%), Australia (46%), Scotland (40%), England (38%) and New Zealand (25%). The main cause for rejection was lack of cost-effectiveness, apart from New Zealand where this was secondary to the assessment of overall cost. However, they note that many of the initially rejected medicines in these countries were later approved through managed entry agreements and pricing arrangements, which were mainly utilised to contain costs.

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- 31 Chabot and Rocchi, "How do cost-effectiveness analyses inform reimbursement decisions for oncology medicines in Canada? The example of Sunitib for first-line treatment of metastatic renal cell carcinoma", *Value in Health* 13-6, 2010.
- 32 Shah, KK et al. "A Review of Health Technology Appraisals: Case Studies in Oncology", *International Journal of Technology Assessment in Health Care*, 29(1):101-109, 2013.
- 33 Cheema et al. "International variability in the reimbursement of cancer drugs by publically funded drug programs", *Current Oncology*, 19, 2012.
- 34 Countries: Australia, Canada (Ontario), England, Finland, France, Italy, Germany, Japan, New Zealand, the Netherlands, Scotland, Sweden and the United States.

A recent analysis by Lin et al. (2013) found that heterogeneity and inconsistency in reimbursement of oncology technologies is influenced by the impact of ICER, financing of the health system and the affiliation of the HTA agency to the government.³⁵ They grouped countries according to their Fairness Index (FI) determined by the impact of ICER on reimbursement and observed the decisions on 19 indications.³⁶ However evidence of the decision for reimbursement is mixed, as France was one of the least restrictive countries with 16 out of 19 indications reimbursed, whereas Sweden and England were one of the most restrictive with five out of 19 and six out of 19 positive reimbursement decisions.

The existing literature illustrates the difficulty in drawing simple conclusions. Although, HTA bodies using cost-effectiveness may be more likely to restrict the use of an oncology product, oncology also receives special attention as a clinically important but costly therapeutic area. Thus, there is a tendency to apply special arrangements, such as managed entry agreements (MEAs) or price arrangements to allow greater access, with potential for improvement in these areas.

The study of MEAs and how they interact with the HTA process in different markets has been quite limited and largely descriptive to date.³⁷ The majority of the MEA literature has focused on developing taxonomies for categorising such schemes.³⁸ The most comprehensive analysis of MEAs was sponsored by the European Commission, which provides a good description of their increasing use but does not discuss the interaction with HTA or provide much evidence regarding their impact.^{39,40}

2.3. Recent contributions to the literature and the implications for the updated Comparison report

There has been a large number of studies on use and impact of HTA since the publication of the first Comparison report. These studies have debated the use of best practice principles in

35 Lim et al., "International comparison on the factors influencing reimbursement of expensive cancer drugs", *Journal of Clinical Oncology*, 31, 2013.

36 Countries: France, Germany, South Korea, Japan, England, Sweden, Canada, Taiwan, Australia and the United States.

37 "Managed entry agreements for pharmaceuticals: The European experience", Health Policy or EMINET, or Adamski et al. "Risk sharing arrangements for pharmaceuticals: potential considerations and recommendations for European payers", *BMC Health Services Research*, 10:153, 2010.

38 Carlson et al., "Linking payment to health outcomes: A taxonomy and examination of performance-based reimbursement schemes between healthcare payers and manufacturers", *Health Policy*, 96, 3, 2010.

39 P. Kanavos et al., "Managed entry agreements for pharmaceuticals: the European experience", EMINet, Brussels, Belgium, 2013. J. Espín, et al. "Experiences and Impact of European Risk-Sharing Schemes Focusing on Oncology Medicines" Andalusian School of Public Health, January 2011.

40 Garrison, "PBRsAs: Good practices for design, implementation and evaluation", 2012, provides another perspective on the increasing use of MEAs.

HTAs and raised challenges in their application. However, the current best practice principles still appear a reasonable framework for analysis.

Further comparison studies of decisions again highlight variability across countries, which are influenced by both the priorities set in the different markets and the approach to HTA. The analysis remains focused primarily on decisions and how this varies across institutions. There has been relatively little analysis on the impact on prices and reimbursement or the way that HTA affects the incentives to innovate. Instead, considerable attention has focused on describing the development of MEAs and focusing on particular therapeutic areas such as oncology.

3. Comparing the 2013 to the 2011 assessment

In this chapter, we present the updated assessment and how this has changed for those countries included in the first Comparison report and the 2013 assessment for those countries included in the assessment for the first time. We have grouped the countries by region:

- Australia and Canada;
- Latin America (Brazil, Mexico);
- Europe (France, Italy, Germany, the Netherlands, Sweden, UK);
- Asia (South Korea, Taiwan, Thailand); and
- Africa (South Africa).

For each country we first provide a brief description of the role of HTA within price and reimbursement process.

3.1. Australia and Canada

Australia

The use of HTA in Australia is well established. The Pharmaceutical Benefits Advisory Committee (PBAC) is an independent committee, comprised of a range of experts, responsible for assessing all pharmaceutical technologies that will be recommended for inclusion in the Pharmaceuticals Benefits Scheme (PBS).⁴¹ The assessments are based on a clinical and cost-effectiveness analysis and may under some circumstances consider indirect costs and social gains as part of the assessment.

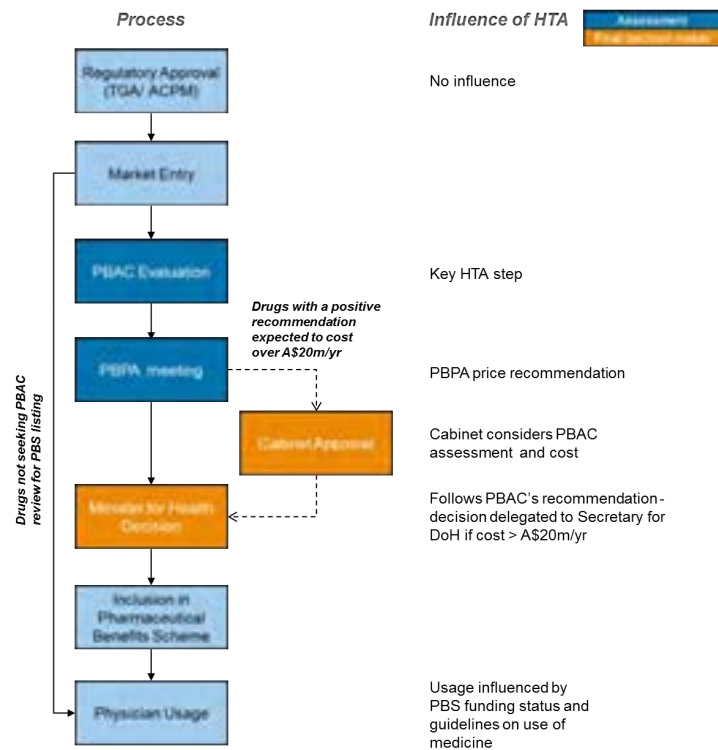
As shown in Figure 9, the regulatory approval is undertaken by the Therapeutic Goods Administration (TGA) in consultation with the Advisory Committee on Prescription Medicines (ACPM) and the HTA recommendation follows this approval. However, in 2011 parallel processing was introduced as part of the Memorandum of Understanding between the Department of Health (DoH) and Medicines Australia. This means that the regulatory approval process undertaken by the TGA and assessment by the PBAC can occur in parallel.⁴² However, PBAC recommendations are not made public until TGA outcomes are known. Prices are negotiated within the Pharmaceutical Benefits Pricing Authority (PBPA),

41 The PBS subsidises payments for most pharmacy prescription medicines within the public healthcare system. It also funds most medicines used within private hospitals and a list of expensive medicines in public hospitals through Section 100.

42 Australian Government, Department of Health (2010), Memorandum of Understanding with Medicines Australia; Australian Government, Department of Health (2011), Framework for the introduction of parallel TGA and PBAC processes.

which takes into account the HTA recommendations from the PBAC regarding cost-effectiveness of the new medicine.⁴³ In addition, medicines that are expected to cost more than A\$20 million per year need approval from the Cabinet of Australia.^{44,45} Medicines funded through state government are not assessed by PBAC. The result of this is that medicines, predominantly dispensed in the hospital, may receive immediate funding from the state government without a HTA.

Figure 9: The impact of HTA process from regulatory approval to physician usage of pharmaceuticals in Australia



Source: CRA analysis; Note: TGA: Therapeutic Goods Administration; ACPM: Advisory Committee on Prescription Medicines; PBPA: Pharmaceutical Benefits Pricing Authority; DoH: Department of Health; PBAC: Pharmaceutical Benefits Advisory Committee

43 Note that in March 2014, the Australian government announced the cessation of the operations of the PBPA to provide pricing recommendations to the MoH for PBAC-recommended medicines. The abolition of PBPA would mean that medicines could be listed on the PBS at least four weeks quicker than under the current system.

44 The Cabinet of Australia is the council of senior ministers of the Crown responsible to Parliament.

45 The threshold increased from A\$10 million to A\$20 million in October 2013, thus the former was applied to PBAC assessments during the period under consideration (i.e. 2012).

The CRA assessment

As shown in Figure 10, the HTA system in Australia performs well against best principles as the system is ranked green and amber in the majority of the 14 principles used in the CRA assessment.

Scope and Prioritisation: The system remains largely the same as in 2011 and displays independence of HTA from market authorisation and a degree of transparency in decision making. All new medicines are reviewed by PBAC, while the assessment of new procedures is conducted by the Medical Services Advisory Committee (MSAC) and that of devices by the Prostheses List Advisory Committee (PLAC). Technologies already in the market can be reviewed again and are on an increasingly frequent basis. On a systematic basis there is the opportunity to discuss with the secretariat on the HTA submission process. PBAC has conducted joint scientific advice pilots with the TGA, but only early support to fill in the application is offered on a systematic basis.

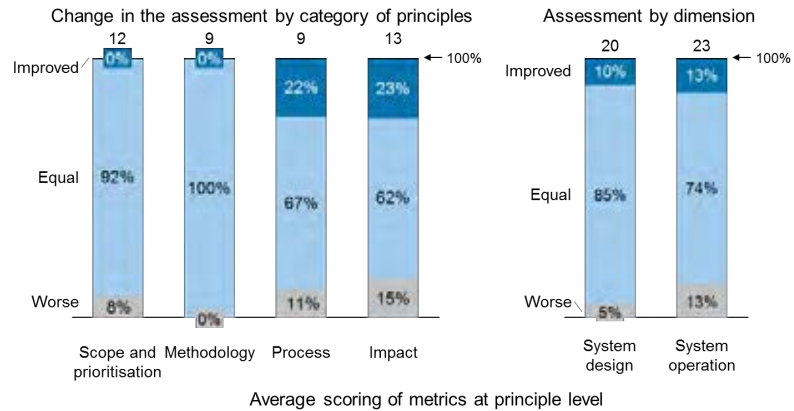
Methodology: There have been no changes in methods that are applied by the PBAC since the CRA 2011 assessment. Therefore all the metrics receive the same score. The assessments include unpublished and non-RCT (randomised controlled trials) data and issues associated to uncertainty are quantified where possible. Managed entry agreements are used when the evidence is inconclusive but could be further developed and there is still little evidence to show how these are taken into account. It is possible to get advice from PBAC on the appropriate comparator (often determined using an algorithm,) but there have been instances when the comparators have changed and there have been disputes regarding the choice.

Process: In principle, most stakeholders are involved in the process. However, in practice, involvement is limited to assessment concerned with serious this depends on the particular conditions under examination (for example, whether a treatment is deemed not cost-effective and where there is no existing alternative). Decisions are publicly available, but expressed using technical language. There is a concern that this means they are not accessible to the wider public. There is no appeal process, but an independent process review is conducted when there is a disagreement with the decision taken. However, the submission is ultimately reconsidered by the same decision makers.

Impact: In terms of timing, the assessments are conducted efficiently within a 17-18 week timeframe. A key improvement is the introduction of parallel processing which allows the assessment to be conducted prior to regulatory approval being granted. This is an important step towards a faster process and improved accessibility. The Australian Government and Medicines Australia monitor the expenditure of the PBS, but there are no systematic reviews of the value of HTA in the system. The latest review completed in 2010 led to some of the recent improvements such as the upgrade of the PBAC website.

As shown in Figure 10, the HTA system in Australia performs well but improved coordination between PBAC, MSAC and PLAC regarding the technologies reviewed could improve the current HTA process in order to avoid unnecessary delay.

Figure 10: The CRA assessment of the HTA system in Australia, 2011 and 2013



Average scoring of metrics at principle level

Principles	2011	2013
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	●	●
METHODOLOGY		
4 HTA should incorporate appropriate methods depending on its goal	●	●
5 HTA 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 on an intervention could be most usefully developed in the future	●	●
IMPACT OF HTA		
12 HTA should be timely	●	●
13 P,R&MA 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; Note that in the 2013 assessments four metrics were added two in Methodology and two in impact. These have been excluded to illustrate the changes

Canada

Once a medicine has received its market authorisation, the Patented Medicine Process Review Board (PMPRB), an independent quasi-judicial body within the federal health department, assigns a maximum price depending on the innovativeness of the new medicine.

The manufacturer makes a submission to the Canadian Agency for Drugs and Technologies in Health (CADTH), which is responsible for issuing recommendations on publicly funded medicines. Reviews could also be initiated prior to market authorisation, which falls under the pre-NOC (Notice of Compliance) reviews category.⁴⁶ The Common Drug Review (CDR)

conducts the assessment and offers a comprehensive and publicly available report on the clinical and the cost-effectiveness of the reviewed technology. Other elements such as social or ethical implications are also included in the review. This forms the basis of the evaluation and recommendation made by a CADTH committee, the Canadian Drug Expert Committee (CDEC), which is comprised of physicians, pharmacists, economists and public members.⁴⁷

Manufacturers have the opportunity to comment on the draft assessment prior to their use by CDEC in making a final recommendation and can contribute with further commentary and request reconsideration during an embargo period (which lasts for 10 business days).⁴⁸ The final decision remains with the federal, provincial and territorial drug plans and is based on the CADTH recommendation. Prices, negotiated with the manufacturer, are also based on the final recommendations. These prices must respect the maximum price assessed by the PMRPB.

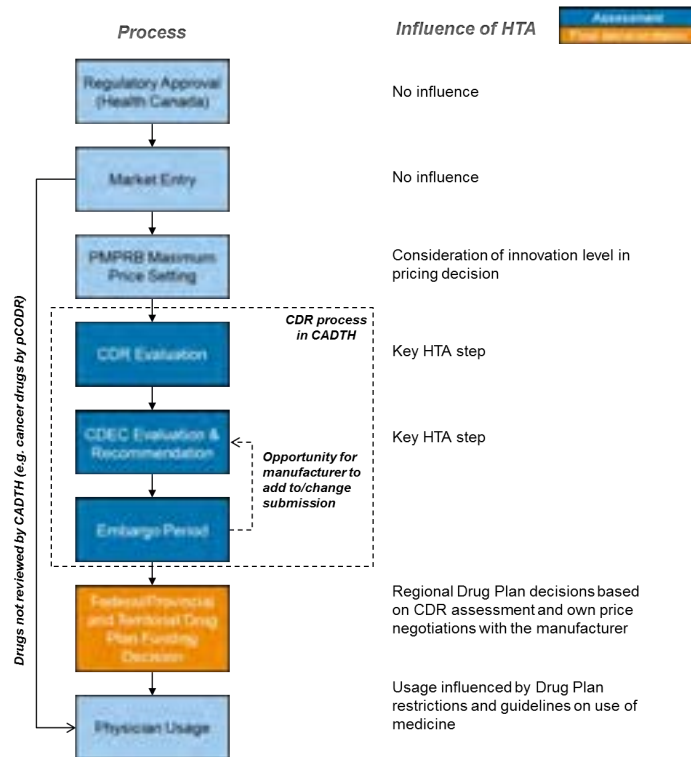
A separate procedure is used for oncology medicines. After a first assessment conducted by CADTH, the pan-Canadian Oncology Drug Review Process (pCODR) reviews the assessment and develops the appraisal.⁴⁹

47 CADTH (2014), "Canadian Drug Expert Committee".

48 CADTH (2013), "Procedure for Common Drug Review".

49 As of 1st April 2014, pCODR was transferred to CADTH, in an attempt to consolidate the policy director of medicine programmes. Available here: <http://www.pdci.ca/news/recent/pcodr.asp>.

Figure 11: The impact of HTA process from regulatory approval to physician usage of pharmaceuticals in Canada



Source: CRA analysis; Note: PMPRB: Patented Medicines Pricing Review Board; CDR: Common Drug Review; CDEC: Canadian Drug Expert Committee; CADTH: Canadian Agency for Drugs and Technologies in Health; pCODR: pan-Canadian Oncology Drug review

The CRA assessment

The Canadian HTA system is well regarded and performs well against our set of principles as shown in Figure 12.

Scope and Prioritisation: CADTH is transparent in its decision-making and has improved its processes by providing formal and more extensive support to manufacturers to fill in the applications prior to their dossier preparation. Different types of technologies are included in the assessments. However, one significant drawback in comparison to the initial CRA 2011 assessment is that priorities are no longer explicit and publicly available. Currently, medicines are assessed on first come, first served basis but the agency is working on re-prioritisation and will publish the guidelines when the process is complete.⁵⁰

Methodology: There have been no major changes in terms of methods used by CADTH. The agency still uses both published and unpublished data, but there have been no further steps to include societal and indirect costs, with the latter remaining optional and no real

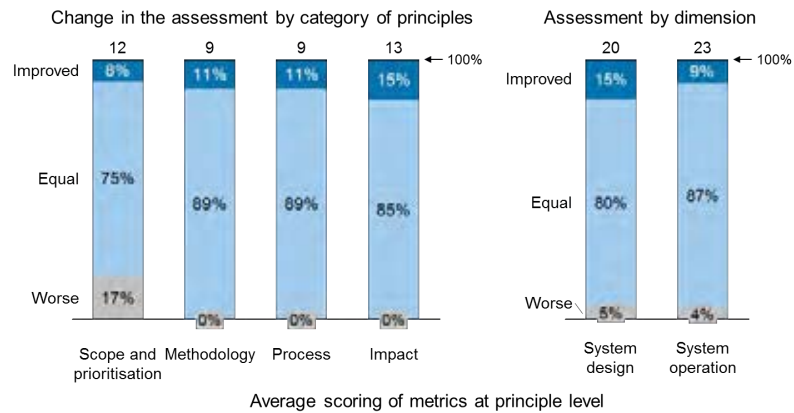
evidence regarding its use. Issues associated with uncertainty are receiving more attention, but the application of MEAs (to the extent they are targeted at managing uncertainty) is still limited.

Process: Inclusiveness of stakeholders in the process has not shown any major changes. Manufacturers and patients are included in the process but restrictions apply to their attendance in meetings. However, the agency has considerably improved the information regarding their decisions and identification of areas where further evidence could be useful for potential re-evaluations.

Impact: Overall, the HTA process remains relatively timely and the initiation of the review is possible before the product has received regulatory approval. However, assessments and recommendations do not directly translate into inclusion in the federal, provincial and territorial medicines plans and there is no formal impact on the clinical guidelines, which are devised and updated by clinical societies. Considerable improvement is noted in assessing the impact of HTA, as independent reports are commissioned and reviews are no longer completed by the government. Such evaluation reports are included by CADTH in the annual report and major issues are recognised, such as the lack of a clear prioritisation, which emerged in one of the recent reports.⁵¹

Overall, HTA in Canada performs well and has demonstrated improvements in all areas except for prioritisation, which is an issue currently being addressed.

Figure 12: The CRA assessment of the HTA system in Canada, 2011 and 2013



Average scoring of metrics at principle level

Principles	2011	2013
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	●	●
METHODOLOGY		
4 HTA should incorporate appropriate methods depending on its goal	●	●
5 HTA 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 on an intervention could be most usefully developed in the future	●	●
IMPACT OF HTA		
12 HTA should be timely	●	●
13 P,R&MA 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; Note that in the 2013 assessments four metrics were added two in Methodology and two in impact. These have been excluded to illustrate the changes

3.2. Latin America: Brazil and Mexico

Brazil

Since the Comparison report, there has been a significant change in the role of HTA in Brazil. The HTA agency, CITEC which was created in 2006, has transformed into CONITEC.⁵² CONITEC was created with the aim to develop a faster, more efficient and transparent committee, which would be using strict cost-effectiveness criteria and budget impact

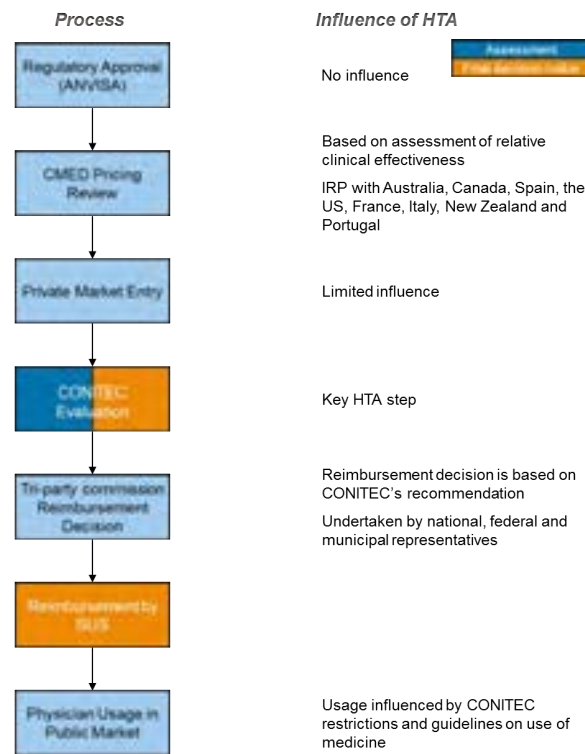
52

"The use of thresholds in the application of Health Technology Assessment in Emerging Markets", A report commissioned by PhRMA, CRA, 2012.

analysis.⁵³ At the moment, CONITEC is working with the Ministry of Health to introduce a cost per Quality Adjusted Life Years (QALY) threshold in their decision-making process. However, discussions are still at an early stage.⁵⁴ All new technologies that will be incorporated in the reimbursement list within the Unified Health System (SUS) need to go through an HTA undertaken by CONITEC. Applications can be submitted by both manufacturers and public health bodies.⁵⁵

As shown in Figure 13, once the technology receives CONITEC approval, the reimbursement level is determined by a tri-party commission composed of national, federal and municipal representatives. The reimbursement decisions are ultimately made by the Ministry of Health based on CONITEC's recommendations, and tend to be aligned with their recommendations. In addition to determining access, CONITEC also has influence on the use of drugs, as they define the restrictions on the use of the medicines.

Figure 13: Impact of HTA process from regulatory approval to physician usage of pharmaceuticals in Brazil



53 Viejo, "New times for health technology assessment in Brazil's public healthcare system", *Global Forum Inform*, 4,5, 2013.

54 Machado, "The use of QALYs in health care decision making in Brazil", *ISPOR Latin America Consortium*, June, 1, 3, 2013.

55 Bruce, "Brazil: the hardest nut to crack?", *Scrip* 100, 2013.

Source: CRA analysis; Note: ANVISA: National Health Vigilance Agency; CMED: National Chamber for Regulation of Medicines Market; CONITEC: Commission on Health Technology Incorporation; SUS: Unified Health System

The CRA assessment

The introduction of CONITEC and the resulting changes in the HTA process has improved the assessment of the HTA system in Brazil, primarily because it has become more transparent.

Scope and priorities: While the reforms have resulted in a more open and transparent process, concerns still exist regarding the potential for conflict of interests, the method of prioritisation and process. First, CONITEC is part of the Ministry of Health, which means that the assessments are conducted by parties with a vested interest in the outcome. Second, it is still not clear how CONITEC prioritises the assessments that they choose to review and evidence suggests that most of the reviews were commissioned by the SUS or other public stakeholders. Finally, there is no process that manufacturers can use to appeal the decisions made.

Methodology: In general, CONITEC is using a similar approach to that of CITEC (and hence the assessment is similar to 2011). However, the updated guidelines, which set out a range of possible methodologies, are not clear on which is the preferred methodology. It is also unclear how the system deals with uncertainty. According to CONITEC guidelines, molecules should be compared with products used to treat the same indication, which are funded by the SUS. Indirect costs can be considered when undertaking HTA, however; none of the case studies included in our assessment introduced them in the calculations.

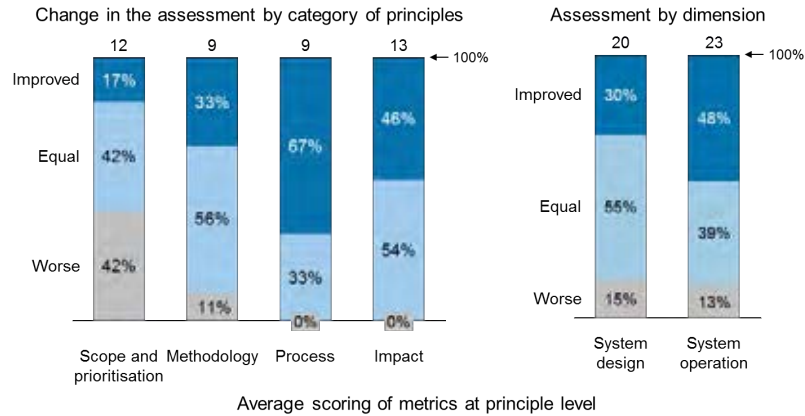
Process: As well as making the completed appraisals publicly available (which was not previously the case), CONITEC established a process of public consultation where stakeholders are invited to comment on the assessments. It also introduced a reassessment process, which can start up to 30 days after the publication of the results. These represent significant improvements.

Impact: There are also some improvements in our assessment of the impact of the HTA system. CONITEC introduced a defined timeframe for decision-making. Appraisals should take 180 days, which is extendable up to 90 days. There was no defined timeframe in the previous regime. Although, it is still too early to assess the full impact of CONITEC, the relationship between the HTA recommendation and pricing and reimbursement decision applied in the public health system in Brazil appears to be clearer. The Ministry of Health uses the CONITEC assessments to determine the discounts requested from manufacturers.

As Figure 14 shows, the majority of improvements within the Brazilian HTA are associated with the process by which HTA is undertaken, mainly through improving the transparency of the system. Overall, the Brazilian HTA has seen the most significant improvements in operation of the system. Indeed, there have not been many fundamental changes in the design or role of HTA since 2011, when the previous CRA assessment was published.

Even though there have been improvements in the Brazilian HTA system, there is still room for improvement, specifically in terms of the prioritisation criteria and a more explicit and transparent process for how the HTA deals with uncertainty.

Figure 14: The CRA assessment of the HTA system in Brazil, 2011 and 2013



Average scoring of metrics at principle level

Principles	2011	2013
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	●	●
METHODOLOGY		
4 HTA should incorporate appropriate methods depending on its goal	●	●
5 HTA 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 on an intervention could be most usefully developed in the future	NA	NA
IMPACT OF HTA		
12 HTA should be timely	●	●
13 P,R&MA 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; Note that in the 2013 assessments four metrics were added two in Methodology and two in impact. These have been excluded to illustrate the changes

Mexico

In Mexico, manufacturers are required to provide cost-effectiveness data within their application for marketing authorisation to the *Federal Commission for the Protection against Sanitary Risks* (COFEPRIS). After the maximum price is set, the *Consejo de Salubridad General* (CSG) undertakes a review to determine if the health technology should be included in the national positive list.

A guideline for economic evaluation was published in 2008, which sets out the methodology for conducting pharmacoeconomic analysis.⁵⁶ This was the first step in formalising the HTA process and it was subsequently updated in 2011. The guidelines specify that the economic evaluation needs to be done using a Cost Effective Analysis (CEA), although a Cost Utility Analysis (CUA) can additionally be developed.

However, it is unclear how in practice the reports are used in the decision-making process as the CSG only makes public the result of the assessments and it does not provide a detailed analysis of the appraisal process. Pharmaceutical companies receive some feedback when their technologies are rejected or accepted with conditions.⁵⁷ Although a formal appeal process does not exist, companies can resubmit their applications addressing the requests of the CSG. Since mid-2013, this can be done on a rolling basis.⁵⁸

The CSG does not have a direct impact in reimbursement decisions, as the inclusion in each benefit plan is decided by each public payer (there are multiple benefit plans, for example, IMSS or ISSTE). Generally, public payers only include technologies that have been approved by the CSG and they are not obliged to include all of them. In order to decide which ones they ultimately include, they may develop additional assessments, including institutional budget impact analysis.⁵⁹

There is an official HTA agency called Centro Nacional de Excelencia Tecnológica en Salud (CENETEC), which was established in 2004. The CSG could, in principle, request CENETEC undertake an assessment of a new technology, but there is no evidence that this has taken place in practice. In fact, CENETEC has only developed reviews on medical devices and clinical guidelines. Figure 15 illustrates the influence of HTA at different stages.

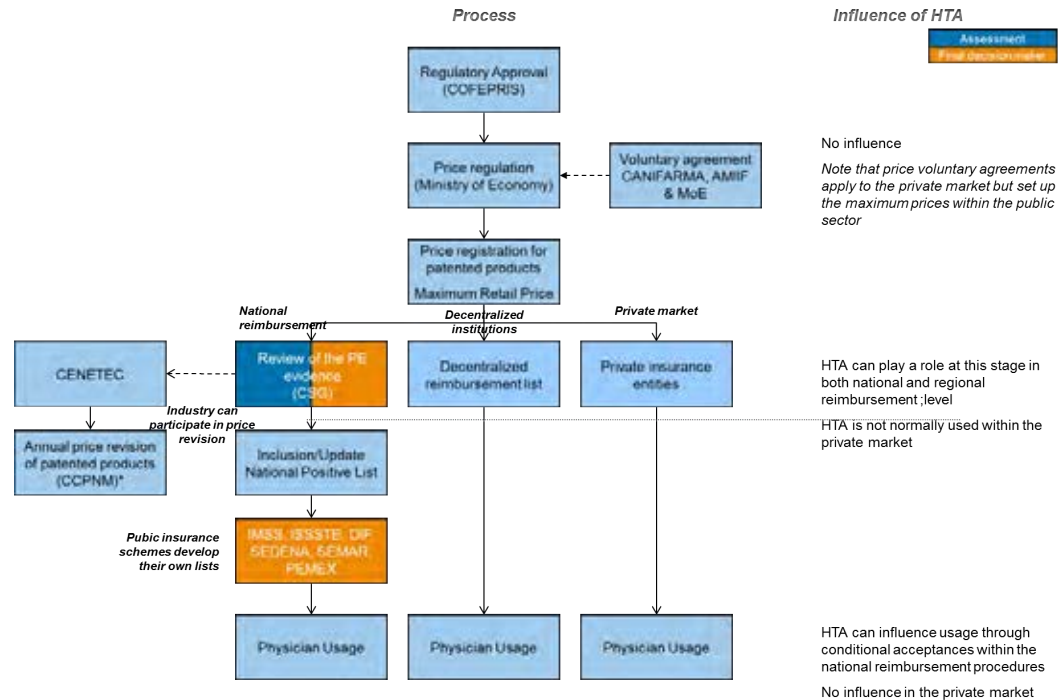
56 "The use of thresholds in the application of Health Technology Assessment in Emerging Markets", a report commissioned by PhRMA, CRA, 2012.

57 CRA interview programme. This information is from industry interviews. We were not able to undertake an interview with anyone at CSG.

58 CRA interview programme; Diario Oficial de la Federación (2011), "Reglamento Interior de la Comisión Interinstitucional del Cuadro Básico y Catálogo de Insumos del Sector Salud", 22 June 2011. Available here: http://www.csg.salud.gob.mx/descargas/pdfs/cuadro_basico/Reglamento_CI_CByCISS_05092011.pdf.

59 CRA interview programme.

Figure 15: The impact of HTA process from regulatory approval to physician usage of pharmaceuticals in Mexico



Source: CRA analysis; COFEPRIS: Comisión Federal para la Protección contra Riesgos Sanitarios (Federal Commission for the Protection against Sanitary Risks); CANIFARMA: Cámara Nacional de la Industria Farmacéutica (Chamber of the National Pharmaceutical Industry); AMIF: Asociación Mexicana de Industrias de Investigación Farmacéutica (Mexican Association of Research-Based Pharmaceutical Industry); CSG: Consejo de Salubridad General (General Health Council); CENETEC: Centro Nacional de Excelencia Tecnológica en Salud (National Centre for Health Technology Excellence); CCPNM: Comisión Coordinadora para la Negociación de Precios de Medicamentos y otros Insumos para la Salud (Coordinating Commission for Negotiating the Price of Medicines and other Health Inputs) could review products which are not reviewed by the CSG

The CRA assessment

The HTA process is still developing in Mexico.⁶⁰ This is clearly reflected in the CRA assessment, as show in Figure 16, for many of the best practice principles relating to the process and the impact it receives a low score on the three-point scale.

Scope and prioritisation: We found that although in theory HTA should be conducted for all relevant technologies and for both old and new technologies, in reality assessments are only undertaken for new pharmaceutical products. Additionally, given that the assessments are not published, the rationale for HTA decisions and recommendations remains unclear.

Methodology: The methodology used is considerably closer to best practice principles. The pharmacoeconomic guidelines allow for a variety of methods and it is clear that both cost-

effective and cost utility analysis can be developed. Additionally, at least in theory, there is flexibility for the use of the comparator, the use of different types of clinical data, the inclusion of societal elements, as well as, the consideration of uncertainty. The problem, once again, is that as the assessments are not published, it is unclear as to what extent the CSG takes the stated methodology into consideration in making its recommendations.

Process: In terms of the process, there remains considerable room for improvement if the Mexican system is to apply best practice principles. First, the current system does not include key stakeholder groups at any part of the process and does not have any official appeals process. Second, the completed assessments are not publicly available and only limited information is provided. Manufacturers often receive minimal feedback.⁶¹

Impact: The CSG has a stated goal to publish their decisions within 10 months from the start of the review. Based on the evidence available for this assessment, we find this was generally adhered to. However, among the 305 technologies reviewed in 2012, only 22% were accepted, 32% rejected and the rest were either non-applicable or no information was provided.⁶² In terms of assessing the role of the HTA process, as is the case in many countries with emerging HTA systems, a process for assessing performance has not yet been formalised.

Overall, there is still room for improvement in the application of HTA in Mexico. In particular, greater transparency is needed to assess how decisions are made and to allow a more inclusive process allowing all stakeholders to contribute to the process.

61 CRA interview programme. Note that we were not able to contrast this information directly from CSG.

62 CSG Updates of the positive lists. Available here:
http://www.csg.salud.gob.mx/contenidos/CB2010/evolucion_act/actualizacion.

Figure 16: The CRA assessment of the HTA system in Mexico, 2013

<i>Principles</i>	<i>2013</i>
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	🟢
METHODOLOGY	
4 HTA should incorporate appropriate methods depending on its goal	🟢
5 HTA 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 on an intervention could be most usefully developed in the future	NA
IMPACT OF HTA	
12 HTA should be timely	🟡
13 P,R&MA 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

3.3. Europe: England, France, Germany, Italy, the Netherlands, Poland, Scotland and Sweden

England

Since 1999, HTA has had a significant role in the English health system, and since 2005, the NHS in England has been legally obliged to provide funding for medicines and treatments recommended by the National Institute for Health and Clinical Excellence (NICE).⁶³ NICE provides guidance on the use of health technologies within the NHS for new and existing medicines, treatments and procedures. In addition to the technology appraisals, it also develops clinical guidelines and quality standards assessments of healthcare services.⁶⁴

In April 2013, Health and Social Care Act (2012) introduced a number of structural changes into NHS in England. The result of this is that NICE has a more significant role in the healthcare system and has initiated a major new programme focused on standards in the social care sector. Additionally, NICE has been given the status of a non-departmental government body (NDGB), meaning that even though NICE is accountable to the Department

⁶³ Sorenson, et al., "National Institute for Health and Clinical Excellence (NICE): How does it work and what are the implications for the US?", National Pharmaceutical Council, September 2009.

⁶⁴ "A Comparative analysis of the role and impact of Health Technology Assessment", a report commissioned by EFPIA, PhRMA, Medicines Australia and EuropaBio, CRA, 2011.

of Health (DoH), they are operationally independent from the government in power.⁶⁵ Finally, the Act also reiterated the legal obligation for commissioners to fund guidance published by NICE through its technology appraisals and highly specialised technologies programme.⁶⁶

As Figure 17 demonstrates, health technology assessments only take place for those technologies that are requested by the DoH. The DoH is responsible for referring technologies to NICE that have a significant health benefit, impact on other health-related government policies or where NHS resources are used inappropriately.⁶⁷ NICE bases its recommendation, primarily on an assessment of the incremental cost-effectiveness ratio of a new technology and how this compares to their cost/QALY threshold.⁶⁸ The commonly agreed threshold in literature is in the range of £20,000 to £30,000 cost per QALY.⁶⁹⁻⁷⁰

Once NICE publishes its recommendation, NHS providers are required to implement NICE guidance. It is important to take into account that the way health technologies are assessed in England is expected to change in the Autumn of 2014. It is expected that “value based assessment” will be introduced, formalising the way that NICE incorporates wider societal benefits and burden of illness into their assessments. Exactly how these wider elements will be taken into account is still under discussion, in the public consultation that began in March 2014.⁷¹ As such, the current CRA assessment does not incorporate any change on NICE methodology.

65 “New challenges and new functions for NICE”, NICE press release, 3 April 2013.

66 CRA interview programme.

67 “Guide to methods of technology appraisal”, NICE, 2013. Available here; <http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9/introduction>.

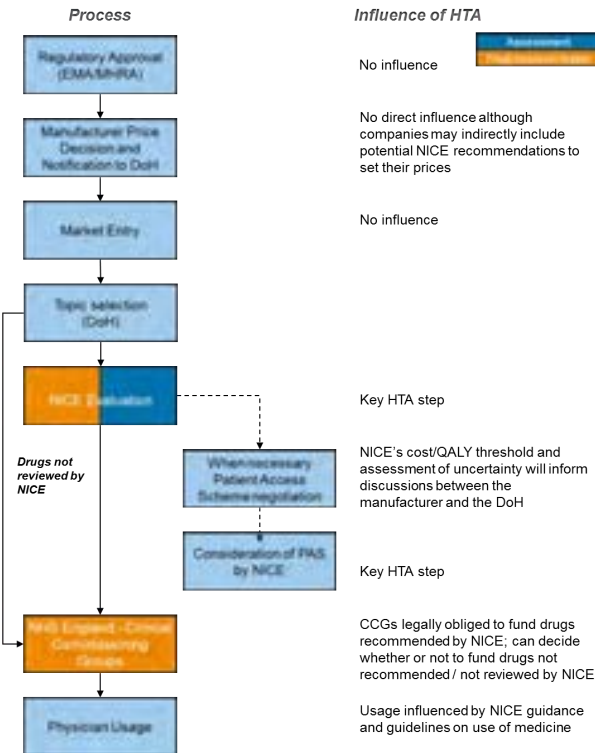
68 “Guide to methods of technology appraisal”, NICE, 2013. Available here; <http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9/introduction>.

69 Devlin et al., “Does NICE have a cost-effectiveness threshold and what other factors influence its decisions? A binary choice analysis”, *Health economics*, 13, 5, 2004.

70 Appleby et al., “NICE’s cost effectiveness threshold”, *British Medical Journal*, 2007.

71 “Value based assessment methods consultation document”, Methods of technology Appraisal Consultation, 26 March 2014. Available here : <http://www.nice.org.uk/getinvolved/currentniceconsultations/MethodsOfTechnologyAppraisalConsultation2014.jsp?do-media=1&mid=FE20429F-FA31-FE7B-0F83F51F35753970>.

Figure 17: The impact of HTA process from regulatory approval to physician usage of pharmaceuticals in England



Source: CRA analysis; Note: EMA: European Medicines Agency; MHRA: Medicines and Healthcare Products Regulatory Agency; DoH: Department of Health; NICE: National Institute for Health and Care Excellence; PAS: Patient Access Scheme; CCGs: Clinical Commissioner Groups

The CRA assessment

The HTA system in England is one of the most well-established systems globally. Over the last three years, most of the changes implemented have been incremental, indeed, the majority of the metrics in 2013 (80%) remained at the same level of scoring as in 2011 (see Figure 18).

Scope and priorities: The fact that NICE is now a non-departmental government body introduced greater independence into the system which is an improvement. However, the rationale for HTA decisions remains somewhat unclear. As mentioned above, the methodology by which NICE is going to incorporate wider social aspects within their assessments will be revealed mid-2014, This is expected to bring more formality into the process.⁷²

Methodology: The use of Patient Access Schemes (PAS)⁷³ has increased since the last assessment. Of the 19 case studies analysed, seven involved the use of a PAS. However, it is not clear if these are used as a method to deal with uncertainty or simply as a method for including price discounts. We also observed less focus on identifying the value of future research in the assessments reviewed in 2013.

Process: There has been an improvement in the NICE appeal processes resulting from the stronger division between the agency and the Government. With NICE being a NDGB, there is now less room for governmental pressure.

Impact: The process for assessing the role of HTA in England and the value it delivers, has not improved since the last assessment. The last external evaluation programme reviewing the evidence on the implementation of NICE decisions was developed in 2007.⁷⁴ However, there is more information to assess the role of NICE, as a result of the creation of the Innovation Scorecard. This provides data on whether medicines recommended by NICE are available to patients. NICE is now more focused on making sure that its recommendations are applied in practice. The latest publication from The Information Centre for Health and Social Care found that the differences between the expected and observed use of NICE appraised medicines varied significantly from molecule to molecule. However, in 2011 the level of usage of NICE recommended molecules was similar to the observed in 2010.⁷⁵⁻⁷⁶

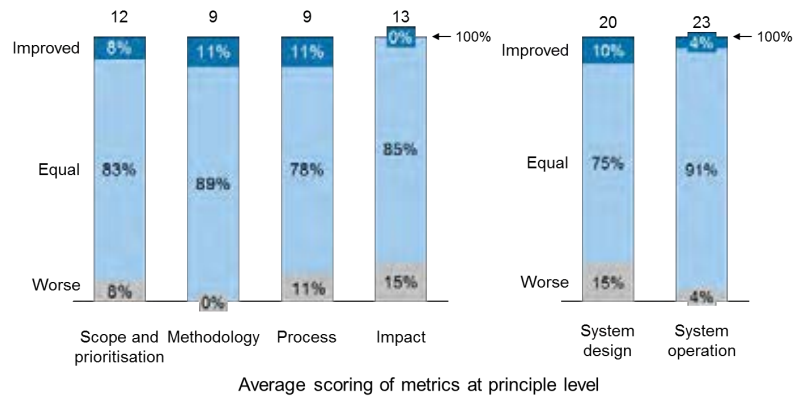
73 "Patient access schemes" is the common terminology used within NICE. In other parts of Europe, these are commonly referred to as management entry agreements.

74 ERNIE results summary. Available here: http://www.nice.org.uk/usingguidance/evaluationandreviewofniceimplementationevidenceernie/ernie_results_summary.jsp.

75 "Use of NICE appraised medicines in the NHS in England – 2010 and 2011, experimental statistics", the Health and Social Care Information Centre, 2012. Available here: <http://www.hscic.gov.uk/catalogue/PUB07985/use-nice-app-med-nhs-exp-stat-eng-10-11-rep.pdf>.

76 Please note that a more recent report has been published in March 2014, Available here: <http://www.hscic.gov.uk/catalogue/PUB13669>.

Figure 18: The CRA assessment of the HTA system in England, 2011 and 2013



Principles	2011	2013
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	●	●
METHODOLOGY		
4 HTA should incorporate appropriate methods depending on its goal	●	●
5 HTA 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 on an intervention could be most usefully developed in the future	●	●
IMPACT OF HTA		
12 HTA should be timely	●	●
13 P,R&MA 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; Note that in the 2013 assessments four metrics were added two in Methodology and two in impact. These have been excluded to illustrate the changes

France

The Haute Autorité de santé (HAS), or National Authority for Health, is the main HTA agency in France. HAS assesses all new drugs, medical devices, and medical procedures to determine if they should be reimbursed by the social health insurance fund (l'assurance maladie). HAS also plays a role in supporting medical professionals by producing medical treatment guidelines and delivers accreditation of healthcare organisations, such as hospitals, and certifications for physicians.⁷⁷

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Haute Autorité de santé, "Mission de la HAS". Available here: http://www.has-sante.fr/portail/jcms/c_1002212/fr/missions-de-la-has.

Through the work of its internal committees, such as the Transparency Commission (TC) for the appraisal of pharmaceutical products, the work of HAS directly supports the function of determining the benefits package (both the inclusion on the positive list and determining the rate of reimbursement) as well as influencing the price setting process for innovative pharmaceuticals.⁷⁸

As can be seen in Figure 19, the pricing and reimbursement process in France is essentially a two-step process. First, HAS provides an assessment of the clinical and therapeutic benefit (SMR) of a new technology and the relative benefit (ASMR), whilst a separate pricing committee (the CEPS) will negotiate the price using the HAS evaluation as well as wider economic considerations.

In the past, HAS assessments and evaluations did not include formal health economic assessment techniques (i.e. cost-effectiveness). However, in 2008, the Social Security Financing Act gave HAS a mandate in the area of economic evaluation. A new committee, known as the CEESP (Commission évaluation économique et de santé publique), was created and tasked with encouraging cost-effective therapeutic practices and drive efficiency savings throughout the healthcare system. The CEESP published health-economic recommendations and opinions on care strategies, including prescription guidelines to encourage healthcare professionals to make the most efficient use of resources.

Since October 2013, the mandate of the CEESP has evolved to include product-by-product cost-effectiveness assessments (avis d'efficience),⁷⁹ which will feed directly into the decision-making process of the pricing committee by providing additional information to complement the clinical effectiveness assessment of the TC.⁸⁰ For the time being, these assessments are restricted to products which are deemed to demonstrate significant added value (ASMR of I-III) and/or are likely to have a significant financial impact⁸¹ on pharmaceutical spending.⁸²

Whilst some information on the evaluation procedure is now available, the way these economic assessments will be executed in practice remains uncertain. Significant changes in

78 Haute Autorité de santé, "Rapport d'activité 2011 de la Commission de la Transparence". Available here: http://www.has-sante.fr/portail/jcms/c_412210/fr/commission-de-la-transparence.

79 Haute Autorité de santé, "Brochure de la Commission évaluation économique et de santé publique (CEESP)". Available here: http://www.has-sante.fr/portail/upload/docs/application/pdf/2012-11/quest-ce_que_la_ceesp-brochure2clics_2012-11-22_10-13-34_631.pdf.

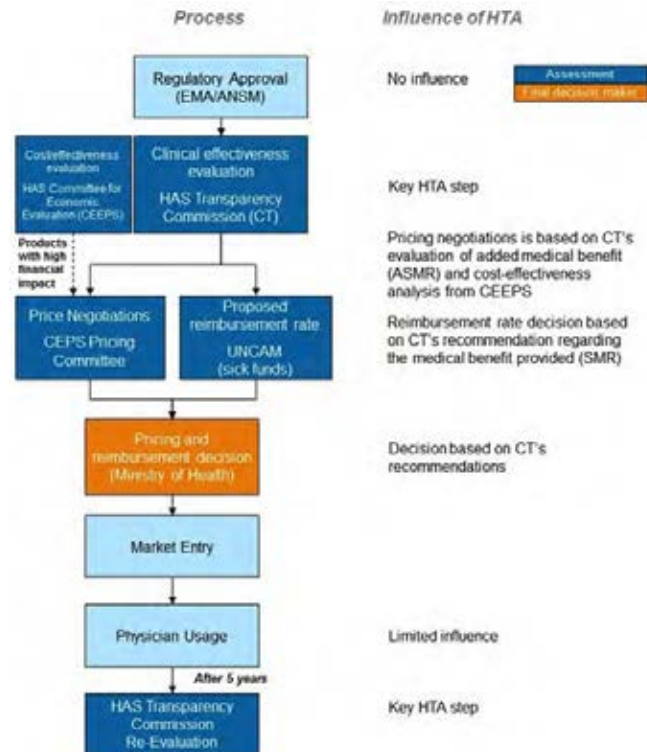
80 Pharmaceutiques.com, "Actualité Mai 2013 : La HAS met le cap sur la médico-économie", 2013. Available here: http://www.pharmaceutiques.com/archive/une/art_1467.html.

81 The HAS defined this significant impact as product which have a gross sales forecast of 20 million euros after two years of commercialisation.

82 Pharmaceutiques.com, "Actualité Septembre 2013 : HAS : un plan stratégique basé sur l'efficience", 2013. Available here: http://www.pharmaceutiques.com/archive/une/art_1477.html.

HTA are therefore expected to take place over the coming years. The first ‘avis d’efficience’ on Jetrea® (ocriplasmine) produced by the CEESP should be available in 2014.⁸³

Figure 19: The impact of HTA process from regulatory approval to physician usage of pharmaceuticals in France



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

The CRA assessment

Reforms within the HAS have largely focused on operational improvements, with the exception of the introduction of a cost-effectiveness assessment in late 2013. Hence, the HTA system in France has remained relatively stable over the past three years when assessed against the HTA best practice principles.

Scope and prioritisation: One important improvement in the decision-making process of the TC has been the publication of a set of evaluation criteria (known as Doctrine d'évaluation)⁸⁴,

83 Commission d'évaluation économique et de sante publique, "Compte rendu de la séance du mardi 17 Décembre 2013". Available here: http://www.has-sante.fr/portail/upload/docs/application/pdf/2014-03/pv_ceesp_du_17_decembre_2013.pdf

84 Haute Autorité de santé, "Rapport d'activité 2012 de la Commission de la Transparence". Available here: http://www.has-sante.fr/portail/upload/docs/application/pdf/2013-09/rapport_activite_2012_ct.pdf.

with a view to improve the transparency and predictability of decisions. This document provides a full description of the TC's rating criteria for each SMR and ASMR category, thereby providing manufacturers with greater transparency over the decision-making process as well as greater predictability.

Methodology: There have been relatively few changes in the way that HAS undertakes its clinical evaluation. However, some progress has been made in recognising and reflecting uncertainty in the assessments. There has been a greater use of "follow up studies" as well as the recent application of conditional reimbursement schemes at the level of the pricing committee (for two oral anticoagulants) to facilitate access to these product whilst confirming information on clinical benefit.⁸⁵ In 2012, the transparency committee has also begun to include data and clinical outcomes from other European countries and HTA organisations into the assessment report.⁸⁶

In 2011, the department for Evaluation of Medicinal Products (SEM) at the HAS introduced a series of pilot "early dialogue" meetings with manufacturers (rendez-vous précoces).⁸⁷ The objective of these meetings is to support pharmaceutical companies in designing and conducting their phase III clinical trials to ensure that these trials capture the right clinical end points and that companies applying for reimbursement are able to provide the necessary evidence required for the cost-effectiveness evaluation."

Process: Whilst the TC does allow a limited role for stakeholders⁸⁸ to take part in the discussion, it has been argued the process still lacks an "open" decision-making process. This should include a wider set of stakeholders (including patients and civil society representatives). According to industry, the members of the TC were under pressure from the payers (i.e. Ministry of Health/sick fund) and this was reflected in the smaller proportion of ASMR I and II in recent years, although this has recently bounced back.⁸⁹ The LEEM (the innovative industry association) has been calling for more open and transparent discussion platform with the TC.⁹⁰

Impact: The length of time taken for reviews by both the TC and the CEPS has improved since 2010. However, according to industry patient wait indicator (the OSCAR Dashboard by

85 Comité Economique économique des produits de santé (CEPS), "Rapport d'activité 2012 (September 2013)". Available here: http://www.sante.gouv.fr/IMG/pdf/RA_2012_Final.pdf.

86 Haute Autorité de santé, "Rapport d'activité 2012 de la Commission de la Transparence (pg 34)". Available here: http://www.has-sante.fr/portail/upload/docs/application/pdf/2013-09/rapport_activite_2012_ct.pdf.

87 Haute Autorité de santé, "Comité économique des produits de santé (CEPS) – rapport d'activité 2012".

88 Stakeholders allowed to participate in the transparency committee include delegates from the Ministry of Health and a representative from the industry (i.e. LEEM). However, to date, no representatives from patient groups are invited to take part.

89 CRA interview programme.

90 CRA interview programme.

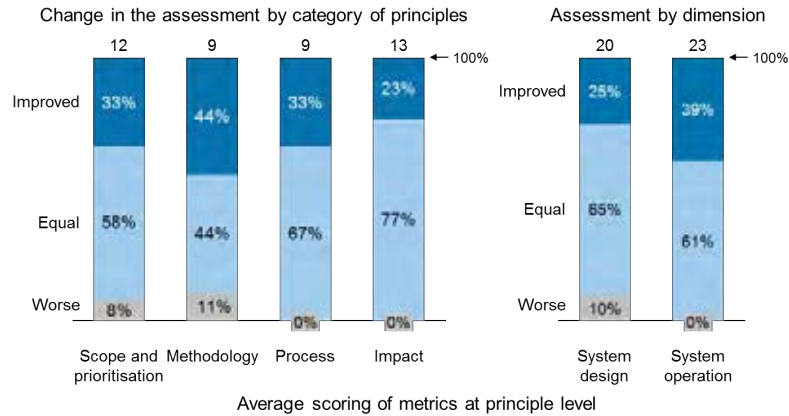
LEEM)⁹¹, which only takes into account products that apply for pricing and reimbursement registration for the first time, the CT and CEPS often go a little beyond the published timeline. However according to the HAS figures⁹² which take into account the entire set of assessment, these meet the expected deadlines.

As Figure 20 demonstrates, the majority of improvements within the French HTA system are on the operational side of the system. However, whilst the introduction of cost-effectiveness analysis within the new CEESP committee represents an important change in the process, the scope, methods and impact of the CEESP assessments remain unclear at this time. The impact of this change has not been captured in our analysis as the changes took place as the report was being developed.

91 Observatoire de Suivi et de Coordination des Activités Réglementaires et Scientifiques , “Tableau de Bord Oscar du 2 Aout 2013”. Available here : <http://www.bonusage.fr/services/oscars>.

92 Comité Economique des produits de santé, “Rapport d’activité 2012 (September 2013)”. Available here: http://www.sante.gouv.fr/IMG/pdf/RA_2012_Final.pdf.

Figure 20: The CRA assessment of the HTA system in France, 2011 and 2013



Average scoring of metrics at principle level

Principles	2011	2013
SCOPE AND PRIORITISATION		
1 HTA should be an unbiased and transparent exercise	Yellow	Green
2 HTA should include all relevant technologies	Yellow	Yellow
3 A clear system for setting priorities for HTA should exist and the costs of HTA should be proportionate	Yellow	Green
METHODOLOGY		
4 HTA should incorporate appropriate methods depending on its goal	Yellow	Green
5 HTA should consider a wide range of evidence and outcomes	Green	Green
6 A full societal perspective should be considered when undertaking HTAs	NA	Yellow
7 HTAs should explicitly characterise uncertainty surrounding estimates	Red	Yellow
PROCESS		
8 Those conducting HTAs should actively engage all key stakeholder groups	Red	Yellow
9 HTA findings need to be communicated appropriately to different decision makers	Green	Green
10 Evaluations should allow new data to be considered	Yellow	Yellow
11 HTA should identify areas in which the evidence on an intervention could be most usefully developed in the future	Green	Green
IMPACT OF HTA		
12 HTA should be timely	Yellow	Yellow
13 P,R&MA should reflect the HTA assessment in a transparent, clearly defined way and be implemented as intended	Red	Yellow
14 The impact of HTA findings and how they are used needs to be monitored	Red	Red

Source: CRA analysis; Note that in the 2013 assessments four metrics were added two in Methodology and two in impact

Germany

Among the countries included in the previous first Comparison report, the Germany HTA process experienced the most notable changes. Indeed, the German law on medicines, *Arzneimittelmarktneuordnungsgesetz* (AMNOG) introduced a more formal role for HTA in price formulation. This makes comparison across years particularly challenging. In 2011 report we were primarily assessing the role of IQWiG prior to AMNOG. In 2013, we have focused the assessment on the GBA process using the assessment provided by IQWiG,

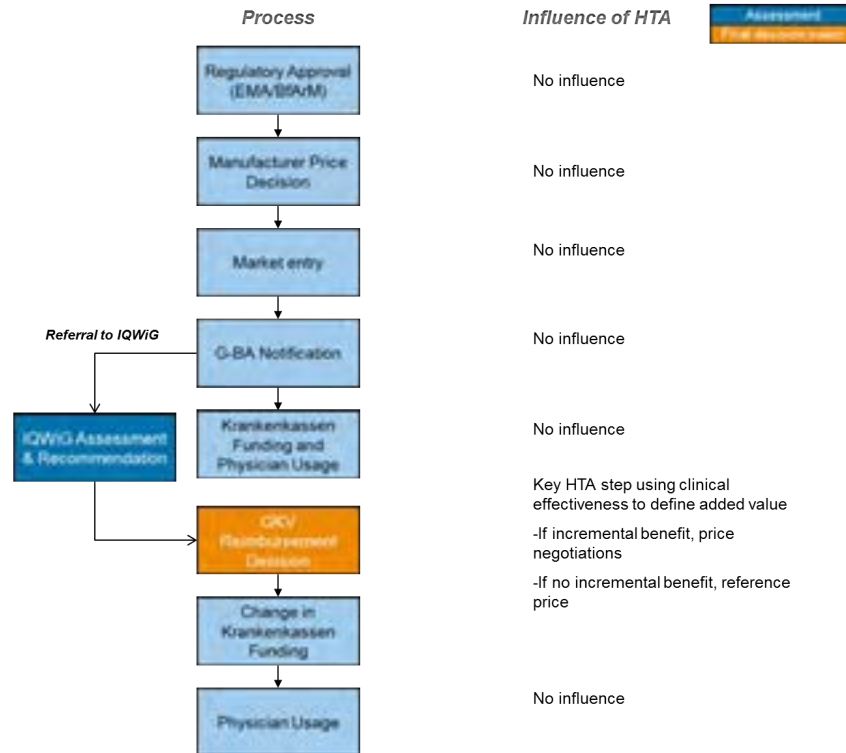
The reform, implemented in January 2011, established that the maximum reimbursement levels for new drugs should be based on proven incremental therapeutic benefits compared to an appropriate comparator given by G-BA. Manufacturers are now required to submit a benefit dossier to the Federal Joint Committee (Gemeinsame Bundesausschuss, G-BA) which commissions the assessments mostly to the Institute for Quality and Efficiency in

Healthcare (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG). For products that have been given an innovative status, prices are negotiated with the German sick funds (Gesetzliche Krankenversicherung, GKV).⁹³

As illustrated in Figure 21, free pricing is now limited to a maximum of 12 months after launch. Then the GKV-SV (GKV-Spitzenverband, umbrella association of GKV) and the manufacturer negotiate the reimbursement depending on the level of incremental benefit found through the assessments. New molecules are assessed using a clinical benefit methodology which defines the added value using a five-level scoring system (major, significant, marginal, no quantifiable, no additional benefit and less benefit) compared to an appropriate comparator given by G-BA which feeds into pricing decisions.⁹⁴ Products deemed innovative have greater pricing freedom when negotiating with the GKV-SV and can charge a premium over comparator(s). The annual therapy costs of the appropriate comparator are the maximum ceiling products that are defined as non-innovative can reach.

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- 93 "AMNOG: seven learnings for strategic market access decisions in Germany", IMS Consulting Group, 2012. Available here: http://www.imsconsultinggroup.com/deployedfiles/consulting/Global/Content/Our%20Latest%20Thinking/Static%20Files/AMNOG_seven_learnings_strategic_access_germany.pdf.
- 94 Rouf et al., "Early benefit assessment (EBA) in Germany: analysing decisions 18 months after introducing the new AMNOG legislation", *European Journal of Health Economics*, 2013. See the IQWiG updated "General Methods" guide. Available here: https://www.iqwig.de/download/IQWiG_Methoden_Version_4-1.pdf.

Figure 21: The impact of HTA process from regulatory approval to physician usage of pharmaceuticals in Germany since AMNOG



Source: CRA analysis; Note: 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

The CRA assessment⁹⁵

When comparing the results from the 2011 assessments to the 2013 findings, it is important to keep in mind that the AMNOG reform changed the fundamentals of the HTA process. Prior to 2011, the HTA process was not systematically applied and did not directly feed into price negotiation. As such, the previous assessment based on 2009-2010 data, was primarily focused on IQWiG. Today, HTA is a key step in determining reimbursement within the German system so the 2013 assessment looks at the G-BA. Based on best practice principles, the HTA system in Germany has improved since the 2011 assessment. This is due to changes in the design of the system rather than in operational terms (Figure 22).

Scope and prioritisation: We found that the AMNOG reform brought clarity to the HTA process and defined a rationale for setting priorities. Since January 2011 all new medical technologies need to be assessed to prove clinical improvement. Previously, the rationale that IQWiG used to select the medicines reviewed was not clearly stated. However, HTA is

95

Note that the CRA methodology aims to assess the role of HTA in a country, so should not be considered as focusing only on IQWiG or the GBA. .

currently only targeted to new technologies. Furthermore, the new system has become more focused on reviewing new medicines. As a consequence of the reform in 2012, 80% of the reviews were pharmaceutical products while in 2009 these represented only 22%.⁹⁶

Methodology: The G-BA includes into its decisions the recommendation derived from IQWiG, which uses a similar methodology to that used in 2009. Therefore, we did not find many changes in the metrics assessing methodology. There is a concern regarding the choice of comparator, GBA using different comparators to those suggested by the industry. In a few cases and there has been a preference for the lowest cost comparator. Since June 2013, the German Ministry of Health made clear that more than one comparator can be given as appropriate based on medical reason. This should ensure the acceptance of clinical evidence derived conducted for the regulatory approval process. The price will afterwards be negotiated between the manufacturer and the GKV-SV.⁹⁷ Although at the aggregate level, drawing on a number of metrics as represented in, the system allows for a wide range of evidence, there remains a concern regarding the preference for RCTs and published trial data.

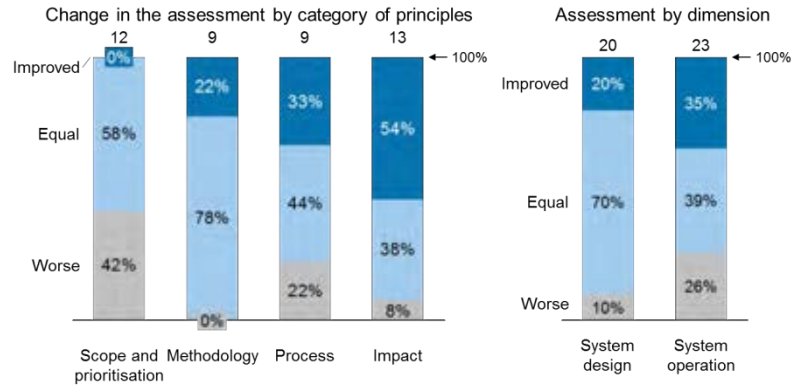
Process: Some improvements in terms of processes have been identified. Findings are now published in a clearer manner as everything is publicly available on the G-BA website. Additionally, the G-BA asks for further data if the evidence available is not enough to reach a conclusion. However we found that the involvement of stakeholders remains limited through the process.

Impact: Since the introduction of the AMONG reform, the impact of the HTA is much clearer. The length of the reviews is now defined and followed and the link between the assessment and reimbursement decisions is defined. However, it is still too early to determine if the G-BA decisions are reflected in the price negotiation process. Based on the interviews, all stakeholders included in the interview programme reported that prices coming out after the price negotiations were lower than what was expected after implementing a formal HTA process.

⁹⁶ Note that the AMNOG reform was focused only on pharmaceutical products, as such, other health technologies are not affected by the requirement of being assessed.

⁹⁷ "AMNOG amendment promises more flexibility in choice of appropriate comparator therapies". IHS Healthcare and Pharma Blog, 2013. Available here: <http://healthcare.blogs.ihs.com/2013/07/02/amnog-amendment-promises-more-flexibility-in-choice-of-appropriate-comparator-therapies/>.

Figure 22: The CRA assessment of the HTA system in Germany, 2011 (Old system) and 2013 (AMNOG)



Average scoring of metrics at principle level

Principles	2011	2013
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	●	●
METHODOLOGY		
4 HTA should incorporate appropriate methods depending on its goal	●	●
5 HTA 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 on an intervention could be most usefully developed in the future	●	●
IMPACT OF HTA		
12 HTA should be timely	●	●
13 P,R&MA should reflect the HTA assessment in a transparent, clearly defined way and be implemented as intended	NA	●
14 The impact of HTA findings and how they are used needs to be monitored	●	●

Source: CRA analysis; Note that in the 2013 assessments four metrics were added two in Methodology and two in impact. These have been excluded to illustrate the changes

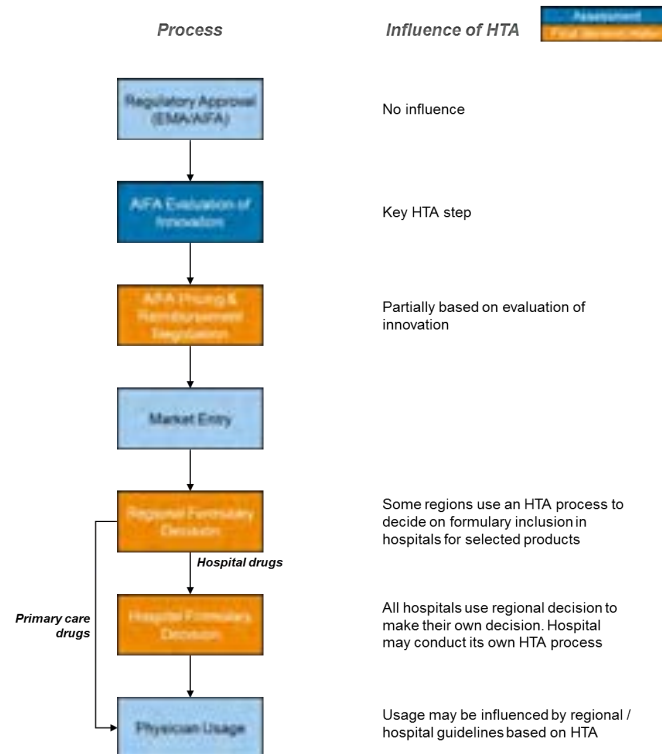
Italy

The HTA agency in Italy, the Italian Medicines Agency (AIFA), is responsible for both regulatory approval and for pricing and reimbursement decisions (including conducting HTA) of all new medicines in the market at the national level. As Figure 23, demonstrates, manufacturers make a submission to AIFA, which first assesses clinical effectiveness and categorises the technology as an important, moderate or modest innovation. Medicines are classified as fully reimbursed in Class A, out-of-pocket in Class C and for hospital reimbursement and administration in Class H.

AIFA’s evaluations are taken into account when pricing medicines at a national level. Hospital formularies are defined at a regional level. The method and process for which regions decide what to include differ across regions, with some regions using a cost-effectiveness analysis to determine reimbursement. For instance, the Veneto and Emilia-Romagna regions use cost-

effectiveness analysis and release public information regarding their results. The rest of the regions form decisions on the basis of more basic budget impact analysis and the rationale is often not publicly available. Reimbursement is then negotiated at a regional level thus the prices set by AIFA can be further discounted through agreements reached by the regions and manufacturers.

Figure 23: The impact of HTA process from regulatory approval to physician usage of pharmaceuticals in Italy



Source: CRA analysis; Note: EMA: European Medicines Agency; AIFA: Italian Medicines Agency

The CRA assessment

Given the nature of the Italian HTA system, the assessment according to best practice principles depends on the regional systems under consideration. However, as Figure 24Error! Reference source not found. shows, overall some improvements have been identified in the process and the impact of HTA since the CRA 2011 assessment.⁹⁸

Scope and prioritisation: There have been no significant changes in terms of independence and transparency of HTA. There is still a strong influence of payers with relatively little clarity in the decision-making process or any interaction with manufacturers. AIFA only conducts

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Please note that this chart represents the assessment at a national level. Commentary regarding practices that differ at a regional level can be found in the assessment text.

medicines assessments but regional commissions in Veneto, Lombardy and Emilia-Romagna may also perform assessment of devices. All new medicines that require inclusion are assessed by AIFA, but selection and prioritisation at a regional level remains at the discretion of the regional authorities.

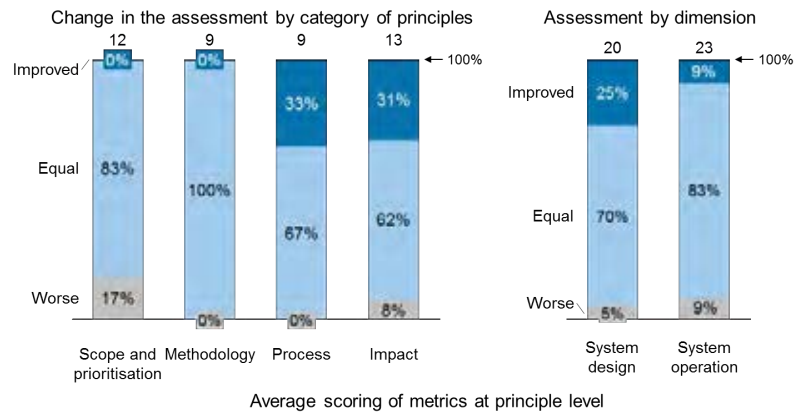
Methodology: AIFA applies an algorithm to assess clinical effectiveness of new pharmaceuticals. A new algorithm is being developed, but this has not yet been published. The use of cost-effectiveness remains limited and the assessment is primarily based on budget impact analysis. There is a need to address a number of methodological issues including: the range of data that is considered, the recognition of uncertainty, and the approach to including indirect costs and wider societal elements. In some of the regions mentioned above there is evidence of the use of methods that are more clear and established.

Process: The involvement of different stakeholders in the process is limited. A further issue is the lack of published detailed decisions. The agency still uses the national bulletin, *Gazzetta Ufficiale*, to announce decisions regarding price and reimbursement, but the rationale or analysis remains confidential. Some regions have more established systems of communicating their decisions, as well as, allowing for an appeal against the final recommendation; however, this is not done at a national level.

Impact: There are concerns regarding the length of time it takes to complete the assessments in the Italian HTA system. However, the recent introduction of a fast-track system for potentially innovative technologies is seen as a significant improvement. Under this system, the assessment should be completed within 100 days. Although there is a relationship between the assessment by AIFA and the price of the assessed technologies, in terms of reimbursement, the relationship between HTA and the decision-making process is potentially duplicative (both AIFA and regions assessing the same technology) and this is not currently transparent. A longer term impact of such decisions and trends is not systematically reviewed, but AIFA's Observatory for Medicines Usage releases annual reports which indicate useful information on diffusion of medicines and addresses issues of specific therapeutic categories.

As reflected in Figure 24, some steps have been taken to address concerns regarding the process and the impact of the HTA process. However, the Italian HTA remains highly fragmented across regions making the assessment challenging. The transparency regarding the role of HTA in the decision-making process remains unclear.

Figure 24: The CRA assessment of the HTA system in Italy, 2011 and 2013



Average scoring of metrics at principle level

Principles	2011	2013
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	●	●
METHODOLOGY		
4 HTA should incorporate appropriate methods depending on its goal	●	●
5 HTA 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 on an intervention could be most usefully developed in the future	NA	NA
IMPACT OF HTA		
12 HTA should be timely	●	●
13 P,R&MA 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; Note that in the 2013 assessments four metrics were added two in Methodology and two in impact. These have been excluded to illustrate the changes

Netherlands

The HTA system in the Netherlands went through considerable restructuring in 2012. Upon market authorisation, the manufacturer can submit a dossier for HTA to the CVZ (College voor Zorgverzekeringen), the Dutch HTA body, but the process varies depending on whether the product is a hospital or retail medicine. In 2012, it was announced that hospital medicines will receive immediate reimbursement subject to budget constraints upon approval. These may be subsequently selected for review by the CVZ. Non-hospital medicines must go through the HTA to be included on the reimbursement list.⁹⁹

In terms of organisation, the process has also changed. The Scientific Advisory Committee (WAR) within the CVZ is responsible for assessing the therapeutic value and cost-effectiveness of the new medicines. This is composed of the Medicines Committee (CG) and Pharmacotherapeutic Committee (CFK). WAR replaced the Committee for Pharmaceutical Help (CFH).¹⁰⁰

As reflected in Figure 25, medicines deemed to have a high therapeutic value, but that are not considered to be cost-effective, will be further reviewed by WAR and the Social Advisory Committee (ACP) to assess indirect and societal costs.¹⁰¹ CVZ will take a final position on inclusion, based on the recommendations of the above, which will form the basis of the final decision taken by the Ministry of Health. There is a possibility for price agreements as a further condition for reimbursement.

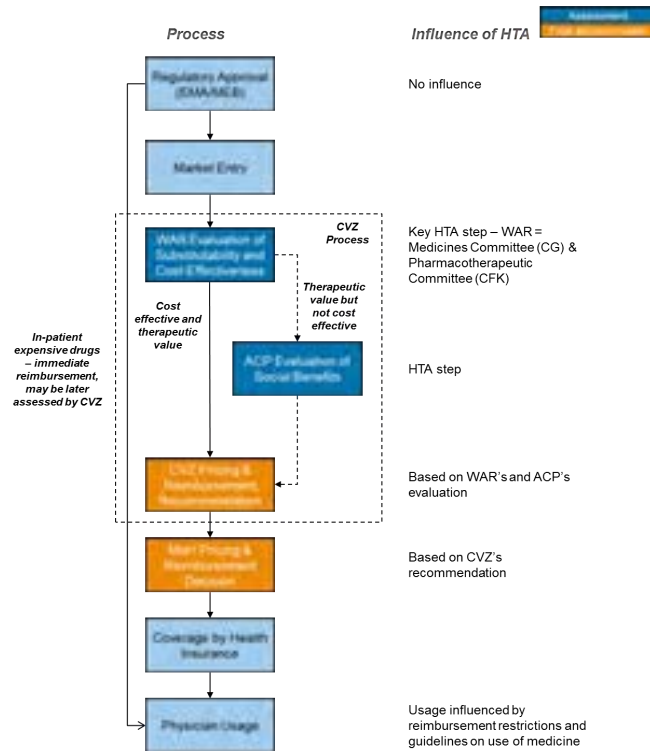
The system is going to change further. In April 2014, the CVZ became the National Health Care Institute and will aim at further emphasising the quality of treatments and impact on health outcome.¹⁰²

100 “CVZ Commissies”, CVZ, 2013. Available here: <http://www.cvz.nl/organisatie/structuur/commissies>.

101 “Reglement Adviescommissie Pakket”, CVZ, 2012.

102 “CVZ will become Zorginstituut Nederland”, CVZ, 30 January 2014. Available here: <http://www.cvz.nl/publicaties/nieuwsberichten/2014/cvz-will-become-zorginstituut-nederland.html>.

Figure 25: The impact of HTA process from regulatory approval to physician usage of pharmaceuticals in Netherlands



Source: CRA analysis; Note: EMA: European Medicines Agency; MEB: Medicines Evaluation Board; WAR: Scientific Advisory Committee; CG: Medicines Committee; CFK: Pharmacotherapeutic Compass Committee; ACP: Social Advisory Committee; CVZ: Health Care Insurance Board; MoH: Ministry of Health

The CRA assessment

The Dutch HTA system performed well against best practice principles in the CRA 2011 assessment and the changes described above led to improvements in scope and prioritisation, process and impact, as seen in Figure 26.

Scope and prioritisation: A key change in the HTA system has been the emergence of two separate processes for expensive hospital medicines and non-hospital medicines. The former are now reimbursed immediately after regulatory approval is received and CVZ may subsequently assess the technology and make a recommendation regarding the permanent inclusion in the reimbursement list. However, the rationale for the hospital medicines selected for review is not clear or publicly available.

The CVZ remains an independent, inclusive and transparent body. The Dutch system was positively assessed in CRA 2011 for the support given to manufacturers and it has improved since the previous report. As of September 2012, the CVZ and the MEB, the regulatory body,

provide simultaneous scientific advice to manufacturers' prior marketing authorisation and reimbursement decisions in one single procedure.¹⁰³

Methodology: Overall, the HTA system in the Netherlands uses widely accepted methods to assess technologies (based on a cost/QALY approach but without a specified threshold). It is one of the systems pioneering the inclusion of societal benefits and costs in the assessments, which is further enhanced by the creation of the ACP within CVZ. A discussion of the impact of uncertainty regarding the decisions is included in most cases and the use of conditional reimbursement has improved and been made more explicit since the last assessment. Expensive medicines are conditionally reimbursed and reassessed after four years on the basis of further evidence.

Process: In terms of stakeholder involvement, CVZ performs relatively well, including different stakeholder views at different stages of the process. The level of interaction between stakeholders is good, with public and detailed information available on the CVZ website and the possibility to appeal or request reassessment. However, it is very difficult to assess whether there is a real impact of involvement of different parties in the decision-making process. The agency conducts re-evaluations by its own initiative, such as in the case of expensive medicines, and occasionally mentions further evidence that may be of interest when making a recommendation.

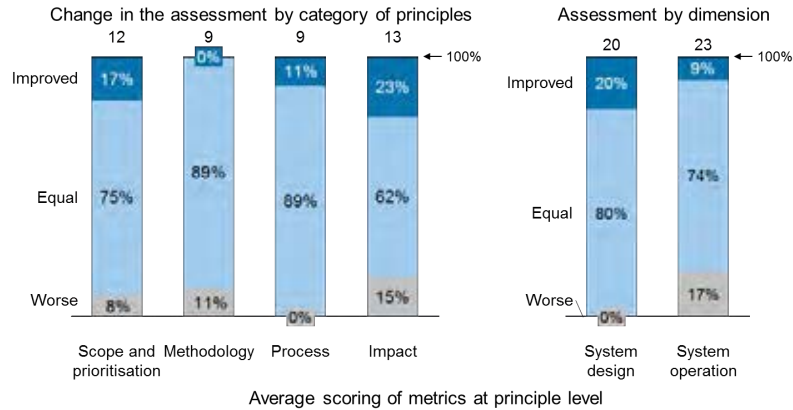
Impact: The entire process can be considered timely, despite the requirement to perform the assessment within 90 days not always being respected. Non-hospital medicines are accessible as out-of-pocket if market authorisation is received but they are only reimbursed after a positive decision of the MoH, while hospital medicines will be reimbursed directly after marketing authorisation.¹⁰⁴ CVZ recommendations affect reimbursement decisions but a well-established body that systematically assesses the value of the HTA process does not yet exist.

Since the last report, the changes in the use of HTA in the Netherlands bring it closer to best practice principles. However, some of the current policies and transformations will have longer term implications and cannot be immediately assessed.

103 "Joint advice from the Health Care Insurance Board and the MEB", CBG,. Available here: <http://www.cbg-meb.nl/CBG/en/human-medicines/scientific-advice/default.htm>.

104 However, due to financial constraints, it is not always possible for specialists to prescribe these medicines.

Figure 26: The CRA assessment of the HTA system in Netherlands, 2011 and 2013



Average scoring of metrics at principle level

Principles	2011	2013
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	●	●
METHODOLOGY		
4 HTA should incorporate appropriate methods depending on its goal	●	●
5 HTA 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 on an intervention could be most usefully developed in the future	●	●
IMPACT OF HTA		
12 HTA should be timely	●	●
13 P,R&MA 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; Note that in the 2013 assessments four metrics were added two in Methodology and two in impact. These have been excluded to illustrate the changes

Poland

The Polish HTA system is one of the most established in Central and Eastern Europe. The Agency for Health Technology Assessment in Poland (AOTM) reviews medicines, therapeutic programmes and medical devices to be included in the reimbursement list funded by the National Health Fund (NHF).

The system has faced many challenges and has experienced considerable restructuring in the past years. At the beginning of 2012, the Reimbursement Act brought in a number of significant changes. This introduced greater stakeholder involvement in the process, including

manufacturers, medical experts, patient organisations and political elites.¹⁰⁵ Another change resulting from the Act was the renaming of the Consultative Council to the Transparency Council.¹⁰⁶

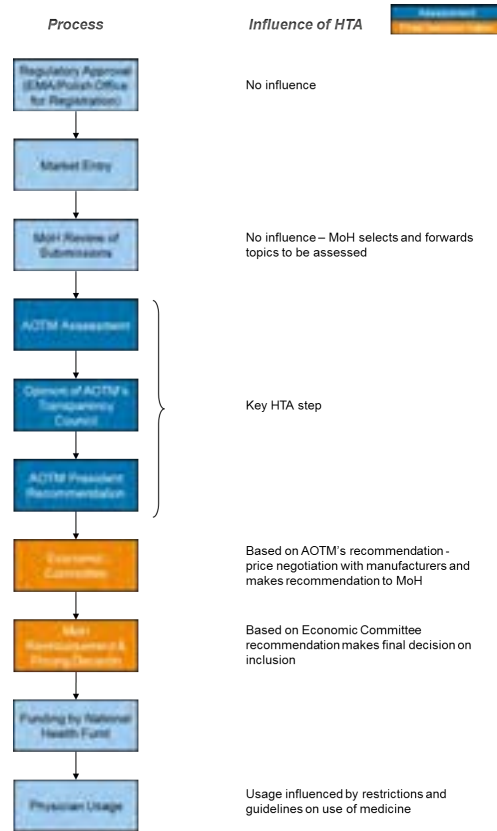
As shown in Figure 27, the Ministry of Health (MoH) is the body with responsibility for the selection of topics and the submissions of the application for reimbursement of new medicines and indications to the AOTM. The agency conducts the assessment which in turn feeds into the appraisal process undertaken by the Transparency Council, an independent body within the agency. The Council will prepare a position to be taken but the final recommendation is issued by the President of AOTM, with a commitment that the entire process should take no longer than 60 days from the date of submission.

An Economic Committee, established in 2012 by the MoH, including representatives from the NHF, chambers of doctors and academics, uses the assessment to conduct price negotiations with manufacturers and makes a final decision regarding reimbursement. The Minister of Health is informed of such positions and will make a final decision regarding pricing and reimbursement of the technology. These decisions are published periodically on the AOTM website together with the analysis and detailed recommendations for inclusion.

105 Ozieranski, "The politics of health technology assessment in Poland", *Health Policy*, 108, 2012.

106 The Transparency Council has more members than its predecessor, including 20 representatives of: MoH (four), NHF (two), The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (two) and the Patients' Rights Advocate (two). Normally, 10 randomly chosen members will take part in each decision making process.

Figure 27: The impact of HTA process from regulatory approval to physician usage of pharmaceuticals in Poland



Source: CRA analysis; Note: EMA: European Medicines Agency; MoH: Ministry of Health; AOTM: Health Technology Assessment Agency

The CRA assessment

The HTA system in Poland performs relatively well ranking amber in more than half of the 14 principles used in the CRA assessment. The changes discussed above have generally improved the assessment of the method, process and impact.

Scope and prioritisation: The system remains largely unchanged, with the regulatory and HTA bodies operating independently. An area where the system performs well is an inclusive treatment of different types of technologies. However, the introduction of a 60-day timeframe for completing the reviews has disrupted priorities and inclusiveness. The result of this has been to improve the speed of medicine reviews, but it has also resulted in a decrease in reviews of other technologies due to restricted resources available. Two main drawbacks remain: there is no scientific advice available to the manufacturer during the preparation stage and a lack of opportunity to appeal decisions.

Methodology: AOTM considers a wide range of data and a pilot programme in cooperation with the MoH, Ministry of Economy and social interest groups, is being developed to encourage inclusion of social and indirect costs. The 2012 Reimbursement Act also formalised the use of risk-sharing schemes (managed entry agreements, MEA), previously

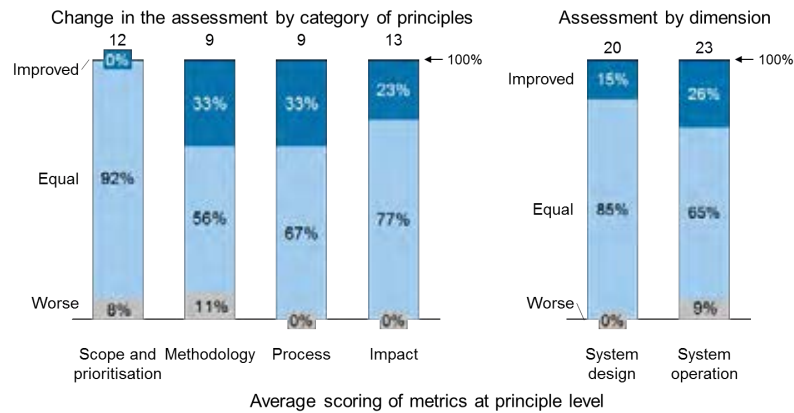
used informally. However, discrepancies exist on this issue with some stakeholders reporting that all forms of MEAs had been stopped since the introduction of the Act. This suggests the need for better cooperation between agency and industry especially in times of policy change.

Process: The involvement of different stakeholders in the process has also changed. Medical experts are now involved throughout the process, the manufacturer is involved through the submission and prior to the appraisal, patients are invited in the Transparency Council meeting and the public can send their comments. There remains a concern about the relative importance of different stakeholders in the process, but there has clearly been progress made towards an inclusive system. There is common agreement between the industry and HTA agency on this issue. Generally, the system is considered relatively transparent with recommendations and decisions being publicly available, but the rationale is only shared with the manufacturer. There is a positive approach by the agency in identifying the value of further evidence and re-evaluations may occur.¹⁰⁷

Impact: Considerable limitations remain in assessing the impact of HTA in Poland. There has been evident improvement in timing of the review process (now set at 60 days) and it is generally applied within the timeframe. However, there is still uncertainty regarding the impact of HTA on decision-making, as some of the recommendations are not accepted. There is no process for assessing the value of HTA, which may lead to inadequate policy making or implementation.

As shown in Figure 28, improvements have been identified across three areas. In methods, there is evidence of social elements being considered in the assessment and the introduction of formal managed entry agreements. The process involves more stakeholders across the different stages and there is a timeline in place which is respected. Most changes since the CRA assessment in 2011 were triggered by the Reimbursement Act, enacted in 2012. However, challenges remain especially in areas of impact, where a systematic assessment and monitoring of the HTA does not exist. Finally, it is worth highlighting that there were diverging views between the interviewed individuals, most notably on the use of managed entry agreements.

Figure 28: The CRA assessment of the HTA system in Poland, 2011 and 2013



Average scoring of metrics at principle level

Principles	2011	2013
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	●	●
METHODOLOGY		
4 HTA should incorporate appropriate methods depending on its goal	●	●
5 HTA 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 on an intervention could be most usefully developed in the future	●	●
IMPACT OF HTA		
12 HTA should be timely	●	●
13 P,R&MA 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; Note that in the 2013 assessments four metrics were added two in Methodology and two in impact. These have been excluded to illustrate the changes

Scotland

The HTA system in Scotland is known for the simplicity of its design and process. The Scottish Medicines Consortium (SMC) is in charge of the development of HTA for all new medicines that have received regulatory approval and applied to be included in the public reimbursement system.

As Figure 29 demonstrates, once the drug has received regulatory approval, manufacturers set the price they want to sell their new products at and communicate this to the Department of Health. The manufacturer then submits their HTA dossier to the SMC. The SMC bases its decisions using clinical and cost-effectiveness analyses (allowing flexibility if the medicines

are categorised as orphan medicines or “end of life” drugs). The “modifiers”, as SMC calls these exceptions to the assessments, relate to those classes where more uncertainty in the economic case could be accepted.¹⁰⁸

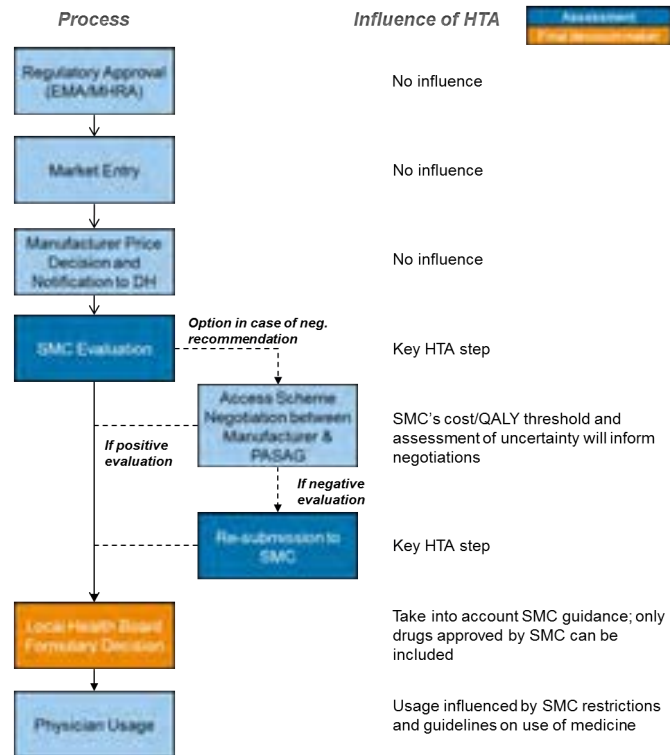
SMC recommendations are based on evidence in the manufacturer’s application, which is then reviewed by a group including representatives of all stakeholder groups (clinicians, economists, patient groups, industry and the general public). All the members have a full vote and, therefore, participate in the review of the assessment.

Although the relationship between the SMC assessments and reimbursement decisions is not explicit, SMC recommendations are used as a guide to local health boards to define their drug formulary which determines the medicines that are reimbursed. Only medicines approved by the SMC can be included in the formularies. Once local health boards recommend the medicines that should be used in their area, clinicians then decide what to prescribe.¹⁰⁹

108 The Scottish government is now reviewing some aspects of the SMC including how the agency looks at the modifiers. Experts contacted by CRA believe that more formality on how SMC treats the modifiers will be included. The final review will be published in early 2014.

109 “The SMC explained”, SMC. 2013. Available here:
http://www.scottishmedicines.org.uk/Public_Involvement/SMC_Explained/SMC_Explained.

Figure 29: The impact of HTA process from regulatory approval to physician usage of pharmaceuticals in Scotland



Source: CRA analysis; Note: 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

The CRA assessment

The HTA system in Scotland appears to perform well according to best practice principles. Indeed, the Scottish HTA system ranked green and amber in the three point scale on most of the 14 principles used in the CRA assessment as illustrated in Figure 31

Scope and prioritisation: The major change observed in Scotland's HTA system between 2011 and 2013 is the type of technologies included in the assessments. Although the SMC only reviews pharmaceutical products, Healthcare Improvement Scotland (HIS) is becoming more active in reviewing other medical technologies.¹¹⁰

Methodology: On average, all the principles relating to the methodology used by the SMC have been scored at a similar level as in 2011. We found that uncertainty is considered within the assessments, but could be dealt with more explicitly. Managed entry agreements are now

110

CRA interview programme. Note that medical technologies as well as treatment strategies are assessed by the Scottish Health Technologies Group (SHGT).

commonly used; however, these are mainly as a form of achieving price discounts rather than to deal with uncertainty.¹¹¹

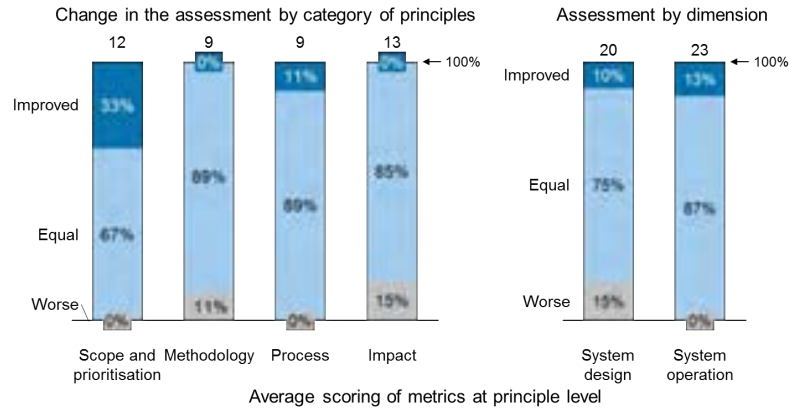
Process: Again, the CRA assessment on the HTA process in Scotland remained similar to the last report. The one metric where SMC does not meet best practice principles relates to identifying areas where future evidence would be beneficial, this appears to reflect the limited resources and recognition that Scotland is a relatively small market from a global perspective. However, it is worth noting here that reassessments are not undertaken as only new molecules are reviewed. Therefore reviews are developed only when a manufacturer receives a rejection and needs to resubmit the application.

Impact: The HTA system in Scotland works within the defined time. Indeed, both industry and the HTA agency believe that having a simplified HTA system (e.g. one agency assessing new technologies based on company submissions) is beneficial for a small country with limited resources.¹¹² However, there is still some room for improvement in terms of how the SMC decisions are used. First, the SMC does not treat innovation explicitly. Indeed, last year the "unique" classification which allowed for an explicit treatment of innovation was removed, as it was not being used. Second, the link between SMC decisions and the incorporation to clinical guidelines is still limited, although some assessments have been used to define oncology guidelines. Finally, we found some concern with the industry and some patient groups arising from the fact that local health boards did not always follow SMC recommendations.

111 CRA interview programme.

112 For example, within the last year the SMC removed the "unique" classification, which dealt with the explicit treatment of innovation as it did not necessarily mean better treatment within the assessment and it was only used once.

Figure 30: The CRA assessment of the HTA system in Scotland, 2011 and 2013



Average scoring of metrics at principle level

Principles	2011	2013
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	●	●
METHODOLOGY		
4 HTA should incorporate appropriate methods depending on its goal	●	●
5 HTA 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 on an intervention could be most usefully developed in the future	●	●
IMPACT OF HTA		
12 HTA should be timely	●	●
13 P,R&MA 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; Note that in the 2013 assessments four metrics were added two in Methodology and two in impact. These have been excluded to illustrate the changes

Sweden

HTA in Sweden is used to decide what to include within the public reimbursement system. As is shown in Figure 31, manufacturers make a submission to the Dental and Pharmaceutical Benefits Board (TLV), the HTA agency, which makes a decision regarding reimbursement status and pricing level. The assessments can be initiated prior to market authorisation providing approval is received within 90 days of starting the process.

The agency will assess medicines in chronological order of dossier submission (i.e. first submission received, first submission reviewed). The evaluation is done on the basis of the human value principle (everyone is equal), solidarity principle (priority given to greater

medical needs) and cost-effectiveness, with the first two overriding the latter.¹¹³ TLV decisions regarding reimbursement are binding at the price level provided by the manufacturer in the application and all technologies with a positive decision will be included in the Pharmaceutical Benefit Scheme (PBS). The agency systematically re-evaluates technologies reviewed prior to the establishment of the current scheme in 2002.¹¹⁴

The Swedish system displays a further layer of assessment and decision-making, at a county level. The rate of adoption of technologies included in PBS depends on county councils, but there have been cases of medicines rejected by TLV but included for reimbursement in a certain county. Also, further discounts to the national price may apply. The New Drug Therapies (NLT) Group established in 2010 on behalf of Swedish County Councils directors, can request which in-patient medicines are assessed by TLV. The latter issues the assessment but no decision regarding the reimbursement status as these are covered directly on a county level.¹¹⁵ The NLT has gained more prominence since our last assessment and is now one of the stakeholders involved in the HTA conducted by TLV, which enhances cooperation and positively influences alignment of decisions at national and county level.

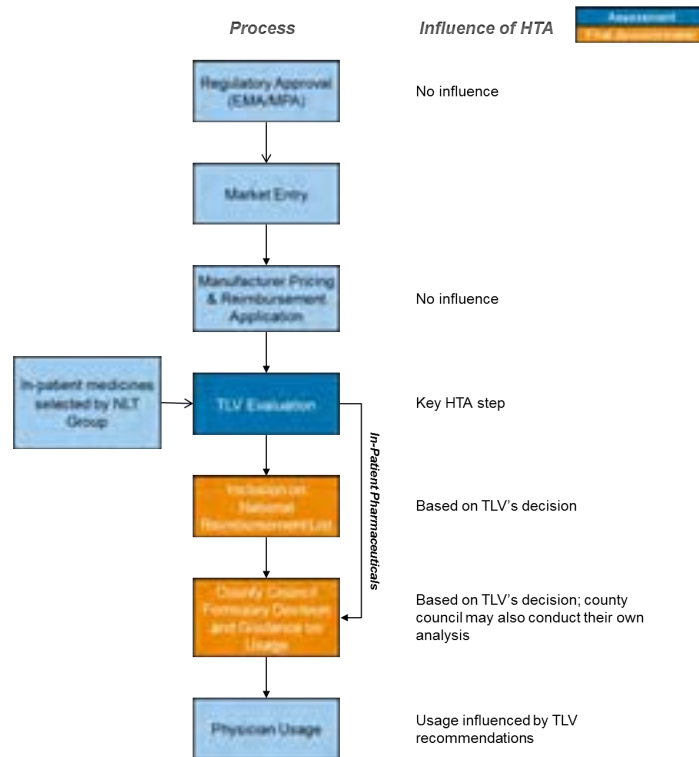
A separate HTA body, the Swedish Council on Technology Assessments (SBU), conducts scientific reviews of technologies without a manufacturer's submission, but these do not influence price or reimbursement.

113 "Guide for companies when applying for subsidies and pricing for pharmaceutical products", TLV, 2013.

114 Persson, "Value based pricing in Sweden: lessons for design?", Office of Health Economics, 2012.

115 "Commission to evaluate the usefulness of the pharmacoeconomic assessments of in-patient medicines", TLV, 2012.

Figure 31: The impact of HTA process from regulatory approval to physician usage of pharmaceuticals in Sweden



Source: CRA analysis; Note: EMA: European Medicines Agency; MPA: Medical Products Agency; TLV: Pharmaceutical and Dental Benefits Board; NLT Group: New Drug Therapies Group

The CRA assessment

The Swedish HTA system performs well according to best practice principles, similar to the 2011 assessment. A green and amber rating is assigned across all principles, indicating a well-established and well-functioning system is in place.

Scope and prioritisation: The process for applying and prioritising topics is clear and applied as stated. The manufacturer submits the dossier and the agency assesses the requests on a first come, first reviewed basis, using input from other agencies particularly for inpatient medicines. There was an attempt to introduce a prioritisation system where certain therapy areas would be given priority into the process but this was reversed as it was not found to be efficient. Compared to the last assessment, we can observe some improvements including a better interaction of TLV with the manufacturer in the pre-submission phase. TLV offers advice in preparing the dossier application prior its submission. Furthermore, TLV

along with the regulatory body, the MPA, also provides scientific advice.¹¹⁶ The agency assesses new and existing technologies and both medicines and devices.

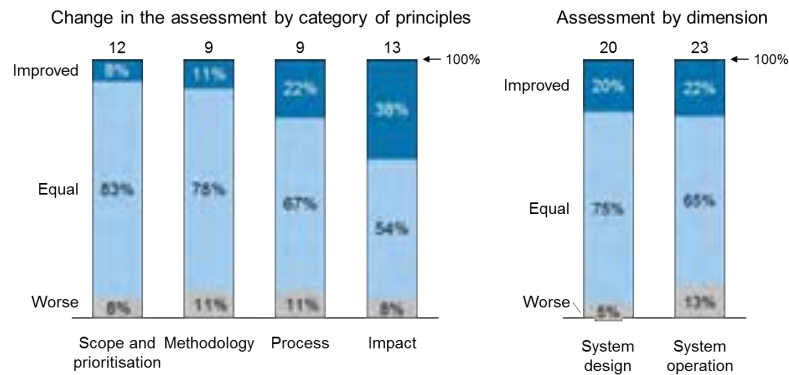
Methodology: Similar to 2011, methods are largely well established, with the assessment including a wide range of data, using a societal approach and accounting for uncertainty, which may translate into a conditional reimbursement in the form of access with evidence development.

Process: A major improvement in the Swedish HTA system has been the increasing relevance of NLT which ensures inclusiveness of different stakeholders in the process and is viewed as an important improvement by all stakeholders. The manufacturer is involved throughout the process and has the possibility to appeal against decisions. TLV publishes all decisions but details of the analysis are only available for in-patient medicines. The agency systematically re-evaluates technologies, mainly in the form of therapeutic class reviews or in cases of a request for a higher price.

Impact: TLV is timely and assesses submissions within the given timeframe of 180 days. The possibility to initiate the review prior to approval is still a possibility and should the product receive regulatory approval prior to the announcement of TLV's decision, the manufacturer can apply free pricing and have the product available in the market. There is clear evidence that HTA recommendations determine the reimbursement status and no evidence of discrepancies. However, the assessment does not have a direct impact on clinical guidelines, as these are region-specific and not updated systematically or uniformly across regions. TLV is an agency that monitors its own operations and is due to release a report on the effect of HTA in the system, but it is unclear whether this will be a systematic procedure in the future. However, there has been evidence in the past that criticism in previous evaluations has triggered changes in the system, such as the publication of all assessments, which was previously only done for approved technologies.

Overall, as demonstrated in Figure 32, the HTA system in Sweden performs well and continually targets areas that require improvement. Most weaknesses are observed in impact, but this is also where most recent developments have occurred.

Figure 32: The CRA assessment of the HTA system in Sweden, 2011 and 2013



Average scoring of metrics at principle level

Principles	2011	2013
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	●	●
METHODOLOGY		
4 HTA should incorporate appropriate methods depending on its goal	●	●
5 HTA 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 on an intervention could be most usefully developed in the future	●	●
IMPACT OF HTA		
12 HTA should be timely	●	●
13 P,R&MA 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; Note that in the 2013 assessments four metrics were added two in Methodology and two in impact. These have been excluded to illustrate the changes

3.4. Asia: South Korea, Thailand and Taiwan

South Korea

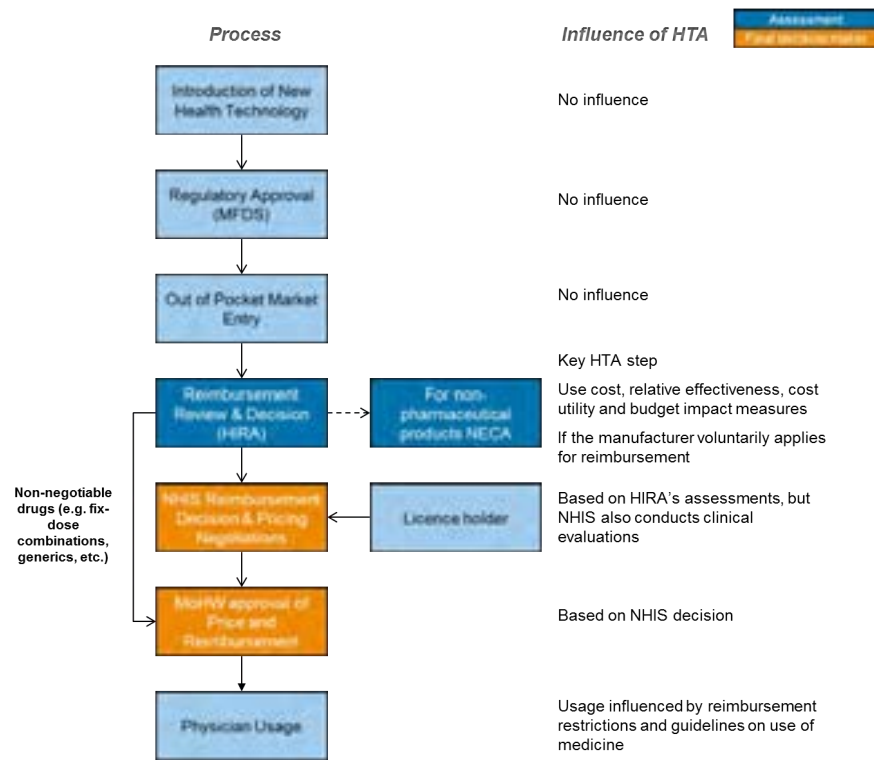
Since 2006, HTA is required to include medicines and medical devices within the South Korean public reimbursement list.¹¹⁷ Health Insurance Review & Assessment Service (HIRA) is in charge of developing the HTA and making reimbursement recommendations to the

117 Bong-min, "HTA under Korea's NHI: Background and Issues", Presentation for Networking Round Table in the ISPOR 4th Asia-Pacific Conference, September 2011.

National Health Insurance Service (NHIS).¹¹⁸ Upon HIRA's assessment results, the NHIS negotiates the price with the pharmaceutical company. There appears to be some duplication in the system, with both NHIS and HIRA undertaking clinical assessments of new medicines.

The President of the Health Insurance Review and Assessment Service (HIRA) reports the assessment results to the Ministry of Health and Welfare (MoHW). After a review by the National Health Insurance Service (NHIS) policy committee, the Minister determines whether the medicines are covered and makes the results public by publishing the final price. The role that HTA has, from regulatory approval to physician usage, is displayed in Figure 33.

Figure 33: The impact of HTA process from regulatory approval to physician usage of pharmaceuticals in South Korea



Source: CRA analysis; Note: MFDS: Ministry of Food and Drug Safety; NECA: National Evidence-based Healthcare Collaborating Agency; HIRA: Health Insurance Review and Assessment Service; NHIS: National Health Insurance Service; MoHW: Ministry of Health and Welfare

118

Note that NECA now undertakes clinical analysis for medical devices and new medical technologies to be included in the positive reimbursement list. This task was removed from HIRA in 2011. The manner in which the two institutions cooperate is not clear, but the Korean HTA system seems to delegate clinical assessment of clinical safety and efficacy for medical devices, diagnostics and medical equipment to NECA and economic assessment and reimbursement decisions to HIRA for all drugs and devices.

The CRA assessment

The main changes observed within the HTA system in South Korea refer to methodological elements as can be seen in Figure 34.

Scope and prioritisation: Since the last report, we found that HIRA has become more transparent. HIRA now offers a pre-submission consulting service where manufacturers receive support to fill in an application. However, the recommendations received by manufacturers from HIRA are not legally binding. In terms of what is reviewed, HIRA focuses only on new medicines and does not develop reviews for old technologies.

Methodology: We found little criticism of the methodology used by HIRA to develop the assessments, although the current pharmacoeconomic guidelines could be made more specific. For instance, there is sometimes uncertainty about the appropriate comparator and this has led to cases where the manufacturer has been forced to change the comparator after submitting their dossiers to the HTA agency.¹¹⁹ Improvements have been noticed in willingness to accept unpublished and non-RCT clinical data, although there remains a clear preference for RCT and the use of non-RCTs needs to be justified in the assessments.¹²⁰

Another element that differs from the 2011 assessment relates to the inclusion of societal benefits within the HTA. However, as in other countries, when looking at the case studies, we did not find any appraisal that included these wider benefits. We found that uncertainty is now considered within the HTA and conditional reimbursement is a common practice. Furthermore, managed entry agreements will be included in January 2014 and will be applied within four major disease areas (stroke, cardiovascular, oncology and rare diseases).¹²¹

Process: Although all stakeholders are invited to contribute to the process, it is not clear how these inputs are taken into account. Furthermore, when looking at the appraisal committee we found that neither industry nor patients play a role in this. An appeal process is now in place, although no appeals were registered in 2012. Regarding the publication of HIRA's decisions, we found that positive recommendations are always available, however, rejections are not always published.

Impact: Clarity regarding the impact of the HTA in the pricing and reimbursement process has also improved. In addition, to a larger number of positive recommendations, the relationship between HIRA recommendations and the Ministry decisions appear clearer. Furthermore, HIRA is now starting to monitor drug diffusion and the utilisation of healthcare resources although the consequences of the analysis are not clear.

Overall, we found that the HTA system in South Korea has improved since the last review. However, there are still areas that could be improved such as clearer guidelines to reduce

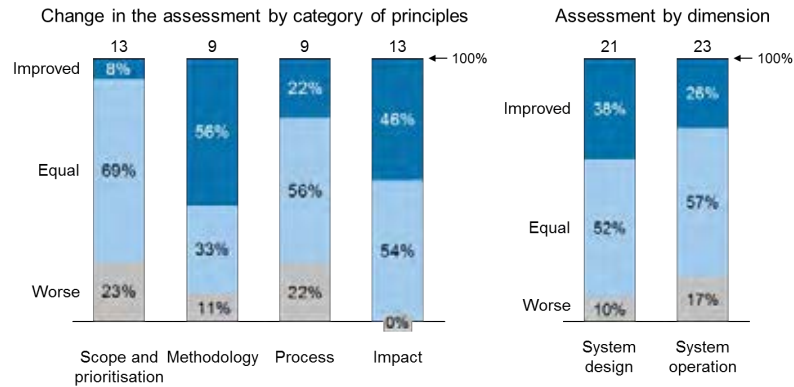
119 CRA interview programme.

120 Ibid.

121 Ibid.

confusion regarding the appropriate comparator and developing a more sophisticated system to oversee the impact of HTA and implement the appropriate changes to improve it.

Figure 34: The CRA assessment of the HTA system in South Korea, 2011 and 2013



Average scoring of metrics at principle level

Principles	2011	2013
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	●	●
METHODOLOGY		
4 HTA should incorporate appropriate methods depending on its goal	●	●
5 HTA 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 on an intervention could be most usefully developed in the future	●	●
IMPACT OF HTA		
12 HTA should be timely	●	●
13 P,R&MA 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; Note that in the 2013 assessments four metrics were added two in Methodology and two in impact. These have been excluded to illustrate the changes

Thailand

Health Intervention and Technology Assessment Programme (HITAP) was established in 2007 as a semi-autonomous, non-profit organisation that reports to the Bureau of Policy and Strategy under the Office of the Permanent Secretary of the Ministry of Public Health.¹²² It is

the only centralised HTA unit in Thailand that assesses devices, pharmaceuticals and health policies.¹²³

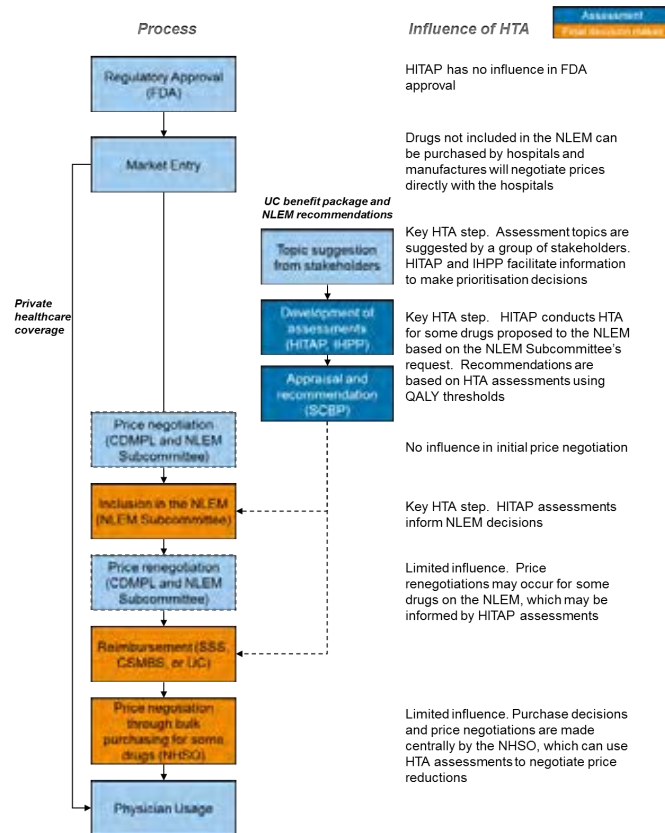
Not all pharmaceuticals or devices are assessed by HITAP. Representatives from a group of stakeholders, including the government, civil society, health professionals, health managers, healthcare insurers, academics, patients and the private sector, annually submit proposals for topics that HITAP should assess to determine coverage for the universal healthcare (UC) benefit package.¹²⁴

As shown in Figure 35, the NLEM (National List of Essential Medicines) subcommittee and the National Health Security Office (NHSO) Subcommittee for the UC benefit package can use HTAs within the price negotiations and decide what to include on the basis of those assessments. However, HITAP assessments inform, rather than dictate, coverage decisions. As such, pharmaceuticals that were not assessed by HITAP or that received a negative recommendation from HITAP may still be included on the NLEM or in the UC benefit package. Additionally, HITAP assessments may be taken into consideration during price renegotiations if an assessment is available. It may also inform price negotiations if the NHSO makes bulk purchases of an assessed drug.

123 For example, the International Health Policy Program (iHPP) evaluates health policies, but not devices and pharmaceuticals. We understand that HITAP works in close collaboration with iHPP.

124 "Health technology assessment process guidelines"; HITAP, 2012. Mohara et al., "Using health technology assessment for informing coverage decisions in Thailand", *Journal of Comparative Effectiveness Research* 1(2), 137-146, 2012.

Figure 35: The impact of HTA process from regulatory approval to physician usage of pharmaceuticals in Thailand



Source: CRA analysis; FDA: Food and Drug Administration; CDMPL: -Committee for Development of the Medicine Price List; SCBP: Subcommittee for the Development of the Benefit Package and Service Delivery; HITAP: Health Intervention and Technology Assessment Program; IHPP: International Health Policy Program; NLEM: National List of Essential Medicines; NHSO: National Health Security Office; SSS: Social Security Scheme; CSMBS: Civil Servant Medical Benefit Scheme; UC: Universal Health Coverage Scheme (THB30 Scheme)

The CRA assessment

As can be seen in Figure 36, the HTA system in Thailand works relatively well compared to the best practice principles. However, there are some areas where there is still room for improvement.

Scope and prioritisation: We observe that HITAP assessments use an unbiased approach and the rationale of the recommendations are clearly stated within the assessments. This has been confirmed not only by HITAP itself but also by industry representatives. Furthermore, HITAP develops assessments for all types of technologies, including both new and old technologies. However, in 2012, 92% of the assessments were conducted for pharmaceutical products, suggesting a greater focus on pharmaceuticals compared to medical devices and

health strategies. All stakeholders are invited to suggest topics to review, although the metrics used to prioritise and select topics are not clearly defined.¹²⁵

Methodology: HITAP defined pharmacoeconomic guidelines which are normally followed. If local data or local RCTs are not available, HITAP will conduct meta-analysis of peer-reviewed papers and RCTs to assess clinical effectiveness.¹²⁶ Guidelines recommend using a societal perspective using publicly-available national data.¹²⁷ The HTA guidelines also recommend conducting sensitivity analyses, such as the probabilistic sensitivity analysis or reporting the mean and standard-errors.¹²⁸ Despite considering uncertainties in the analysis, there does not appear to be the opportunity to use conditional reimbursement.

Process: A wide range of stakeholders are engaged in the topic selection process, and the HTA analysis is usually conducted by HITAP with some stakeholder involvement. However, manufacturers are not involved in developing the HTA. Additionally, there is no systematic reassessment of technologies that have already been assessed to allow for new data to be considered. However, the results of assessments are appropriately communicated and evidence gaps are consistently identified.

Impact: The impact of HTAs is where we have found the largest limitations of the system. HITAP aims to take less than a year to develop their assessments,¹²⁹ but it is difficult to determine whether this goal is achieved. Additionally, the relationship between HITAP recommendations and pricing, reimbursement and market access decisions are not clearly defined, as HITAP recommendations inform rather than dictate results.¹³⁰

125 Lertpitakpong, "A determination of topics for health technology assessment in Thailand: making decision makers involved", *J Med Assoc Thai* 91(2), 2008; Youngkong, "Multicriteria decision analysis for including health interventions in the universal health coverage benefit in Thailand", *Value in Health*, 15, 2012. According to a HITAP representative, the prioritisation metrics that were considered for the 2007 HITAP assessment are no longer used.

126 Teerawattananon and Thavorncharoensap, "Measurement of clinical effects", *J Med Assoc Thai* 91(2), 2008.

127 Riewpaiboon, "Measurement of costs", *J Med Assoc Thai* 91(2), 2008.

128 Limwattananon, "Handling uncertainty of the economic evaluation result: sensitivity analysis", *J Med Assoc Thai* 91(2), 2008.

129 "Health technology assessment process guidelines", HITAP, 2012.

130 For example, pegylate interferon alpha 2a and ribavirin for Hep C was initially not recommended for reimbursement due to its high budgetary impact. However, at the end of 2011 this combined intervention was included in the benefit package because of the lower price due to extensive price negotiation between the MOPH and the pharmaceutical companies. See Youngkong, "Multicriteria decision analysis for including health interventions in the universal health coverage benefit in Thailand", *Value in Health*, 15, 2012. However, this is the exception rather than the norm.

Figure 36: The CRA assessment of the HTA system in Thailand, 2013

Principles	2013
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	●
METHODOLOGY	
4 HTA should incorporate appropriate methods depending on its goal	●
5 HTA 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 on an intervention could be most usefully developed in the future	●
IMPACT OF HTA	
12 HTA should be timely	●
13 P,R&MA 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

Taiwan

HTAs need to be conducted for new medicines that represent a high economic burden if they are to be included in the Drug Benefit and Fee Schedule (DBFS) and reimbursed by the National Health Insurance Programme. HTA is only required for those chemical entities, new administration routes or new fixed-dose combinations approved within five years that have a unit price greater than NT\$10 (US\$ 0.345) and an estimated annual expenditure exceeding NT\$100M (US\$ 3.45M).¹³¹

As shown in Figure 37, upon market authorisation, the manufacturer makes the submission to the National Health Insurance Administration (NHIA). Previously, the HTA was a two-step process, where the Centre for Drug Evaluation (CDE) performed the technical review and the Drug Benefit Committee (under the BNHI)¹³² made the final decision. However, this has been recently reformed by the Second Generation National Health Insurance Act.¹³³

131 Ming-Chin Yang, "Current applications of HTA in the National Health Insurance system in Taiwan", Presentation given during the PhRMA Asia Pacific HTA workshop, Hong Kong, 14-15 November, 2013.

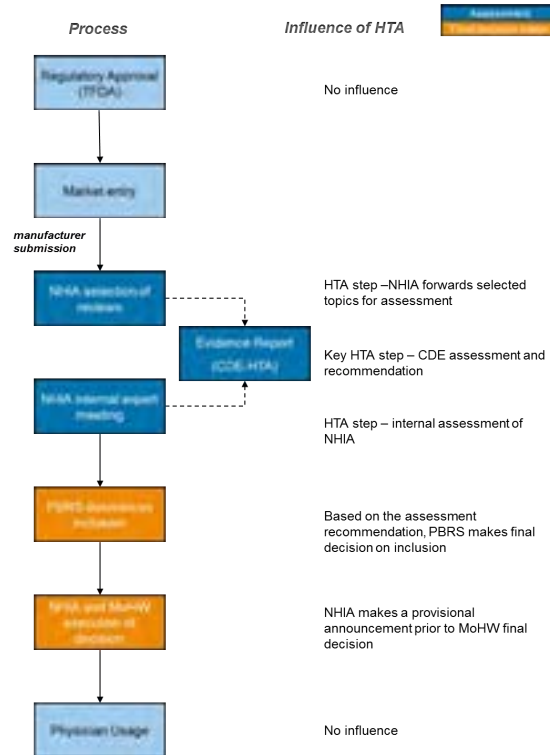
132 Bureau for National Health Insurance (BNHI) is now named National Health Insurance Administration (NHIA) and is the responsible agency for health and insurance planning and implementation under the Ministry of Health and Welfare.

133 "NHI 2012-2013 Annual Report", National Health Insurance Taiwan, 2013. Available here: http://www.nhi.gov.tw/Resource/webdata/13767_1_NHI_2012-2013%20ANNUAL%20REPORT.pdf.

Under the new system, the NHIA receives the manufacturer's submission and forwards selected topics for assessment to the HTA division of CDE. The latter is responsible for developing the HTAs using evidence from three international agencies (NICE, PBAC and CADTH). The approach of using evidence from other countries (rather than full assessments) was chosen because data specific to Taiwan is rarely available, which makes this approach a more resource efficient process.¹³⁴ The agency takes a clinical effectiveness and budget impact analysis approach and on that basis makes reimbursement recommendations to the NHIA, which subsequently reviews the submissions through an internal expert group meeting and makes the reimbursement and pricing recommendations.

Recommendations are then discussed at the newly established Pharmaceutical Benefit and Reimbursement Scheme (PBRS) committee, which makes a final decision on reimbursement, indications and price. The PBRS is composed of various stakeholders and it represents a first step towards a more extensive involvement of stakeholders in the decision-making process, but is still at very early stages. The PBRS is composed of representatives from the insurer, government agencies, experts, academics, employers, medical and manufacturers. Patient groups may be invited to comment in principle but, until now, no patient groups have yet been invited. The decisions on reimbursement and price are executed by the NHIA and formally announced by the Ministry of Health and Welfare (MoHW) once a year.

Figure 37: The impact of HTA process from regulatory approval to physician usage of pharmaceuticals in Taiwan



Source: CRA analysis; Note: TFDA: Taiwan Food and Drug Administration; NHIA: National Health Institute Administration; CDE-HTA: Centre for Drug Evaluation – Health Technology Assessment; PBRB: Pharmaceutical Benefit and Reimbursement Scheme; MoHW: Ministry of Health and Welfare

The CRA assessment

Since the creation of the HTA system in Taiwan considerable changes have taken place. In particular, there have been efforts to improve transparency and the involvement of different stakeholders. However, as can be seen Figure 38, there are a number of areas where there could be improvements in order to meet best practice principles.

Scope and prioritisation: There are a number of challenges in terms of scope and prioritisation. The fact that only new pharmaceutical products are reviewed limits the scope of HTA. However, old products could be reassessed if manufacturers request a reassessment (for example, if the drug could be used earlier in the treatment pathway). However, we understand this has not occurred.

Methodology: In terms of the methods used, the Taiwanese system performs poorly as it rates as amber and red against best practice principles. HTA uses a clinical effectiveness approach, but this is not uniform on all assessments as it depends on data availability. The cost analysis is based on international comparisons and health insurance expenditure but this varies depending on the particular assessment. Further limitations concern the data considered and the absence of a societal perspective in the analysis. The system does not have any requirements on how to deal with uncertainty and conditional reimbursements are

done on an irregular basis. The limitations in the methodology partly reflect that local data is rarely available. The government is working to encourage the development of local clinical trials, as premiums are given to those drugs for which local R&D and clinical trials are provided. An additional premium is given for those manufacturers that provide a pharmacoeconomic analysis.¹³⁵

Process: Although improvement has been observed, there are still limitations in the process, as the HTA agency does not engage with key stakeholder groups at all stages. In addition, there is no official appeals process involving an independent institution. However, there is public and detailed information available regarding the decisions taken. An interesting characteristic of the Taiwanese system is the public provision of recordings of the appraisal committee meeting, which further clarifies rationale for decisions.

Impact: HTA in Taiwan is considered timely with the CDE assessment taking no longer than 42 days and allowing an extra seven days for manufacturer comments. The NHIA and PBRs stages can extend this up to three months, but these stages are not always consecutively followed, which may cause delays. An assessment only starts when the NHIA requests the CDE to initiate the evaluation and this can act as a bottleneck when requests are not forwarded in a timely manner. There is an uncertain impact of the assessments on the reimbursement decisions, as there have been a number of cases when a medicine has been recommended for inclusion on the positive list, but then was not included.

Figure 38: The CRA assessment of the HTA system in Taiwan, 2013

Principles		2013
SCOPE AND PRIORITISATION		
1	HTA should be an unbiased and transparent exercise	Yellow
2	HTA should include all relevant technologies	Yellow
3	A clear system for setting priorities for HTA should exist and the costs of HTA should be proportionate	Yellow
METHODOLOGY		
4	HTA should incorporate appropriate methods depending on its goal	Yellow
5	HTA should consider a wide range of evidence and outcomes	Yellow
6	A full societal perspective should be considered when undertaking HTAs	Red
7	HTAs should explicitly characterise uncertainty surrounding estimates	Yellow
PROCESS		
8	Those conducting HTAs should actively engage all key stakeholder groups	Yellow
9	HTA findings need to be communicated appropriately to different decision makers	Green
10	Evaluations should allow new data to be considered	Yellow
11	HTA should identify areas in which the evidence on an intervention could be most usefully developed in the future	Red
IMPACT OF HTA		
12	HTA should be timely	Yellow
13	P,R&MA should reflect the HTA assessment in a transparent, clearly defined way and be implemented as intended	Yellow
14	The impact of HTA findings and how they are used needs to be monitored	Red

Source: CRA analysis

3.5. Africa: South Africa

Even though there has been a long-standing policy debate since the late 90s, HTA in South Africa is still at a very early stage of development. In 1997, the South African National Department of Health (DoH) published a policy paper on HTA, where the benefits of using HTA were discussed.¹³⁶

It is important to distinguish between the public and the private sector. Currently, only two universities in the country offer formal HTA programmes and there is no national HTA body. As such, HTAs are not formally required to include medicines within the National List of Essential Medicines. However, there have been cases where pharmacoeconomic evidence has been used within the selection process. An example is the selection of capecitabine for the treatment of metastatic colorectal cancer, which led to the treatment being approved by the NEMLC in 2012.¹³⁷

The use of HTA is more developed within the private sector, as each medical scheme can use evidence-based medicine, cost-effectiveness and affordability to decide what to include within its own formulary. These need to be consistent with the prescribed minimum benefits (PMB) set by the government. In order to standardise the HTA process in South Africa's private sector, the DoH published health economic guidelines in December 2012. However, the use of HTA within the private market is not mandatory. Figure 39 shows the difference on the use of HTA within the public and private market in South Africa.

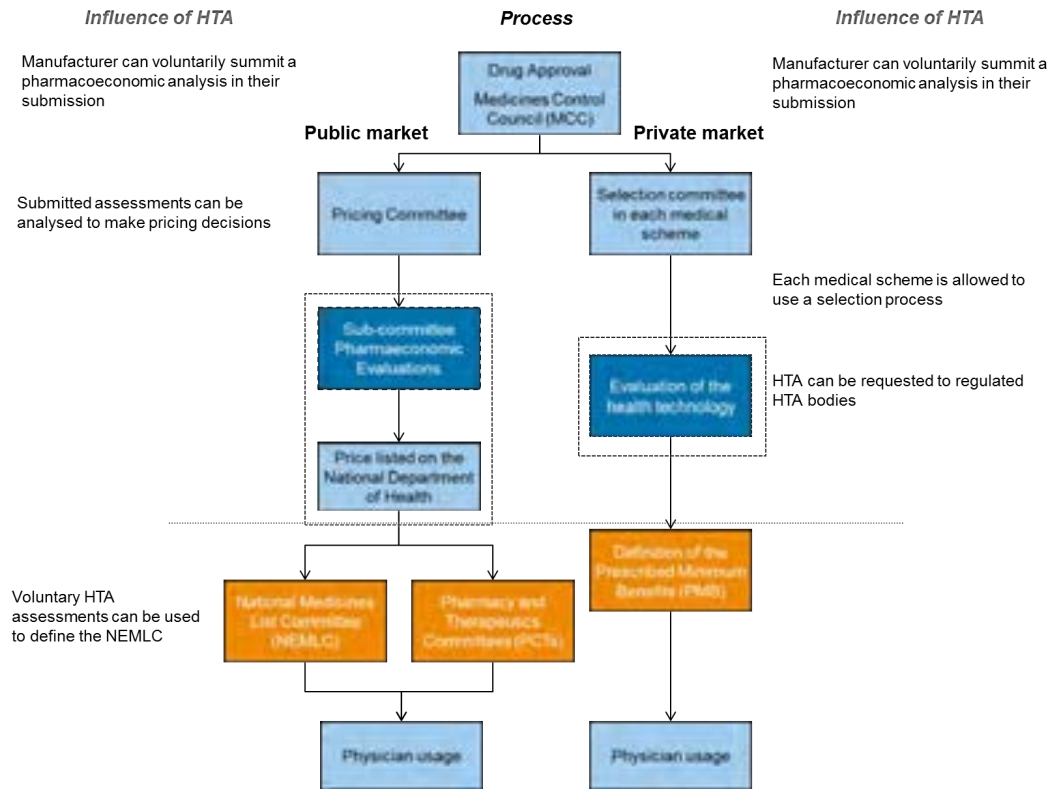
It is envisaged that a centralised process for HTA will be required as South Africa moves towards the introduction of a National Health Insurance (NHI) system. The Human Resources for Health South Africa strategy paper indicates that a "NDoH National Coordinating Centre for Clinical Excellence in Health and Health Care will be established".¹³⁸ However, as of writing this report, there has been relatively little progress in the application of a national HTA.

136 Tekletsion, "A review of 'Health care technology assessment – the South African health care system in transition' transition" by Ogembo and Boozaier", 2000. Available here: <http://www.africantechologyforum.org/HCTAinSA.htm>.

137 Gray, et al., "South African Health Review 2012/13", Health Systems Trust, 2013. However, even in this case the process for undertaking the assessment is unclear.

138 "Human Resources for Health South Africa: Strategy for the health sector 2012/13-2016/17", National Department of Health, 2011.

Figure 39: The impact of HTA process from regulatory approval to physician usage of pharmaceuticals in South Africa



Source: CRA analysis; Note: MCC: Medicines Control Council; NEMLC: National Essential Medicines List Committee; PMB: Prescribed Minimum Benefits; PCT: Pharmacy and Therapeutics Committees

The CRA assessment

In reality, although much has been written about the development of HTA in South Africa, there is no formal HTA process in the public sector (the focus of this report). We cannot therefore assess the scope and prioritisation, process or impact of HTA today.

Assuming the public sector follows the Department of Health guidelines, we can undertake a high-level review of the methodology.

Methodology: There are some areas where South Africa would perform well according to best practice principles. There is a willingness to use appropriate methods at least at the academic level. Indeed, when assessments are developed the selection of the comparator is clear, a wide range of evidence is used and uncertainty is clearly explicit. However, there is no evidence of this being used in practice, so any assessment is premature.

In terms of the HTA, it is too early to undertake an assessment of this kind in South Africa, but this should be included in future updates to this report.

Figure 40: The CRA assessment of pharmacoeconomic guidelines published by the Department of Health, 2013

Principles	2013
METHODOLOGY	
4 HTA should incorporate appropriate methods depending on its goal	
- The approach used in HTA is clearly stated	●
- Methods are deemed appropriate by experts (from literature)	NA
- Clarity of selection method of comparator	●
- The selection criteria is reflected in the assessments	NA
5 HTA should consider a wide range of evidence and outcomes	
- HTA considers unpublished trial data	●
- HTA considers data not from RCTs	●
6 A full societal perspective should be considered when undertaking HTAs	
- 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	NA
7 HTAs should explicitly characterise uncertainty surrounding estimates	
- Uncertainty regarding decisions is explicit	●
- Existence of conditional reimbursement to facilitate access (risk-sharing/access with evidence development).	●
- Schemes are used in practice	NA

Source: CRA analysis

3.6. Overall assessment of changes since 2011

Figure 41 summarises the aggregate changes that have occurred since the 2011 report. Most systems have undergone incremental change with the majority of metrics assessed as performing at the same level as in the CRA 2011 report. Indeed, almost 70% of the 43 metrics analysed in the 2011 and 2013 assessments received the same score in both years.

However, there are some exceptions where significant change has occurred. This is the case for Brazil, Germany and Poland and is reflected in the updated CRA assessments. In other countries, like France and South Korea, where the reforms introduced have been more evolutionary, the CRA assessment remained more stable. Overall, we conclude that even though there is a trend to move towards best practice principles, there is room for improvement in some areas in all the studied markets. To follow, we consider the overall trends by category.

Scope and prioritisation: In general, in terms of scope and prioritisation of HTA systems, the picture remains quite similar to the 2011 report. Most of the metrics assessed received the same scoring. Transparency has improved in a number of countries (France, Germany, Sweden, South Korea, Thailand and Taiwan). However, we found that the rationale for undertaking reviews remains unclear in many markets (Mexico, Brazil or Poland are examples of this). In addition, we have introduced new countries into the assessment that do not perform well on this metric. A number of the HTA systems only review new pharmaceutical products.

Methodology: As in the 2011 report, we found that most of the studied countries have guidelines to help pharmaceutical companies develop their assessments. We found, at least on paper, an increase in the number of countries that include societal elements (for example,

in South Korea, Taiwan, Mexico). However, the countries where we can find evidence that this is included in the assessments remain small. In fact we only have evidence that the Netherlands, Sweden and Poland include societal aspects. We observed an increase in the use of MEAs although, in general, these are mainly applied to deal with financial restrictions rather than uncertainty (England, Scotland or Australia).

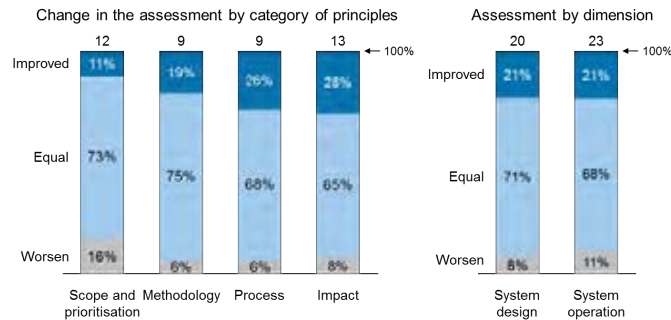
Process: We have observed improvement in 26% of the metrics associated to the HTA process. Most of the improvement is linked to a more inclusive process regarding the number of stakeholders involved within the process. This is a trend that has been observed in the Netherlands, Poland and Sweden, for example. Also, some countries have become more transparent in the way results are communicated to the public. Brazil, for example, significantly improved since the creation of CONITEC. This is illustrated by the number of assessments that we were able to review in this update. However, there are still countries, like Mexico or Italy, which do not have wide stakeholder participation and where the rationale behind the conclusions remains opaque.

Impact: As with process, significant improvement has been observed with the metrics to assess the impact of HTA, however this is mainly linked to more timely implementation processes (for example, in Germany, France or Brazil). Additionally, we have observed a greater commitment, at least in principle, to monitor the impact of HTA. However, in practice only a few countries have developed ways of doing this (Canada and England). In other areas, there are still significant concerns, particularly, the link between price, reimbursement, market access and HTAs is still not clear in some of the markets analysed.

As in the previous assessment, the way HTA is used constantly evolves. We identified changes in all of the markets covered by both reports. There are significant changes in some of the HTA systems expected in the future. These are not yet incorporated in the assessments, but were highlighted in the discussions. Examples include:

- In England, value based assessment is expected to be introduced in the Autumn of 2014. This should incorporate in a more formal way wider societal value and unmet needs within the HTA process.
- In France, a country where HTA was focused primarily on relative effectiveness, the CEESP, a commission created in 2008 to carry cost-effectiveness studies, has been given a greater role and since October 2013 is tasked with supplying the CEPS with product-by-product, cost-effectiveness assessments as well as providing HAS opinions on the most efficient strategies for products which demonstrate significant added value (ASMR of I-III). Although this is included in the assessment above, this has not affected the case studies.
- The Netherlands has created a separate committee to assess societal benefits. This suggests that greater focus will be given to wider social benefits within the Dutch HTA system in the future.

Figure 41: The CRA assessment of the HTA systems in selected countries, 2011 and 2013 comparison



Average scoring of metrics at principle level

Principles	2011	2013
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	●	●
METHODOLOGY		
4 HTA should incorporate appropriate methods depending on its goal	●	●
5 HTA 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 OF HTA		
12 HTA should be timely	●	●
13 P,R&MA 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; Note that for the change in the assessment only countries included the 2011 and 2013 reports have been included. For the average scoring, South Africa was removed as HTA is still in an early stage of development

For countries included for the first time, we found that the assessment varies depending on the maturity of the HTA system. Taiwan, Thailand and Mexico clearly have more developed systems than South Africa, which has not developed a formal HTA system. However, we found all these countries could improve the process for including different stakeholders into the decision making. The impact of HTA was the area where the assessment for these countries was weakest.

4. Lessons from the 2013 assessment

Drawing on the updated literature review, the country assessments and the analysis of the 19 case studies included in the CRA assessment, it is useful to return to some of the themes identified in the 2011 report. In this chapter, we consider whether the conclusions regarding scope and priorities, methodology, process and the impact of HTA have changed. We also consider some of the new areas included in the updated assessment.

4.1. Scope and prioritisation

Looking first at issues associated with the scope and priorities of HTA in each country, we examined whether the bodies conducting HTA are transparent and unbiased, whether they cover all potential technologies and how they prioritise their efforts. We identified several trends:

Incremental improvement in the level of independence of HTA bodies

We found that in some countries there has been an effort to make the HTA agency more independent to increase the credibility of the assessments and recommendations. In some cases, this was achieved by changing the status of the HTA agency. In England, for example, NICE has been given a non-departmental government body (NDGB) status which means that they have operational independence from the government. This represented an improvement from the 2011 assessment.¹³⁹ Willingness to increase the independence of the HTA agencies undertaking the assessment was also observed in some emerging economies. In Taiwan, for instance, the CDE, the agency in charge of developing the HTAs, is a non-governmental, not-for-profit external organisation.

However, this is not a global trend. There are still countries without institutional independence or where the process does not distinguish between the assessment (where independence is vital to ensure that all stakeholders can contribute to the process) and the appraisal. This is the case of Mexico where both the assessments and the appraisals are undertaken by the CSG.

The focus of the reviews are still pharmaceutical products but interest in the application of HTA to different technology assessments can be observed

In total, across all 16 countries, we found that 78% of the technologies reviewed were pharmaceutical products. As demonstrated in Figure 42, for the 12 countries that are being reassessed, pharmaceutical products represented 75%, nine points more than the assessments undertaken in 2009.

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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. House of Commons Health Committee Report on NICE, 2007.

Although the proportion of non-pharmaceutical reviews has experienced a slight reduction since the 2011 report, in 2013, 12 of the 16 studied countries include other health technologies in their reviews. Interest in reviewing other health technologies is increasing. This is the case in Scotland where Healthcare Improvement Scotland (HIS) is taking a more active role in reviewing other medical technologies.¹⁴⁰ Within the last couple of years, medical technologies as well as treatment strategies have been assessed by the SHGT (Scottish Health Technologies Group).

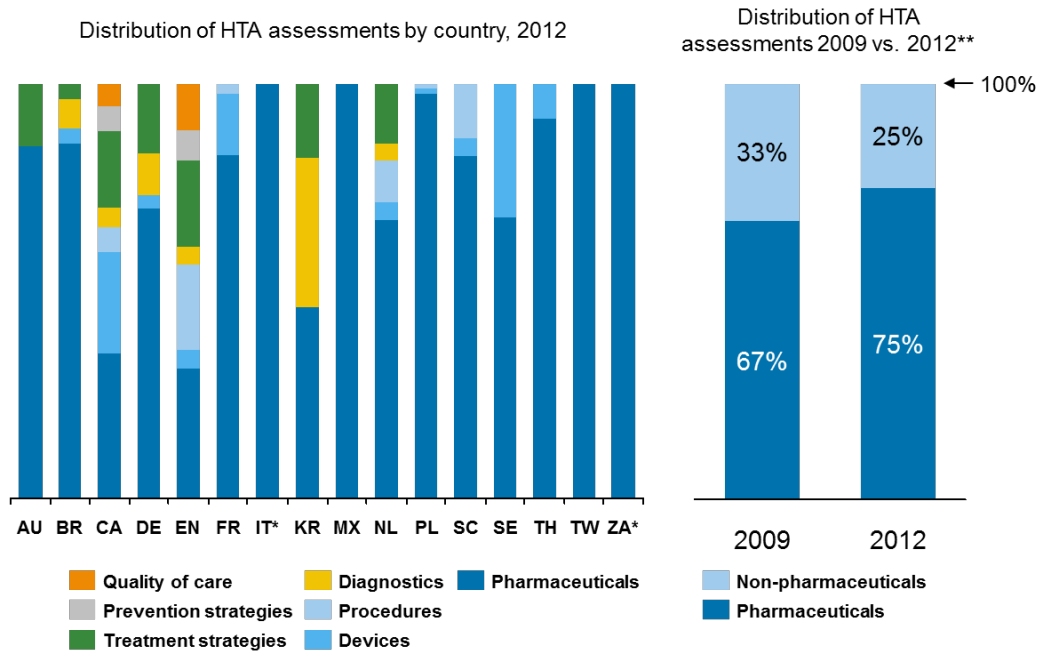
In many cases where non-pharmaceutical products are reviewed, these are developed by a different body than the one in charge of developing pharmaceutical assessments. For instance, in Australia PBAC undertakes pharmaceutical reviews, while the Medical Services Advisory Committee reviews medical devices. In South Korea, HIRA is in charge of reviewing drugs while NECA reviews medical devices and treatment strategies. Although, different agencies taking responsibility for different technologies is not of concern, the way non-pharmaceutical technologies are reviewed can be, as these are not always subject to the same approach. In Poland, for example, only pharmaceutical products are subjected to strict assessment guidelines whereas medical devices are not. For instance, there are no time constraints on the review of medical devices, which means that these tend to be pushed at the end of the review list.¹⁴¹ Greater consistency or an explanation as to why the process varies is needed.

It is worth noting that in systems that have implemented formal HTA processes more recently, the main focus has been the review of pharmaceutical products. In Taiwan, for example, the CDE only reviews pharmaceutical products. In theory, the Medical Device Experts Committee can request an evaluation of non-pharmaceutical products but up to December 2013, this was not observed in practice. Similarly, the CSG in Mexico is meant to be looking at all type of health technologies, although in 2012 they only reviewed pharmaceuticals. That said, in some markets, emerging HTA agencies have reviewed different types of technology, even though these represent a small fraction of the number of appraisals. This is the case in Thailand or Brazil.

140 CRA interview programme.

141 Ibid.

Figure 42: Distribution of HTAs by type of technology, 2012



Source: CRA analysis; *Note: Data on 2012 assessments in Italy and South Africa are not published but it was confirmed in interviewees with the agencies and industry that only pharmaceutical assessments were conducted; ** The 2009-2012 comparison only includes those markets that were also included in the 2011 report

We conclude that many HTA processes still appear to be too focused on assessing pharmaceuticals at the expense of a wider consideration of medical technologies or different health strategies. This is particularly relevant for markets with emerging HTA systems.

HTA processes are still applied primarily to new products

According to best practice principles, HTA can be usefully employed to assess new technologies and reassess them over time to allow for new information and changing market conditions. As can be seen in Figure 43, we found that in 2012 there were slightly less first time reviews, in comparison with what we found for 2009 assessments analysed. (The distinction between non-first time assessments that are resubmissions, after a medicine has been rejected and re-evaluations are discussed in Section 4.3).

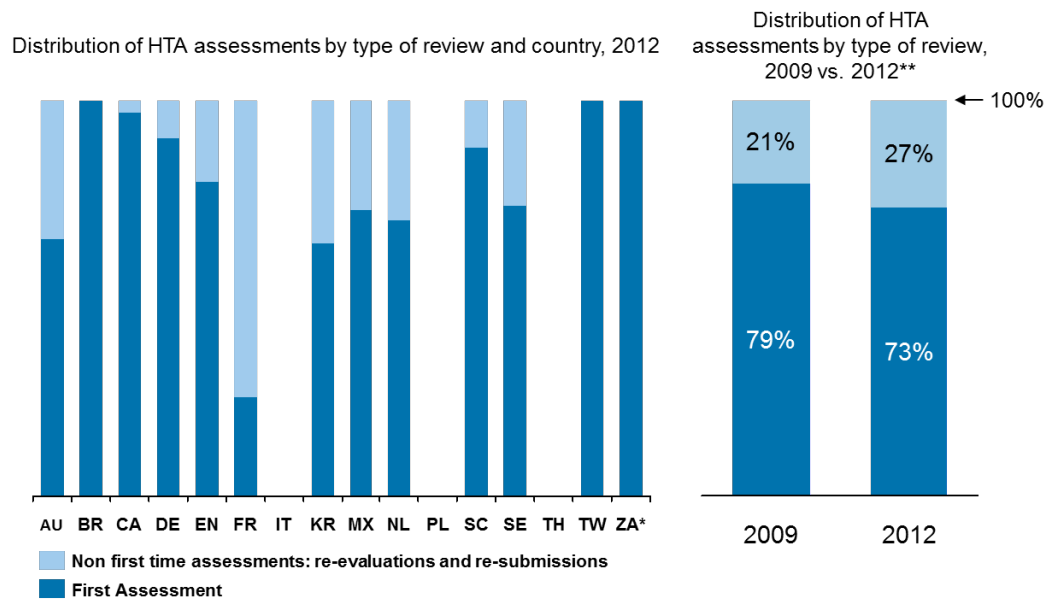
Overall, looking at the mandate of the HTA agencies, the majority are tasked with reviewing new medicines rather than looking at both old and new technologies. For example, after the implementation of the AMNOG in Germany, only new drugs are assessed. Similarly in Scotland, the SMC only looks at new pharmaceuticals.

In some emerging HTA systems, the selection criteria of what can be submitted for review is less clear. In these countries, old technologies could be reviewed if requested by the Ministry of Health. This is the case of Taiwan and Brazil. However, we found no evidence that the MoH has requested the review of old technologies. Based on the interviews both countries remain focused on the assessment of new medicines.

Even where the HTA process technically includes new and old technologies, we find that the majority of the assessments are for new technologies. Sweden, for example, has a process in place to assess old technologies,¹⁴² but in 2012 more than 70% of the reviews were first time assessments.

As discussed in the last report, this is a good example of how the best practice principles need to be interpreted with significant care. In many countries, there is considerable pressure to undertake the reviews quickly. This means that the agencies prioritise the review of new technologies.

Figure 43: Distribution of assessments by type, country and year



Source: CRA analysis; Note: *Only one assessment was available for South Africa; ** The 2009-2012 comparison only includes those markets that were also included in the 2011 report

The budget of HTA agencies is publicly available in developed HTA systems

In terms of resources, in 2011 we were concerned with how few agencies were aware of their own costs. Without understanding the cost they impose, it is difficult to assess whether the current HTA process imposes too significant a regulatory burden. Awareness of the cost of the HTA process (at least in terms of the cost of the HTA agency itself) has improved in the 2013 assessment. As Table 5 shows, information on the budget of HTA agencies was found for the majority of countries.

In general, we found that the budget of the HTA agency tends to be publicly available for those mature agencies, with agencies like NICE, TLV, CADTH or HAS publishing accurate

information. The information was more limited within emerging economies such as Brazil, Mexico or South Africa.

However, in some cases the agencies are responsible for a range of tasks, beyond the development of technology appraisals, thus differentiating between the HTA activities and other tasks is sometimes a challenge. In Germany, for instance, the G-BA budget comprises a large number of activities. The same applies to HIRA in South Korea.

However, we conclude that overall there is greater awareness of the direct costs of the HTA process (although cost incurred by other stakeholders received limited attention).

Table 5: The cost of HTA agencies

Country	Annual cost of HTA agencies
Australia	€6.1M (revenue generated by PBS)*
Brazil	No data available
Canada	€16.6M (CADTH), of which €3.5M on CDR
England	€71.7M (NICE) of which €10.5M in health technology evaluation
France	€62.2M (HAS) of which €2.6M in pharmaceutical evaluation
Germany	€30M (includes all G-BA activities)
Italy	No data available
Mexico	No data available**
Netherlands	€54.1M (CVZ) of which €2.3M in research programmes
Poland	€4.5M (AOTM)
Scotland	€1.21M (SMC)
South Africa	No data available
South Korea	€131M (includes all HIRA activities)
Sweden	€4.1M (TLV)
Taiwan	€0.6M (CDE)
Thailand	€0.74M (HITAP)

Source: CRA analysis from different sources; ¹⁴³ Note: *The PBS provides the “cost recovery” which includes the revenue generated by the PBS through submissions, no evidence on the total budget is available; **The CSG budget could be requested to the Ministry of Health but the interviewee was not aware of the total costs

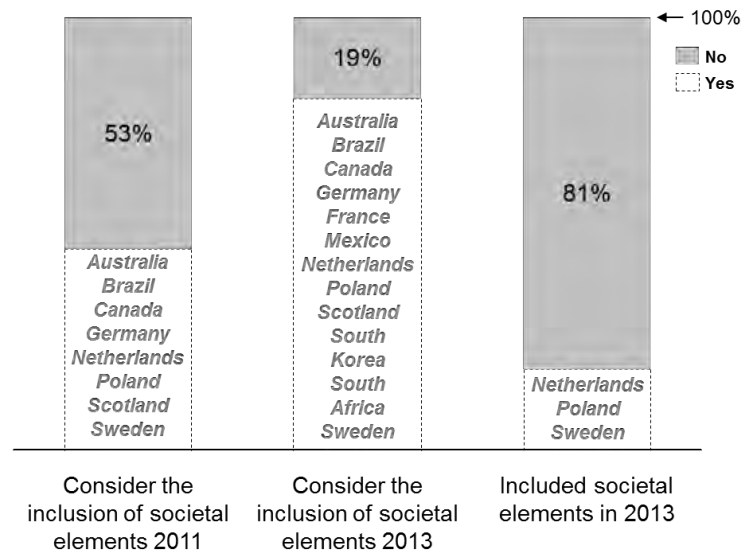
4.2. Methodology

Turning to the HTA methodology, our assessment focuses on whether the HTA agency is using a methodology that is consistent with the role of the HTA process in that country. Several trends have been identified:

Increasing interest in including a full assessment of societal value

At least on paper, many markets have chosen to recommend the inclusion of societal elements in the assessments. In the CRA 2011 report we found that less than a half of the countries included stated that they took some form of societal costs into account. In the 2013 report, 80% of the markets studied take societal elements into consideration. However, when looking at the case studies, only the Netherlands, Poland and Sweden include societal elements in the assessments. This is illustrated in Figure 44.

Figure 44: Inclusion of societal elements among the studied countries, 2011 vs. 2013



Source: CRA analysis

The Swedish HTA system has always been associated with a broad assessment of value and the inclusion of societal elements, so it was not surprising to see that in the 2013 guidelines explicitly mention the inclusion of indirect cost and some case studies included societal

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The majority of information is taken from public sources, either from the HTA agencies’ annual report or from academic papers. For Germany, Poland, Scotland, Taiwan and Thailand the information was collected during the interviews with HTA representatives.

elements. However, even in Sweden, it is still not clear what effect inclusion of indirect costs has in the decision-making process. Looking at the case studies, in four out of 15 assessments, indirect costs such as absenteeism or indirect social cost are mentioned. Of these, one was accepted without restrictions, one was rejected and two are still under review. As such, the effect of including indirect costs remains unclear.

The interest in including wider societal elements is also noticeable in the Netherlands. The CVZ not only recommends its inclusion in their pharmacoeconomic guidelines, but gives greater attention to societal elements when cost-effectiveness cannot be proven. In 2012, the Social Advisory Committee was created to assess the societal benefits of all drugs that are deemed to have therapeutic value but are not shown to be cost effective. Looking at the case studies, six of the 17 assessments highlighted the value of societal benefits.

Poland seems to be following the lead of Sweden and the Netherlands by suggesting the inclusion of some societal benefits under certain conditions. Indirect costs can be included when other members of the society (e.g. family, guardians) are also affected to a considerable extent. The inclusion of indirect costs needs to be justified by the manufacturer within the dossier submission. In reality only two of the 17 molecules analysed actually included societal aspects in their assessments. Once again, it is not clear how that particular piece of information is reflected in the decision, as both were approved with major restrictions.

Within our database we found that the molecules, for which societal elements were included in the assessments, differ across countries. Of the three countries with evidence, we found social elements to be included when assessing oncology treatments (four out of six in Netherlands and one out of two in Sweden) and a multiple sclerosis treatment (in Poland and the Netherlands).

It is worth taking into consideration that HTA agencies have designed mechanisms to account for non-cost elements. NICE, for example, considers other decision-making criteria as well as cost-effectiveness under what is called “special circumstances”. These aim to reflect societal preferences based on the views of the Institute’s Citizens Council. Recent evidence shows that more positive recommendations have been given to some products with incremental cost-effectiveness above the £30,000 threshold in the following cases:¹⁴⁴

- Severity of underlying illness: more generous consideration is given to the acceptability of an ICER in serious conditions, reflecting society’s priorities;
- Stakeholder insights: Insights provided by stakeholders (e.g. on the adequacy of measures used in trials to reflect symptoms and quality of life);

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Rawlins, et al., “Pharmacoeconomics: NICE’s approach to decision-making”, *British Journal of Clinical Pharmacology*, 70,3, 2010.; See Dakin et al., “The influence of cost-effectiveness and other factors on NICE decisions”, CHE Research Paper 93, 2013, for an empirical model on elements influencing NICE decisions. The authors found that 82% of the recommendations could be predicted using cost-effectiveness analysis and that other variables were mostly non-significant and lead to small variations in the predictions.

- End of life treatments: this is intended to reflect that the general public values treatments that prolong life at the end, providing that life is of reasonable quality;
- Disadvantaged populations: special priority is given to improving the health of the most disadvantaged members of the population; and
- Children: given methodological challenges in assessing quality of life in children, society would prefer to give “the benefit of the doubt”.

How to incorporate wider assessments of value within NICE methodology is still under discussion. In March 2014 NICE set out the proposed methodology for value based assessment in a consultation document. This proposed two main additions to the appraisal methods. Firstly, a more systematic and explicit consideration of the ‘burden of illness’ replacing the ‘end of life treatments protocol’ and, secondly, consideration of ‘wider societal impact’.¹⁴⁵ The final decision regarding these changes to the methodology has not been announced.

The SMC uses a similar approach to NICE. They refer to these as modifiers. A higher cost per QALY may be accepted under particular circumstances either due to the clinical benefits of the new molecule or due to other special issues which can be highlighted by the manufacturer, clinical experts and/or patient groups.¹⁴⁶

In other markets, the inclusion of societal elements is only in the recommended guidelines, with little evidence in the assessments. HIRA, in South Korea, recommends inclusion of indirect costs and other benefits in the assessments. However, it is not clear how this is used in practice. In reviewing the case studies, we did not find any evidence on the inclusion of indirect costs or other societal elements, a fact that was supported by the experts interviewed.

In 2011, although a number of agencies included a societal perspective in their guidelines, we found little evidence of this being included in the assessment. In this update, societal issues are much more visible although the impact on the decision is still hard to determine.

Explicit recognition of the uncertainty in the assessments is a growing trend

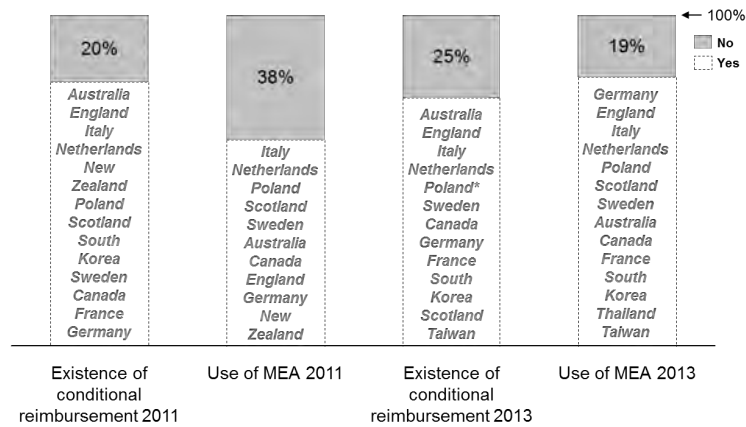
In the 2011 report, CRA observed that more attention was being given to uncertainty in the assessment of a new therapy at the time of assessment. The 2013 report confirms that countries recognise the problem of uncertainty and are starting to implement solutions.

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- 145 “Value based assessment methods consultation document”, NICE Methods of Technology Appraisal Consultation, 26 March 2014. Available here: http://www.nice.org.uk/getinvolved/currentniceconsultations/MethodsOfTechnologyAppraisalConsultation2014.jsp?do_media=1&mid=FE20429F-FA31-FE7B-0F83F51F35753970.
- 146 “SMC modifiers used in appraising new medicines”, SMC, 2012. Available here: https://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/SMC_Modifiers_used_in_Appraising_New_Medicines.

We observed an increase in use of MEAs as an operational tool to deal with the uncertainty of the assessments. There are different types of MEA and some clearly reflect a commercial negotiation rather than managing risk or encouraging the revelation of new information. In some countries there is a clear trend toward using MEAs that are focused on confidential discounts rather than managing uncertainty.

As reflected in Figure 45, the number of countries using some form of MEA in 2013 increased from 62% in the initial Comparison report to 81%. However, it is worth noting that the number of countries where conditional reimbursement existed stayed roughly the same (12 countries in both years).

Figure 45: Existence of conditional reimbursement and use of MEA, 2011 vs. 2013



Source: CRA analysis; Note: *In Poland there was a disagreement between the industry association and the AOTM regarding the use of MEAs

In England, for example, the number of Patient Access Schemes (PAS) has increased since the last assessment. In 2012 eight PAS were agreed, this compares to five that were agreed in 2009. In Australia, Managed Entry Schemes (MES) are also used although only in five of the 123 recommendations given in 2012.¹⁴⁷

In Sweden, TLV can reimburse on the condition of follow-up assessment within a certain period of time. This is referred to as Coverage with Evidence Development (CED), which allow for reimbursement conditional on additional data submission in within a specified timeframe. However, we found a limited use of these practices as only one of the 15 case studies reviewed for Sweden used a CED.¹⁴⁸

147 This is consistent with the recent reports on the use of MEAs. See for example, Ferrairo and Kanavos, “Managed entry agreements for pharmaceuticals: the European experience”, LSE discussion paper, June 2013.

148 Note that CEDs are also used in the Netherlands for selected, expensive hospital medicines.

Alternatively, other systems choose to provide immediate reimbursement for hospital drugs and, if appropriate, submit them to HTA revision after launch. This is the case in the Netherlands where hospital drugs receive immediate reimbursement and the CVZ may assess them later on. The problem here is that a drug receives reimbursement through this process could be removed from the market if the HTA decides that the drug is not cost effective.¹⁴⁹ A similar approach is used in Australia where some high cost medicines that require hospital administration are not assessed by PBAC but are directly reimbursed at the hospital level. Countries that do not currently use MEAs expressed interest in using it in the future.

Although the comparator is mostly based on standard treatment therapy, in some countries there is a preference for using the lowest cost medicine

Most countries agree that the comparator to assess a new technology should be the standard of care. In some cases, like in the Netherlands, the comparator could be a non-medicinal treatment if it was relevant. We have found this to be the case across all the countries included in the analysis. From an economic perspective, the standard of care is the appropriate comparator as this is what will be substituted by the new technology.

However, in some cases we found that the guidelines specify that the cheapest option within the standard of care should be the selected molecule (even if not commonly used). This is the case in Canada, Germany or Thailand, for example, as reflected in Figure 46. In other cases, guidelines can be ambiguous creating confusion among stakeholders. For instance, HIRA allows the inclusion of three substitutable products without specifying which one is preferred.¹⁵⁰ There have been cases where the manufacturer was forced to change the comparator after submitting their dossiers to the HTA agency.¹⁵¹

Figure 46: Definition of comparator suggested in published guidelines

<i>Australia</i>		
<i>Brazil</i>		
<i>France</i>		
<i>Germany</i>		
<i>Mexico</i>		
<i>Netherlands</i>	<i>Canada</i>	
<i>Poland</i>	<i>England</i>	
<i>Scotland</i>	<i>South</i>	
<i>South</i>	<i>Africa</i>	
<i>Korea</i>	<i>Sweden</i>	
	<i>Thailand</i>	<i>Taiwan</i>
Standard of care	Standard of care - low cost preference	Other

Source: CRA analysis

149 CRA interview programme.

150 HIRA website.

151 CRA interview programme.

How the comparator is chosen varies across countries. In England, for example, the comparator will be chosen by the NICE during scoping phase; in Germany the G-BA will provide a list to the manufacturer with available options;¹⁵² in Brazil or Mexico the comparator is determined by what is already included in the national reimbursement lists. In countries like Taiwan where the assessments are developed using a literature review, then it will depend on what has been chosen as a comparator on the reviewed papers.

4.3. Process

We have looked at how the process of HTA works in the selected markets in terms of how different stakeholders are involved within the process; how results are communicated and how new evidence is incorporated within the assessments. Several trends have been identified:

There is a widespread agreement that different stakeholders should be included in HTA processes although only a few countries have a formal process

There is increasing recognition of the value of including all stakeholders in the HTA process. The countries identified as leaders in this area in the initial Comparison report still show relatively good performance.¹⁵³

Canada, England and Scotland are examples of mature HTA systems that include stakeholders throughout the HTA process, from the application to the review of the assessment. In these markets, all stakeholders are represented on the appraisal committee and have a voice during the discussions. In Germany, even though the process is not as structured as in the countries mentioned above, stakeholders are also invited to contribute at both the beginning of the process and once the preliminary results are published. In South Korea, for example, different stakeholders are also involved through the process, but these include only manufacturers and physicians.

In some emerging HTA systems there is also a willingness to include different stakeholders through the process, although in practice it is a bit more limited. In Taiwan, the appraisal committee (PBRs) is formed by experts, scholars, medical societies and providers. In principle, patients could be included but at the time of writing this report there has been no case where they were invited.

In other emerging systems, stakeholders are invited to comment only after the recommendations are made. In Brazil, for example, CONITEC introduced a formal public

152 The selection of the comparator in Germany caused some criticism as it was noted that the cheapest comparator was then also used during price negotiations. The policy on this has been recently clarified and noted that the cheapest comparator could be used to determine the clinical comparison but not the price negotiation, unless the new therapy did not show clinical improvement.

153 Note that in this section we try to capture the role of stakeholders using a general approach. Given that the 2013 report treated the role of patient groups as a separate issue, we leave the specifics on the involvement of patient groups to the next point.

consultation to obtain contributions and suggestions on the evaluated topics. In Poland, anyone can contribute, using requests for expert opinions posted on the AOTM website. Additionally, the Polish HTA invites consultant bodies, specialists as well as the National Health Fund prior to the assessment, so they can also give their opinion.

Unfortunately, France and Italy do not include all stakeholder views in the process. Stakeholder participation was identified as having little impact in France. For instance, the pharmaceutical industry does not have voting rights within the transparency committee. In Italy, there is very little stakeholder involvement and in fact, AIFA can request the manufacturer's participation within the review process only under specific situations. The conditions for participation can be requested, but are not specified on AIFA's website. If stakeholders want to request specific information on the assessment they can, but their involvement is dependent on the decision of AIFA to provide access to such information.

In countries where the HTA is still at an early stage of development, there is little stakeholder involvement. In Mexico, experts may be asked to contribute to the assessments, but it is not mandatory and it is the manufacturer company that normally requests this information. In reality, it is not clear if this has any influence on the decision-making process as the assessments are not publicly available.

Overall, we found that although there are some countries where there is significant involvement of different stakeholders, there are others where the involvement is limited, with room for improvement. This is identified not only in emerging HTA systems but also in some mature countries.

Increasing interest in a formal process for including patients into the stakeholder groups but with significant progress required in emerging HTA systems

There is an increasing recognition of the importance of including patient views within HTA processes, not only by patient groups and international HTA organisations, but also by academics, who are developing methods to systematically incorporate the patient voice.¹⁵⁴ Patients and carers can provide evidence about their experiences, which is valuable in circumstances where there is significant uncertainty regarding the benefits of the assessed technology.

The HTA agencies in Canada, England and Scotland are seen as leading in this area. They have systematic processes and structured forms that patients can document and submit their experiences of living with the condition under assessment and the value of the technologies being studied. In England, for example, patients are involved during the entire HTA process, from scoping to identify outcomes of particular importance to patients. Patient organisations can submit views on a form and in the appraisal; an individual patient can provide expert comments directly to the committee in a similar fashion as evidence provided by clinical experts. In Canada, CADTH has a template that is filled in by patient organisations and then

HTA researchers summarise all patient submissions to the Committee. The SMC uses a submission form that is provided in full to the assessment committee. One of the unique aspects of the SMC is that there is one person specifically employed to help patient organisations complete the submission. In all cases, there are public or lay representatives on the committee who ensure that the patient submissions are given appropriate consideration

However, it is worth noting that after talking to patient representatives, even in Canada, England and Scotland, patient views only seemed to be used in those cases where the appraisal committee was having difficulty assessing the new technology. However, there is recent evidence on CDR recommendations in Canada suggesting that the medicines submitted with a patient recommendation received a higher proportion of conditional approvals than those without patient submission, but less unconditional approvals.¹⁵⁵ The way SMC incorporates patient views into their decision-making is expected to change from May 2014. In early 2014, the Scottish government announced that greater patient involvement in decisions on medicines for use in end-of-life care and the treatment of rare conditions.¹⁵⁶

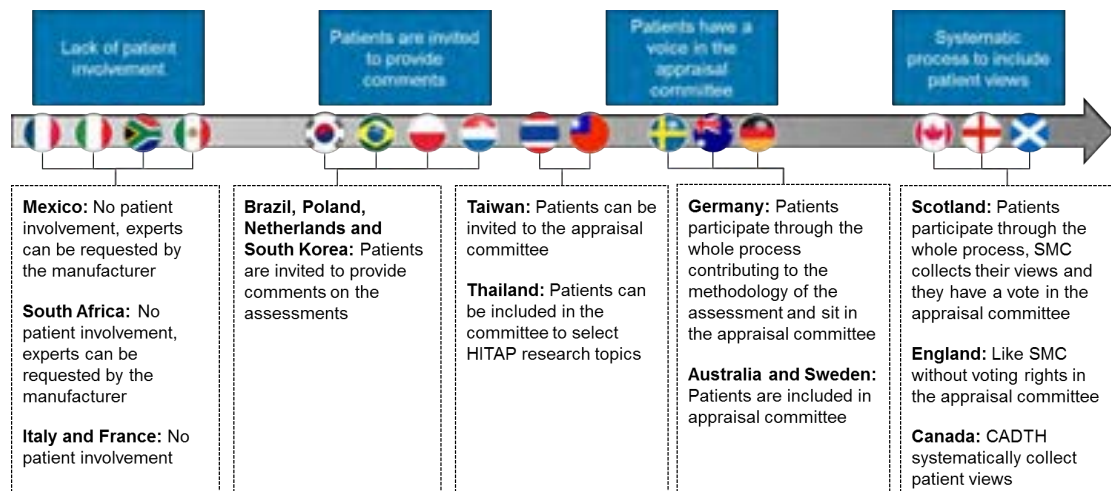
In other countries, the role of patients is more limited. In some cases patients sit on the appraisal committee without a vote (Germany or Australia), in others they are mainly invited to provide comments (Netherlands or Brazil) and in some developed systems such as France patients do not have a role at all. However, generally the role of patients is less noticeable within emerging HTA systems, partly because patient groups are less developed and even when they exist, according to our interviews, there is a perception they may not always have the knowledge required to understand how assessments are developed and used.¹⁵⁷ Therefore, patient contribution is often ad hoc. Even in Taiwan, one of the countries that are leading this field in Asia, there has been no patient participation since the creation of the PBRs. The role of patients within the countries studied in this report is illustrated in Figure 47.

155 Wong-Rieger, "Patients as Partners in HTA", ISPOR Meetings, New Orleans, May 2013. Available here: http://www.ispor.org/meetings/neworleans0513/releasedpresentations/W20_Wong-Rieger.pdf.

156 The Scottish Government, "Enhancing access to new medicines", 31 January 2014. Available here: <http://news.scotland.gov.uk/News/Enhancing-access-to-new-medicines-8e1.aspx>.

157 CRA interview programme.

Figure 47: The role of patients within the HTA systems analysed



Source: CRA analysis

We conclude that, although there is still considerable room for further integration of patient views within HTA process, there has been an improvement within the last few years.

Large disparity on how results are communicated to the public

Overall, the way that decisions are communicated within each country remains quite similar to the 2011 report, with wide variation across the countries studied. We have some mature HTA markets, such as England or Canada, which provide information about HTA decisions in ways the public can understand. In England, results are also available with a phone application.¹⁵⁸ In some countries, like Australia, Sweden and Germany, HTA recommendations are published using technical terminology which limits the ability to communicate to the general public.¹⁵⁹ In other markets, like Italy, decisions are communicated at a high level and the assessments are not publicly available.

There have been some improvements in emerging HTA systems. In Brazil, the creation of CONITEC means that all assessments are published, which was not previously the case. Since 2012 all the reviews are publicly available, including comments received from the public. In Taiwan, the system was created to be as transparent as possible and the NHIA publishes the assessments and resolutions as well as the recordings of the appraisal meetings.

However, we also have countries like Thailand where not all the assessments are made public or Mexico where only the CSG decisions are made public, but there is no information on the assessment of the approved drug or the rationale for decision.

158 NICE has developed a phone application to access NICE guidance from smartphones. Available here: <http://www.nice.org.uk/aboutnice/nicewebsitedevelopment/NICEApps.jsp#X-201206111615112>.

159 CRA interview programme.

Reviews are mainly systematic reviews initiated by HTA agencies

According to best practice principles, the system should be flexible enough to incorporate new evidence (especially real world evidence) and update the assessment. However, reassessment also takes place because a medicine has been rejected and the manufacturers have been asked to resubmit incorporating a managed entry agreement. It is difficult to determine the type of reassessment or to make direct comparisons across countries. Some countries have the manufacturer reapply on multiple occasions whilst others capture this by discussions through a single assessment process.

As mentioned above, 73% of the 2012 reviews were first time reviews, representing a slight decrease in comparison to 2009 reviews.¹⁶⁰ As in the 2011 report, we have attempted to make a distinction between *re-evaluations* that the agency independently conducts and *resubmissions* which are assessments done following a negative recommendation. With the data available, we observed that more countries are performing reassessments (Figure 48).^{161,162}

There is an increase in the proportion of assessments that represent re-evaluations initiated by the HTA agencies. However, this varies from country to country. The TVL in Sweden undertakes systematic re-evaluations and recently, the CVZ in Netherlands began a similar practice for expensive drugs. In Scotland, the SMC does not perform re-evaluations but allows the manufacturer to re-submit if they want to apply for a different indication. In England, NICE focuses less on developing multiple technology appraisals (MTAs) and gives more attention to single technology appraisals (STAs).¹⁶³

As expected, less established systems, such as Brazil, Mexico and Taiwan have developed guidelines that allow for reassessment, but this has not happened in practice in 2012. South Africa, where HTA is still in development phase, does not have any process in place for reassessment or consideration of further evidence.

Overall we observe an increase in re-evaluations (compared to re-submissions), and a slight decrease in re-submissions as displayed in Figure 48.

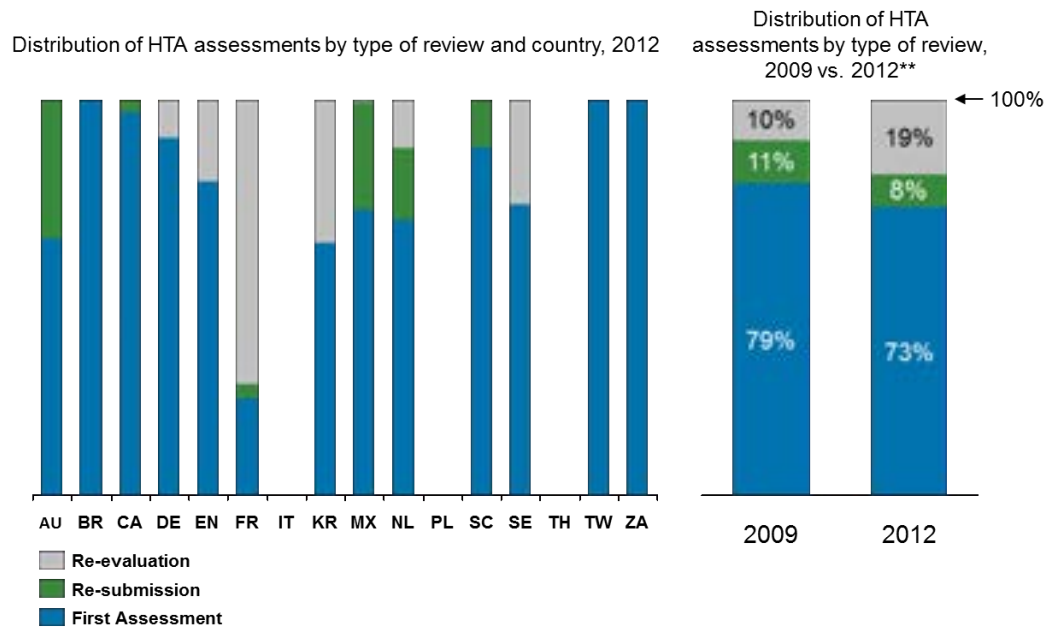
160 Comparing across the markets that have been included in both reports represented an increase from the 35%, in 2009, to 48% in 2012. See **Error! Reference source not found.** for further detail.

161 Please note that the set of countries is not the same as in 2011. In 2011 we had information for eight of the 11 markets, whereas in 2013 we have 13 of the 16.

162 Regarding countries with unavailable data, industry representatives in Poland have confirmed that re-evaluations can be done when requested by the Ministry of Health recently the non-standard chemotherapy is being reassessed.

163 CRA interview programme.

Figure 48: Distribution of assessments by type of review



Source: CRA analysis; Note: *For South Africa only one assessment was available; ** The 2009-2012 comparison only includes those markets that were also included in the 2011 report

4.4. Impact

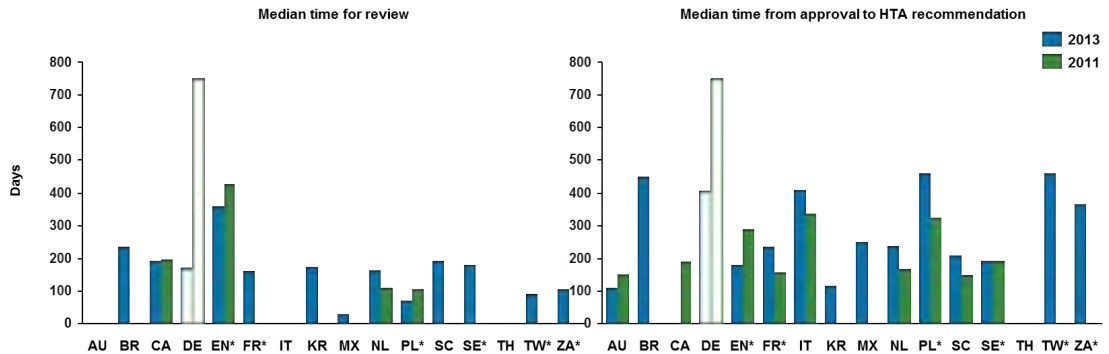
There are a range of different impacts that could be associated to the use of HTAs. In the previous report, we focused on speed of the assessment, the decisions (whether the decision was positive, negative or applied restrictions), the impact on price and whether it allowed for innovation but we did not assess the impact on diffusion.

To identify the length of the HTA processes and whether they delay or speed up access to new molecules, we used published sources on the length of the HTA process or evidence from our case studies where the first is not available. We use 19 case studies to determine the level of restrictiveness of the decision. For the diffusion analysis, we used the molecules studied in the original Comparison report collecting IMS sales data from 2009 to 2012. We identified several trends.

In general, HTA is being undertaken in a more timely fashion within the countries analysed

In the 2011 review, we found that the length of HTA processes varied significantly between markets, reflecting different processes and levels of stakeholder engagement. As seen in Figure 49, the duration of the reviews still varies across markets.

Figure 49: Median duration of the HTA by length of the review and the time from regulatory approval to HTA recommendation, 2011 vs. 2013



Source: CRA analysis; Note: *Reflects numbers collected through interviews with industry and HTA representatives as data was not always available; In Germany time reflects the HTA review and approval to recommendation time and is not indicative of access

On average, looking at those markets included in the 2011 and 2013 assessments, we find that the average length of the process decreased from 317 days to 179 days. In particular, there has been an improvement in those markets where a defined timescale was established for the review process.

In Germany, for example, the AMNOG reform established that the HTA process should be developed within six months. The timing is strictly followed in Germany, as evidence collected from the case studies showed that the median length of the process was 5.6 months. Similarly in Poland, a goal of 60 days was implemented since the last review. From the information available, it seems this has resulted in an improvement although reviews may take up to 80 days.

In Brazil, the introduction of CONITEC introduced a defined timetable. CONITEC should make a recommendation in 180 days (with an extension of 90 days). From the data available, the review process takes a median of 240 days. However, some concern about the speed of the reviews still exist as the submission date is not always publicly available and the industry believes that manufacturer applications are not prioritised within the CONITEC selection and only few of the submitted drugs are reviewed within the specified time.¹⁶⁴

Some markets encourage reviews to start earlier either before the products are given a marketing authorisation (Australia) or allowing simultaneous review when applying for market access (Netherlands or South Korea).¹⁶⁵

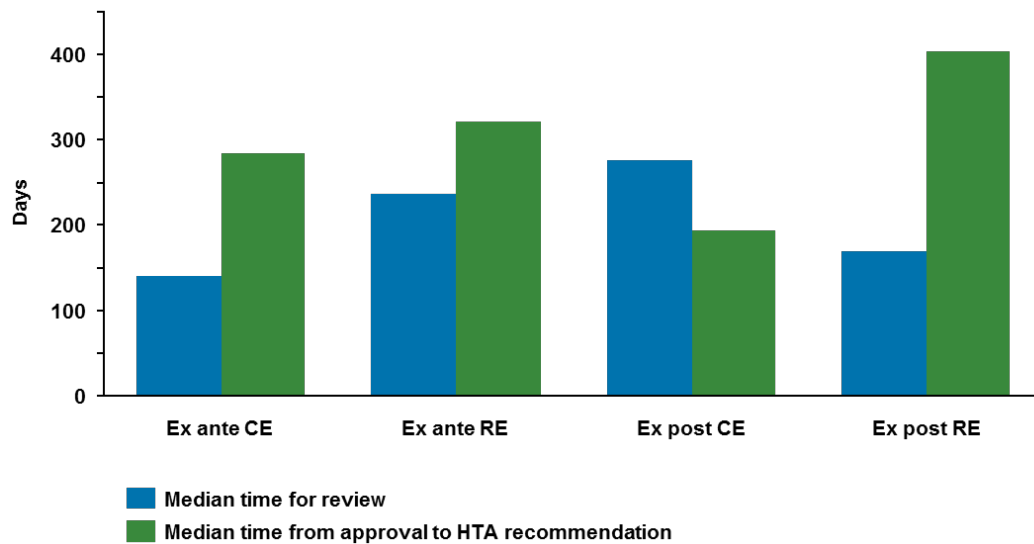
In Figure 50 we look at the length of the reviews for different types of HTA system (distinguishing between ex ante and ex post system and relative and cost-effectiveness

164 "Brazil: the hardest nut to crack?", CRA interview programme and Scrip 2013, Market access in Brazil Emerging Markets.

165 Note that South Korea has just started a pilot program, although it is expected to be implemented in the near future.

systems). This shows that systems that develop ex post relative effectiveness or ex ante cost-effectiveness analysis develop assessments in a shorter period of time, whereas countries that used an ex post cost-effectiveness model experience the longest reviews.

Figure 50: Median duration of the HTA by length of the review and the time from regulatory approval to HTA recommendation



Source: CRA analysis; Ex ante CE includes AU, BR, CA, KR, MX, NL, PL, TH, TW; Ex ante RE includes FR, IT; Ex post CE includes EN, SC; Ex post RE includes DE ¹⁶⁶

A slight increase in the level of the restrictions imposed has been observed

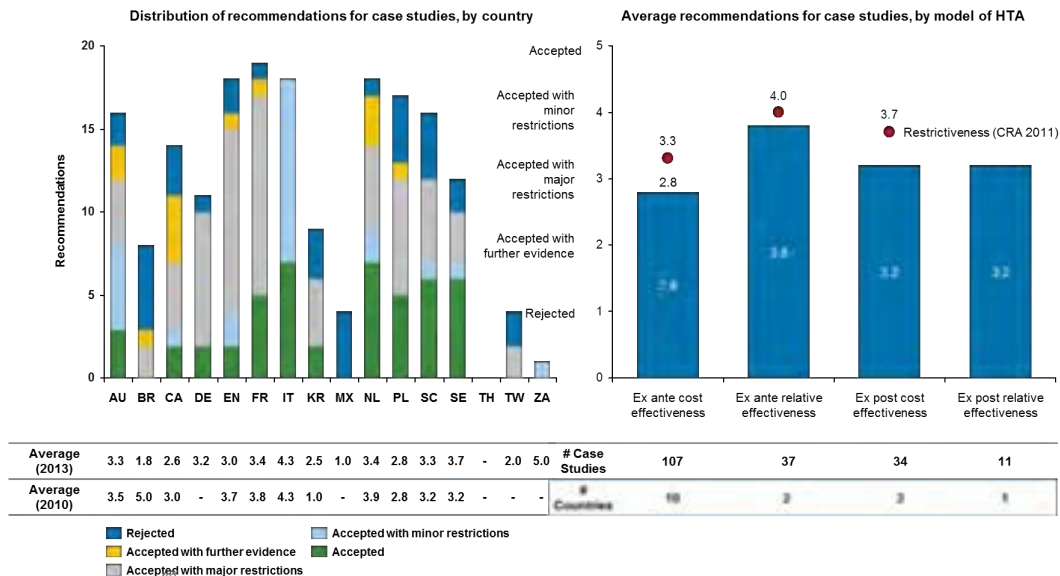
In the 2011 report we found significant variation in whether the HTA process in different countries imposed restrictions on the use of different medicines (for example, in terms of the patient population or if the patient had to have failed on an alternative therapy before initiating a new medicine). We find that the extent of variation across the countries has shown a slight increase in the 2013 assessment.

When looking at the reviews published in 2012, we found a slight increase in the level of restrictions imposed in comparison to what we observed in the 2009 publications. Looking at Figure 51, we see that decisions have become stricter across all the models of HTA. We observe the same pattern across the different types of HTA system, ex ante relative effectiveness is the least restrictive, while ex ante cost-effectiveness is the most restrictive.

At a country level, the findings from the 2011 report are still valid for the 2013 update. Italy was identified as the market least likely to impose restrictions on the use of medicines. This remains the case in 2013, with the Netherlands, Scotland or Sweden now approaching a similar level.

In the first Comparison report, Poland applied the most restrictions. In the updated assessment, they have applied fewer restrictions, with 23% of the 2012 reviews accepted without restrictions.

Figure 51: Variation on the recommendations by country and by model of HTA



Source: CRA analysis; Ex ante CE includes AU, BR, CA, KR, MX, NL, PL, TH, TW; Ex ante RE included: FR, IT; Ex post CE includes EN, SC; Ex post RE includes DE; Note: Please note that averages represent the mean recommendation per country, using the scale 1 to 5

Delay on market entry is related more to administrative elements than the type of product reviewed

Using the assessments reviewed in the 2011 report, we also analysed the length of time before we observe actual sales on the market and whether the therapeutic value of the medicine (as determined by the ASMR in France) correlates with the speed of market entry. Looking at IMS sales data, we defined the delay as the time between the publication of the assessments and the observed market entry. In general, we observed no difference on the delay of market entry based on the level of innovation of the medicine. However, Figure 52 highlights several interesting elements:

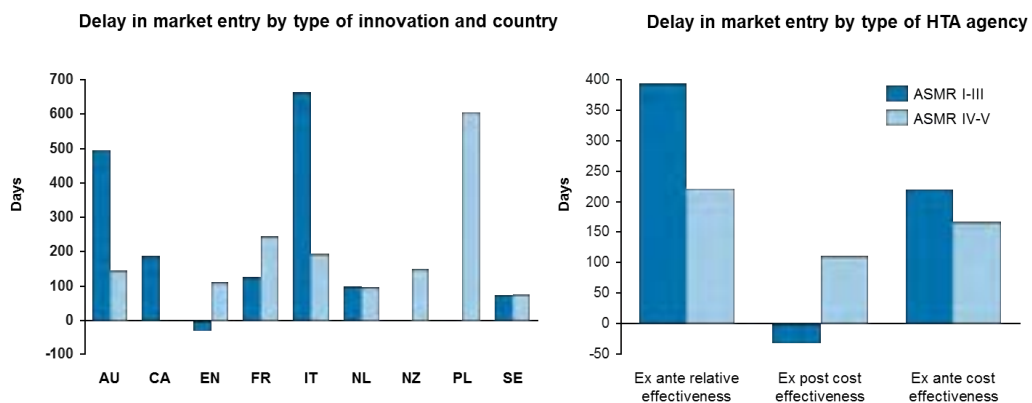
- Australia and Italy show the longest delay for more innovative products which may reflect the administrative hurdles of the system (in particular, the negotiation over the level of prices);
- Allowing a fast-track approval process for HTA could explain the lower delay in France with more innovative drugs;
- Countries using an ex post cost-effectiveness HTA model registered lower levels of delays on entry of both innovative and non-innovative drugs. The result is driven by England and Scotland, and the fact that products can be found in the market before

NICE reviewed them; although this does not account for actual diffusion in the market.

- Larger delays are observed in ex ante RE models although those are driven by the large delays experienced in Italy rather than France.

It is worth mentioning that concern about the need to improve the speed of uptake of innovative drugs was observed in some countries. In Italy, for example, an accelerated HTA process was recently implemented.¹⁶⁷

Figure 52: Delay in market entry by type of innovation, HTA agency and country, in days



Source: CRA analysis using IMS data; Note: Delay is defined as the time between the publication of the assessments and the observed market entry; The analysis is based on the molecules assessed in the 2011 Comparison report thus Ex ante RE composed by France and Italy, Ex post CE by England and Scotland; Ex ante CE by Australia, Brazil, Canada, the Netherlands, New Zealand, Poland and South Korea.¹⁶⁸

The impact that HTAs have on the speed of drug uptake is difficult to observe in practice

We also wanted to see if the HTA recommendations affect the speed of uptake or diffusion. Given the nature of the English HTA system, where medicines can be available in the market before NICE recommendation, it is possible to observe what happens after the HTA publication of the HTA. UK¹⁶⁹ sales data allowed us to compare drug uptake before and after the publication of NICE assessments to see if there is any market response to NICE recommendations.¹⁷⁰ NICE has been criticised for the delay between drug availability and

¹⁶⁷ Article 12 Balduzzi Act of 2012, Pub. L. No 189, 2012, Available here: <http://www.quotidianosanita.it/allegati/allegato7185987.pdf>.

¹⁶⁸ The category for post RE HTA model encountered in Germany is not included as the system has changed and is not comparable between the Comparison report and this report.

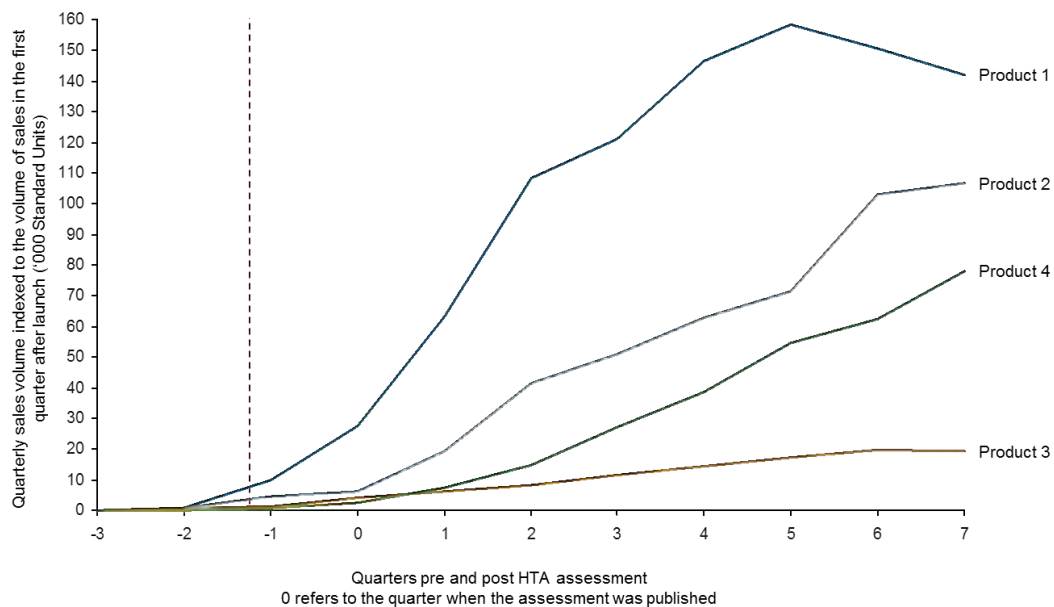
¹⁶⁹ The UK has been used as a proxy for England given that IMS data does not provide separate sales data for England.

¹⁷⁰ The German HTA system can now also be used to determine the effect of diffusion as new molecules have 12 months of free pricing before the G-BA publishes the final recommendation.

publication of NICE guidance, leading to limited access prior to review (so-called “NICE blight”) as clinicians may prefer to wait for NICE’s decision or may be forbidden from prescribing the medicine by their clinical commissioning groups. While this phenomenon is widely recognised, there is little systematic evidence of the frequency and degree to which this happens.¹⁷¹

Looking at a sample of molecules we assessed in 2009, we found little evidence of NICE blight (at least for the product assessed). In fact, looking at Figure 53 it is difficult to identify any change in the sales pattern following the NICE publication of the assessments.

Figure 53: Uptake of selected molecules in the UK using NICE publication date as a reference date



Source: CRA analysis using IMS sales data

Clarity on the relation between HTA and price, reimbursement and market access although the way it is used in practice remains undefined

The relationship between the HTA recommendation and price and reimbursement of the medicine is an area that has received little interest by academics. Using the same approach as CRA (2011), we looked at this in terms of (i) whether there is clear articulation of the link between deemed value and price (ii) evidence that this occurs in practice.

The French, German and Italian systems are specifically designed so HTA determine prices for new medicines. The level of innovation identified within the relative effectiveness is used in the pricing negotiation process. However, the clarity of the relationship between price and reimbursement and the assessment varies significantly between these three countries. In France, the Transparency Commission (TC) provides a relative effectiveness assessment which classifies the molecule in five levels of innovation (ASMR I-V). Prices are negotiated using this assessment as a guide (in addition to the economic evaluation that also feeds into this process). Drugs with ASMR V, tend to have average prices in other countries, while drugs with ASMR I-III, have a price premium. This seems to indicate that innovative drugs are priced at a premium, thus reflecting the impact of HTA on prices.¹⁷²

The AMNOG reform in Germany introduced a similar model of HTA to determine prices of innovative medicines. IQWiG undertakes a relative effectiveness analysis and the GBA determines the level of incremental benefit which then feeds into pricing decisions. It is still a bit early to see the impact that the introduction of relative effectiveness within the Germany price and reimbursement system has had in the market; however, based on interviews, all stakeholders expected prices to be much higher after the negotiations with the GVK-Spitzenverband given the level of innovation determined by GBA.¹⁷³

In Italy, molecules are classified using an algorithm as important, moderate or modest innovations. AIFA distributes new therapies within three reimbursement categories (class A, H and C). The link between the level of innovation defined through the relative effectiveness analysis and the level of reimbursement is not entirely clear.

It is also interesting to look at consistency between the different agencies. As found in previous research, there are considerable differences in the assessment (even though conceptually they are applying a similar approach). This is reflected in Table 6 and Figure 54.

Table 6: Value assessment – comparing the assessment by France's HAS to Germany's IQWiG

Product	Indication	ASMR - HAS	G-BA appraisal
Boceprevir	Hepatitis C	Moderate ASMR III	Ind no quant (IV)
Fingolimod	Multiple Sclerosis	Minor ASMR V	Hint marginal (III)
Retigabine	Epilepsy	No improv ASMR V	No (V)
Telaprevir	Hepatitis C	Moderate ASMR III	Ind no quant (VI)

172 Geoffard, Sauri-Romero, "International comparison for new drug", *IMS Health*, May 2008.

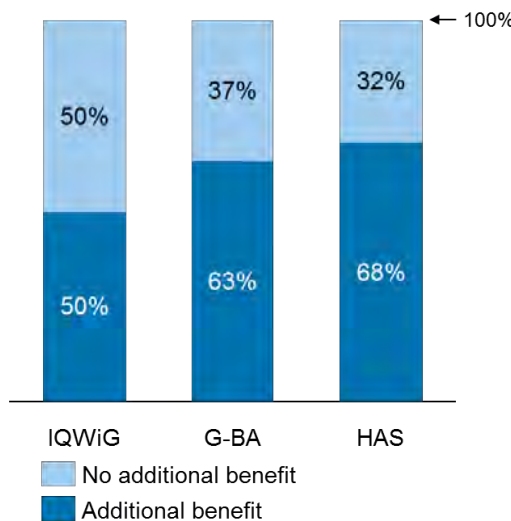
173 CRA interview programme.

Ticagrelor	Cardiology - ACS	Minor ASMR IV	Proof signific (II)
Abiraterone	Oncology	Moderate III	Ind no quant (IV)
Apixaban	Cardiology - venous thromboembolism	Minor ASMR IV	Ind marginal (III)
Cabazitaxel	Oncology	Minor ASMR IV	Ind marginal (III)
Eribulin	Oncology	Minor ASMR IV	Hint marginal (III)
Ipilimumab	Oncology	Minor ASMR IV	Ind significant (II)
Vemurafenib	Oncology	Moderate ASMR III	Ind Significant (II)

Source: Adapted from Rouf et al. (2013), "Early benefit assessment (EBA) in Germany: analysing decisions 18 months after introducing the new AMNOG legislation", *European Journal of Health Economics*; G-BA classification – major (I), significant (II), marginal (III), not quantifiable (IV), no additional benefit (V) and less benefit with proof, indication and hint as conclusion categories; HAS classification – ASMR I major, ASMR II important, ASMR III moderate, ASMR IV minor and ASMR V no improvement

This suggests that even though the relationship between therapeutic improvement and innovator rewards is perhaps more transparent than other markets, anticipating rewards remains problematic.

Figure 54: Presence of additional benefit as reported by IQWiG, G-BA and HAS for selected number of products reviewed during 2012



Source: Rouf et al. (2013), "Early benefit assessment (EBA) in Germany: analysing decisions 18 months after introducing the new AMNOG legislation", *European Journal of Health Economics*

In theory, ANVISA in Brazil classifies new molecules taking into account their value assessment which should then feed into the price negotiation process. However, the way this

occurs is not transparent. In fact in Brazil, assessments are used as a base to negotiate price discounts. Looking at CONITEC assessments we observe the assessment often gives a conditional acceptance where one of the conditions is a price reduction of the assessed technology in order to be accepted in the SUS.

The relationship is even less clear within other emerging HTA systems. We found that HTA is designed to determine the inclusion of health technologies within positive reimbursement; however, budget impact analysis also has a significant role in determining the decision. The result of this is that it is difficult to anticipate how a positive assessment of value will affect the negotiation. Mexico or Thailand would be the clearest examples. Although it is worth mentioning that in Taiwan, first-in-class drugs receive special attention within the HTA reviews.

Taking the above into consideration, the relationship between the HTA and the price and reimbursement decision often remains opaque. Although in principle, HTA allows innovative medicines to receive a price premium relative to less innovative medicines, the evidence that this occurs in practice remains weak.

The speed of uptake of innovative drugs seems to be higher in those markets using an ex ante CE HTA model or where less restrictions are imposed

Using available IMS data we followed the sales for the molecules studied in the 2011 report to see if any relationship could be found between HTA decisions or models and the speed of uptake of reviewed drugs. Given the number of factors that determine the uptake of new drugs it is difficult to establish a direct link,¹⁷⁴ and as illustrated in Figure 50 it is difficult to draw conclusions by the type of HTA process. The results suggest faster uptake for ex ante CE than ex post CE. This is surprising, as we might expect ex post CE to have higher growth than ex ante CE (as the product can be launched prior to any assessment). However, this is likely to reflect slow growth in the UK market (categorised as ex post CE), which is seen as conservative in terms of adopting innovative medicines.

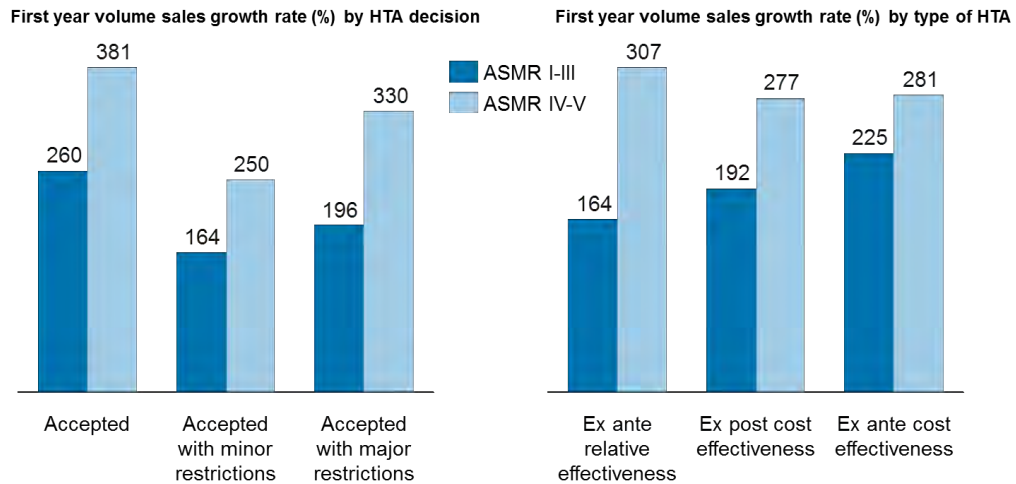
A number of observations can be made:

- Less innovative drugs have a higher speed of uptake during the first year they are observed in the market. This is true independently of the HTA model or HTA recommendation.
- More innovative drugs have a higher speed of uptake if they have been given an unconditional acceptance.

174

For a more detailed discussion see Atun and Sheridan, "Uptake and diffusion of pharmaceutical innovations in health systems", *International Journal of Innovation and Management*, 11,2, 2007, Department of Health, "Extent and causes of international variations in drug usage: a report for the Secretary of State for Health by Professor Sir Mike Richards CB", July 2010, or the EFPIA commissioned reports on uptake of innovative drugs in oncology, rheumatoid arthritis or multiple sclerosis: Wilking, *et al.* "Comparator report on patient access to cancer drugs in Europe", 2009, Kobelt and Kasteng, "Access to innovative treatments in Rheumatoid Arthritis in Europe", 2009; Kobelt and Kasteng, "Access to innovative treatments in Multiple Sclerosis in Europe", 2009.

Figure 55: First year volume sales growth rate, in %, by decision, type of HTA and type of innovation



Source: CRA analysis using IMS data; Note: The analysis is based on the molecules assessed in the 2011 Comparison report thus Ex ante RE composed by France and Italy, Ex post CE by England and Scotland; Ex ante CE by Australia, Brazil, Canada, Netherlands, New Zealand, Poland and South Korea¹⁷⁵

Countries use HTAs to update clinical guidelines although it is normally done indirectly

Although it is not a common practice, we have observed that in some markets HTAs are directly linked to an update of the clinical guidelines. This is sometimes done using a systematic mechanism where HTA recommendations are conditional on the update of clinical recommendations used within the national health system. Brazil would be the clear example.¹⁷⁶

In the majority of markets, however, the process is established the other way round. Only after the publication of a new assessment do the clinicians developing clinical guidelines capture the new information and use it to update the guidelines when possible. This would be the case of England, for example, where NICE publishes the assessments and then makes its clinical recommendations which are then used within NHS England. In Scotland, although the relationship is not defined, SIGN, the organism in charge of developing clinical guidelines, will take SMC recommendations on board when updating the guidelines.

The link between assessment and clinical guidelines could be improved in a number of markets.

175 The category for post RE HTA model encountered in Germany is not included as the system has changed and is not comparable between the Comparison report and this report.

176 Kuchenbecker and Polanczyk, "Institutionalizing Health Technology Assessment in Brazil: Challenges Ahead", *Value in Health regional issues*, 1, 2012.

Monitoring the impact of HTA bodies is still not a common practice although it is receiving more attention in some markets

Audits or investigations of the effectiveness of HTA processes are rare. Even where this is the case, it is often monitored by the same HTA agency. In England, for example, NICE or SMC have their own evaluation programs, although in the SMC the reviews are not developed systematically. Unfortunately it is not always clear how the findings are taken into consideration. Something similar is intended to be implemented in South Korea through HIRA but this has not yet been implemented.

There is interest among all stakeholders to know what the impact of HTA is. This has been reflected in some industry associations commissioning independent academic studies in this area. This has been the case of Brazil and Mexico. However, no evidence was found for other emerging systems.

Given that the role of HTA is evidence-based assessment, it is still surprising how little effort is put into assessing the value of the HTA process.

4.5. The development of HTA systems in emerging markets

The analysis above has looked across the 16 countries included in this update. However, it is interesting to examine the role of HTA within emerging economies in closer detail. In this section we highlight the findings for emerging economies and the barriers identified within the studied countries. Several elements were found:

The role of HTA is developing in emerging markets but often budget impact remains the principle tool used in price and reimbursement decision-making

As mentioned above, HTA within emerging economies has been implemented as a tool to be able to decide what to include within their positive reimbursement lists. However, given the restriction in resources that these markets face, decisions are often based on a combination of factors. In particular, budget impact analysis is still often an important consideration. The result of this is that the decisions made regarding reimbursement are not always consistent with the guidance from the HTA process.

However, as a HTA system matures, greater transparency regarding the role of HTA is introduced. This is illustrated by the changes in Brazil which have introduced a more structured approach, even though budget impact remains an important part of the process. In Brazil, CONITEC brought more transparency into the system with the result that the process for undertaking the assessments is now clear and although not perfect, there is a link between the assessment and the ultimate decision. In contrast, the role of HTA in Mexico remains opaque.

There are a number of operational barriers to the use of HTA in emerging markets

Undertaking HTA is resource-intensive and requires data and technical experience. There are some significant practical barriers to undertaking HTA. Looking in detail at the emerging systems studies in this report we found that:

- **There is a huge gap between the human capital available and what is required to develop, use and understand HTAs.** Indeed, we found a consensus across

different stakeholders that trained and experienced personnel limits the applicability of HTA in some markets.

- **A lack of transparency has been observed across emerging HTA systems.** Although some improvement has occurred in countries such as Brazil or Taiwan there is still work to do to understand what has been reviewed or what has been rejected. The situation is worse in markets such as Mexico or South Africa where HTAs are not publicly available.
- **Methodological guidelines have only been recently defined and it is still not clear how they are applied.** In order to bring coherence to the system, the majority of markets have defined methodological guidelines so manufacturers can have a better understanding of how to develop submissions. However, in some cases the guidelines need greater clarity. In Mexico, the guidelines suggest a wide variety of pharmacoeconomic methodologies without providing guidance on the preferred method.

The wider role of HTA in determining healthcare priorities is even more important in emerging markets

Across all the countries examined, HTA is primarily used to assess new medicines. Less attention is given to the assessment of other technologies or the wider role of HTA in assessing healthcare priorities or allocation decisions. This is even more problematic for HTAs in emerging markets.

Given the limited availability of resources among emerging economies to undertake HTA and the difficulty in developing a technology appraisal based on local data, we might have expected the HTA agencies in these countries to focus on higher level allocation decisions in the healthcare system (sometimes referred to as macro HTA). Instead, we have found HTA agencies building similar approaches to mature HTA agencies or drawing on the results published in these markets. Too little focus is given to the role of HTA in higher-level healthcare decision-making or its role in clinical guideline development.

HTA is more developed in the private market

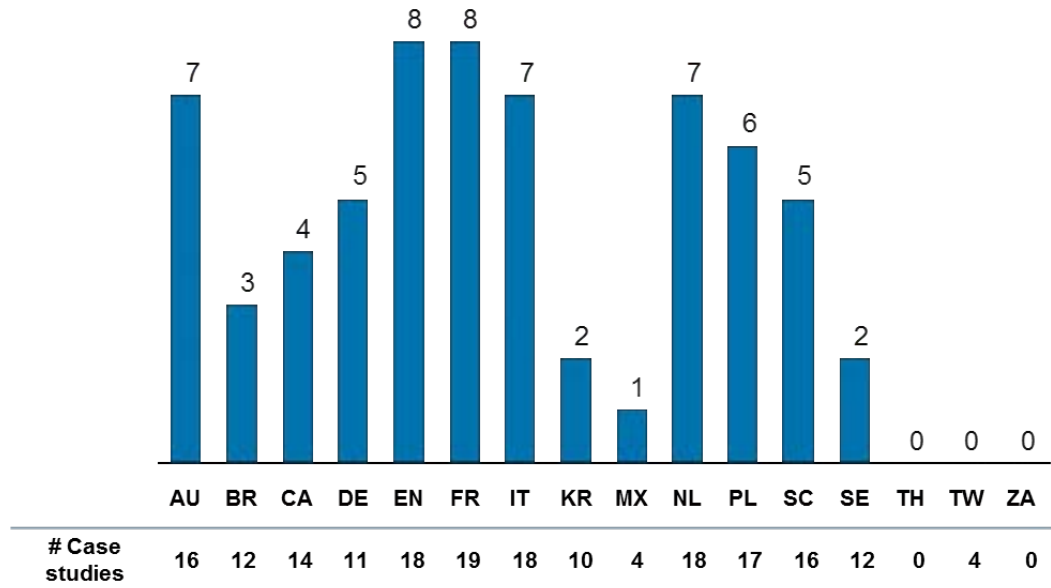
Interestingly, we found that in some emerging economies HTA is more developed in the private market. In South Africa, for example, we found that private insurance companies or medical schemes use HTA tools in order to decide what to cover. This is likely to be beneficial as it builds up the skills and infrastructure that can be used in the public sector. However, given that this relates to use by private insurance companies, it is difficult to determine how HTA is used in practice and if there are more specific lessons for the public sector in these markets.

4.6. Issues for particular therapeutic classes

One of the recommendations for future research identified in the 2011 report was to focus the case studies on particular therapy areas. The academic literature has also drawn special attention to exploring the impact that HTA has on cancer medicines (as discussed in chapter 2). Furthermore, although the methodology used to select the case study molecules explored

in the report was not intended to favour particular therapy areas, it resulted in the selection of 17 molecules used for 19 indications, 7 of which related to oncology treatment, representing 52% of the recommendations (Figure 56). It is therefore interesting to look at this therapy area in more detail.

Figure 56: Number of oncology drugs reviewed within the case studies, by country



Source: CRA analysis; Note that we have removed the South African example as detailed information was not available

In general, oncology drugs face slightly more restrictive recommendations even in those markets where oncology drugs are reviewed by a separate entity and QALY based systems are more restrictive

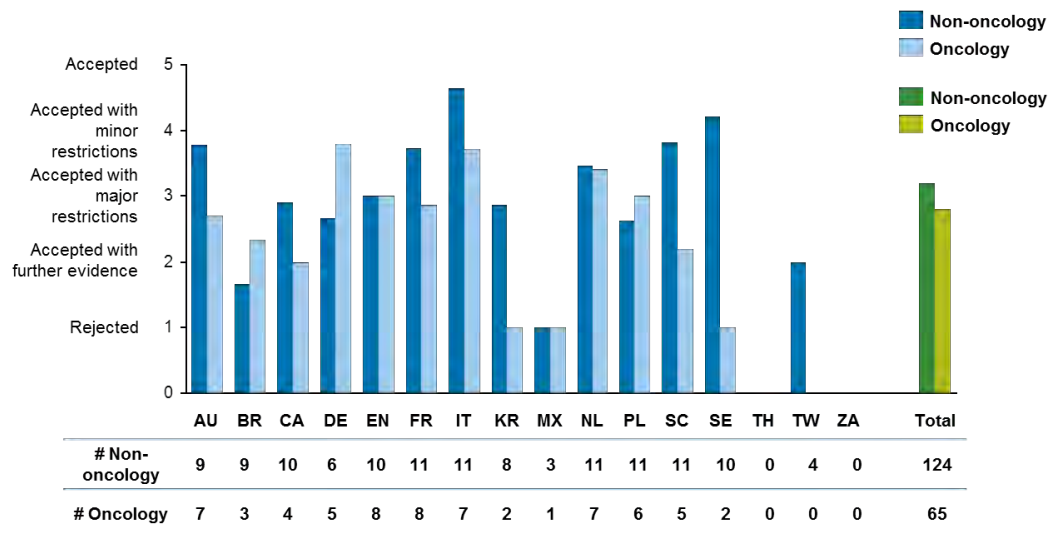
Across all the markets analysed we found that on average oncology drugs received acceptance with more restrictions than non-oncology drugs. However, as Figure 57 displays, differences across markets can be observed. Indeed, while the majority of countries imposed higher restrictions to oncology drugs, Brazil, Germany and Poland imposed fewer restrictions.

For the sample of medicines we have investigated, we do not find that NICE has a more restrictive regime for oncology medicines, as both oncology and non-oncology products tend to be accepted with major restrictions. This is consistent with a recent empirical analysis looking at the relation between NICE decisions and the therapy area. The authors found that

NICE rejections were significantly less likely for cancer and musculoskeletal disease, but significantly more likely for respiratory disease.¹⁷⁷¹⁷⁸

Interestingly in Canada, where oncology drugs are reviewed by a separated entity (pCODR) and follow a different process, oncology drugs have fewer acceptances without restrictions than in other markets where oncology drugs follow the same path as other medicines. It is important to note that this is not consistent with other academic assessments discussed in chapter 2, who found that the oncology process was more flexible in Canada.

Figure 57: Average HTA recommendations by therapy area



Source: CRA analysis

To see if there is a relationship between the use of a threshold and the level of restriction imposed on the different molecules, we classified the countries included in the report by the use of the QALY threshold. In particular we have divided the countries into three different groups:

- Use of QALY analysis and direct application of threshold: Here we include Australia, Canada, England, Poland, South Korea, Scotland and Thailand;

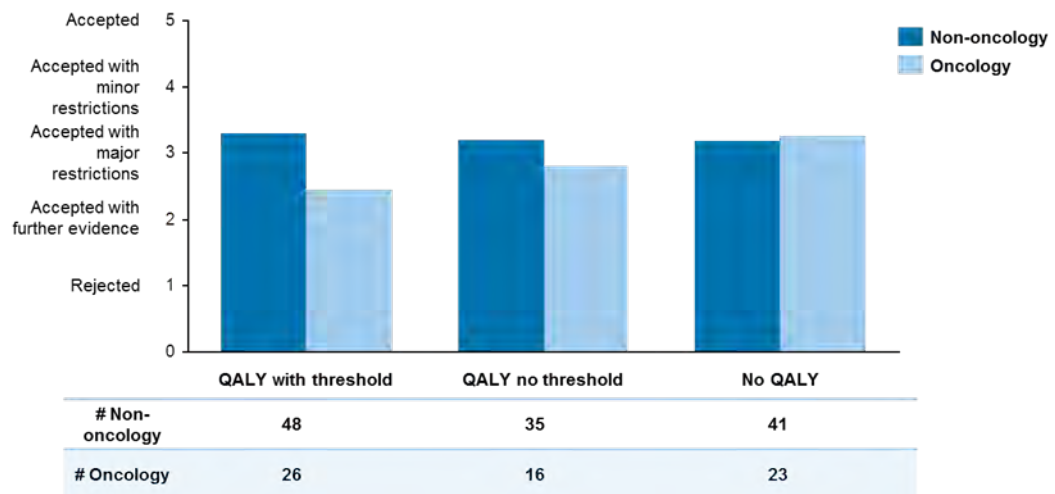
177 However, oncology has been identified as a significant problem in the UK. The DoH identified access to oncology drugs as a source of concern and, among other tools, the Cancer Drugs Fund (CDF), has been established to pay for cancer drugs that have not been approved by NICE and are not available within the NHS in England. “Improving Outcomes: A strategy for cancer”, Department of Health, January 2011.

178 However, as they note, it is not possible to determine if this reflects NICE decision-making, the selection of topics or other characteristics of the decisions within each disease area, patient access schemes or the role of different stakeholders such as patient groups. Dakin et al., “The influence of cost-effectiveness and other factors on NICE decisions”, CHE Research Paper 93, 2013, for an empirical model on elements influencing NICE decisions.

- Use of QALY analysis and indirect use of threshold: including Mexico, Netherlands, and Sweden; and
- No use of QALY analysis: Brazil, Germany, France, Italy, Taiwan and South Africa.

We found that the use of thresholds seems to lead to more restrictions than in systems where a QALY is not used for oncology products as reflected in Figure 58.

Figure 58: Average HTA recommendations by therapy area and model of HTA

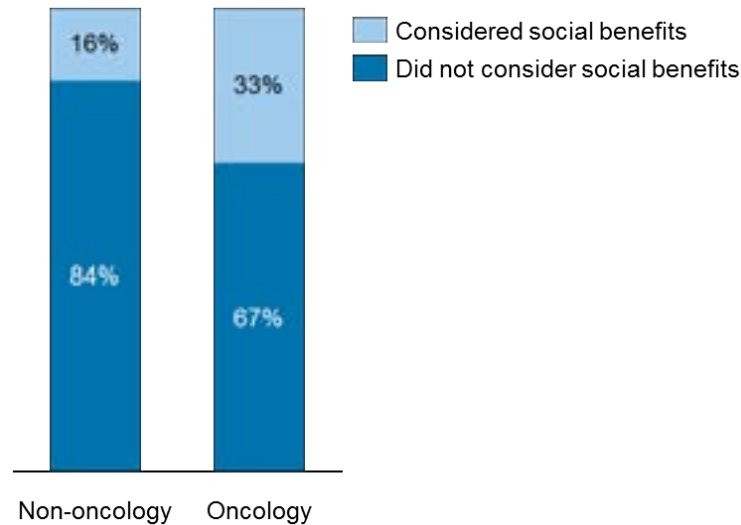


Source: CRA analysis; QALY with threshold includes: AU, CA, EN, PL, KR, SC, TH; QALY no threshold includes: MX, NL, SW; No QALY includes BR, GR, FR, IT, TW and SA

Societal elements are more likely to be included in HTA of oncology medicines

We find that the proportion of reviews taking into consideration societal elements was higher for oncology products than for non-oncology medicines. This is shown in Figure 59 which uses information from the Netherlands, Poland and Sweden, the only countries that refer to societal benefits in their assessments.

Figure 59: Proportion of reviews considering social benefits, by therapy area



Source: CRA analysis

4.7. Overall lessons from the 2013 assessment

In summary, we have identified several trends among the reviewed countries regarding scope and priorities, methodology, process and the impact of HTA.

- Health technology reviews are still mainly focused on new pharmaceutical products although the attention given to other health technologies appears to be increasing. Compared with the 2011 report, we found that more information on the cost/budget of the HTA agencies is publicly available.
- In terms of methods, we found more countries include societal costs in their guidelines. However, we still found few assessments where they were incorporated. This was the case only in Sweden, the Netherlands and Poland. We also found a growing trend to explicitly recognise the uncertainty in the assessments. We found some concern regarding the choice of comparators and the use of the lowest cost comparator.
- Regarding HTA processes, it is widely recognised that different stakeholders should be included in the process; however, only Canada, England and Scotland have a formal process. Interestingly, some progress has been made to incorporate patient views in a formal process and the need to include patients is recognised in countries with an emerging HTA system. However, there is significant room for improvement. As with the 2011 report, we found a large disparity on how the results are communicated with countries like England publishing HTA processes and results and countries like Mexico or Thailand, where the information available is limited.
- The largest change observed within the impact of HTA decisions relates to the length of the HTA process. In comparison to the 2011 report we found that HTA is now

undertaken in a more timely fashion. On average, we found a slight increase in the level of restrictions imposed, with some countries and significant differences across countries, indeed, this variation increased. Delays following the HTA process did not seem to vary by type of medicine. However, in some countries more innovative medicines faced the longest delays. The speed of uptake seems to be higher where less restrictions are imposed, reinforcing our conclusion from 2011 that the impact of the restriction imposed by HTA remains significant. Interestingly, we did not find the link between HTA and updating clinical guidelines is automatic; this could be improved. Finally, the need to assess the role of HTA is more prominent than in the first Comparison report but there is no process for monitoring the impact of HTA in most markets.

5. Ongoing debates and areas for future work

In this final chapter, we consider some of the implications of the analysis presented in the previous chapters, discuss the development of HTA in other countries and set out how this analysis could be extended or improved in the future. We briefly review:

- Emerging debates;
- Regional HTA networks, harmonisation and coordination;
- The development of HTA in emerging economies; and
- How the methodology could be improved in the future if it is updated.

5.1. Emerging debates

In the country analyses undertaken for this project it is clear that there are many countries experimenting with ways to accelerate the assessment process. There are a variety of approaches, for example, providing more guidance on the evidence required, starting the assessment prior to market authorisation, truncating the process for particular medicines or through the prioritisation process. It was noted in the interviews that it will be interesting to assess the degree to which the accelerated HTA processes interact with the ongoing debate regarding adaptive pathways.

During the analysis we discussed the development of value based pricing (or value based assessment). The proposal to introduce this in England was not published while this report was in development. However, based on the interviews undertaken, the current expectation (from all stakeholders) is this will be evolutionary rather than revolutionary. It seems likely that value based assessment will formalise the incorporation of wider social benefits and unmet needs. This should be captured in future analysis but it is unclear if this has implications for the methodology or approach used in this assessment.

5.2. Regional HTA networks, harmonisation and coordination

Over the last five years, we have seen considerable interest and effort to develop regional HTA networks. There are a range of initiatives between specific countries and supported by different forums, but we focus on three: EUnetHTA, Red Etsa and HTAsiaLink.

EUnetHTA was established in 2005 and includes 38 government-appointed organisations from 26 EU member states, Norway and Croatia, and a large number of regional agencies and not-for-profit organisations that produce or contribute to HTA. EUnetHTA Joint Action 1 focused on the development of common protocols and methodologies, Joint Action 2 (which started in 2012) is building on Joint Action 1. The aim is to provide recommendations on implementing a sustainable European network for HTA, continuing to develop the core HTA model and disseminating this through training and report. EU

netHTA is starting to apply these processes through a series of rapid assessment pilots (Rapid Relative Effectiveness Assessment, Rapid REA).¹⁷⁹

At the time of writing this report, three pilot reviews have been developed. The first one, published in December 2012, looked at the relative effectiveness of pazopanib for the treatment of advanced renal carcinoma. The pilot was mainly developed to test the usability of the Rapid REA model rather than provide input for decision making.¹⁸⁰ After the first pilot, the collaborators suggested that the main focus should be in the first four domains (health problem and current use of technology, description and technical characteristics of the technology and safety and effectiveness) and develop a short checklist for the ethical, organisational, legal and social issues. The second pilot looked at renal denervation systems for treatment-resistant hypertension.¹⁸¹⁻¹⁸² Similar information was included but the review mentioned the budgetary impact that renal denervation would have on healthcare resources.

Building on the EUnetHTA initiative and the requirements of the European Cross-border Healthcare Directive¹⁸³, there is now considerable momentum behind proposals to harmonise the principles and practice of relative effectiveness assessment (REA) across the EU. A permanent network exists as of October 2013, however it is too early to assess its impact in this report but this should be analysed in any update. Specifically, to determine if this reduces variation in assessment, increases or decreases the time taken for the assessment, changes the cost of HTA (for HTA agencies and for those submitting evidence).

In other regions, there are networks also in development. For example, in Asia, HTAsiaLink provides a network including organisations from China, Thailand, Malaysia, Singapore and

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- 179 Rapid Relative Effectiveness Assessment. Available here:
[http://www.eunetha.eu/activities/EUnetHTA%20Joint%20Action%2020\(2012-15\)/eunetha-joint-action-2-2012-2015](http://www.eunetha.eu/activities/EUnetHTA%20Joint%20Action%2020(2012-15)/eunetha-joint-action-2-2012-2015).
- 180 EUnetHTA, "Pazopanib for the treatment of advanced renal cell carcinoma. Pilot assessment using the draft HTA Core Model for Rapid Relative Effectiveness Assessment model", EUnetHTA WP5, Relative effectiveness of pharmaceuticals, 2012. Available here:
<https://eunetha.fedimbo.belgium.be/sites/5026.fedimbo.belgium.be/files/WP5%20JA1%20Pilot%20Pazopanib%20Report+Appendix.pdf>.
- 181 EUnetHTA, "Renal denervation systems for treatment-resistant hypertension. Pilot rapid assessment of other health technologies using the HTA Core Model for Rapid Relative Effectiveness Assessment", EUnetHTA WP5 Joint Action 2 Strand B, Rapid assessment of other health technologies such as medical devices, surgical interventions or diagnostics, 2013. Available here:
http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/WP5%20Strand%20B_2nd%20pilot%20rapid%20assessment_RDN%20systems%20for%20treatment-resistant%20hypertension.pdf.
- 182 As part of the second pilot, two additional reviews have been performed; on zostavax for the prevention of herpes zoster and postherpetic neuralgia in September 2013 and canaglifozin for the treatment of type 2 diabetes in February 2014. Both assessments test the methodology of the joint REA.
- 183 Article 15 of the Crossborder Healthcare Directive committed Europe to developing a more formal process for coordinating HTA.

South Korea. This is primarily focused on information exchange and sharing of best practice lessons.¹⁸⁴

In Latin America, a network is being developed called Red ETsa and funded by PAHO. The aim is to monitor the activities of national HTAs on a regional level and it came into force in June 2011, with 13 affiliated members including: Argentina, Bolivia, Brazil, Canada, Chile, Colombia, Costa Rica, Cuba, Ecuador, México, Paraguay, Peru and Uruguay. There are currently 22 international institutions that are members of Red ETsa.¹⁸⁵ Unlike EUnetHTA, these institutions are focused on capacity building and sharing information rather than undertaking assessments.

5.3. The development of HTA in emerging economies

In this report we extended our analysis to include a wider range of countries (while still focusing primarily on countries with an articulated HTA process). Specifically, we included Taiwan, Thailand, Mexico and South Africa. If the analysis is updated in the future, it will be useful to consider a number of other countries:

- China: There is not a formal HTA process in China but there is a debate regarding the application of HTA in the current system. There are a number of academic centres driving discussions on HTA. The primary HTA institution in China is CNHDRC and its Health Policy Evaluation and Technology Assessment office, established in 2007. HTA is also conducted by the Pharmacoeconomics Evaluation & Research Center at Fudan University. An HTA network established at four universities in 1997: economic evaluation at Shanghai, evaluation of a technology standard for medical equipment at Hangzhou, ethics evaluation at Beijing and evidence-based medicine at Chengdu. HTA is scattered among many administrative areas. There is no national HTA commission to coordinate HTA at the different authorities. CNHDRC remains the most active institution and has the closest connection to central government and coordinates the research of international, domestic and medical institutions. Pharmacoeconomic evaluations are increasingly applied and guidelines were published in 2011 by the Chinese Medical Association.¹⁸⁶ Currently, the submission of pharmacoeconomic data is not yet mandatory for pharmaceutical companies. NICE International has advised the Chinese government, however, given the current health system challenges, this advice is focused on development of capabilities and clinical guidance rather than assessing individual therapies. It is too early to include China in a comparison of this kind but this could change in coming years.

184 "First step of the HTA collaboration in Asia". Available here: <http://www.hitap.net/en/news-documents/documents/booklet/10847>.

185 "The role of HTAs in Market Access in Latin America" . Available here: <http://healthcare.blogs.ihs.com/2013/04/22/the-role-of-htas-in-market-access-in-latin-america/>.

186 Hu, "HTA Trends in China – The Present and Future", ISPOR 16th Annual European Congress, 2013.

- India: There is no established HTA practice in India but there is a growing engagement of policymakers in the debate over its introduction. A recent study identified HTA as a necessary tool for efficient allocation of resources as health expenditure in India is increasing.¹⁸⁷ The authors suggest that HTA should be conducted in support of reimbursement and pricing decisions and the division of clinical guidelines. However the process should be adapted to the Indian system which is characterised by serious financial constraints and rapid demographic changes as well as large infrastructure challenges and a lack of health financing. Workshops and training have been organised in India to increase awareness of HTA and prepare the different stakeholders prior to the introduction of this practice.¹⁸⁸ In June 2013 the Department of Health Research in India and NICE in England signed a Memorandum of Understanding to form a partnership for the development of an HTA framework in India.¹⁸⁹
- Russia: There is no formal HTA agency in Russia but assessments are done by the Formulary Committee at the Russian Academy of Sciences to support decisions on inclusion in the primary drug list.¹⁹⁰ A formal set of guidelines for clinical and economic evaluation was published in 2010 by RSPOR, the Russian chapter of ISPOR, and the Russian State Medical University.¹⁹¹ Workshops and trainings are often organised in an attempt to improve system transparency and application of guidelines.¹⁹² However, at the moment there is no formal HTA process, thus HTA does not play a role within the current pricing and reimbursement system in Russia.

5.4. Future coverage and methodological issues

The updated report has covered a similar number of countries and case studies as the 2011 report. This provides a solid database to examine changes over a 3-4 year period and to cover emerging systems. Greater transparency means that many more data points and assessment are available for analysis.

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- 187 Hass et al., "Health technology assessment and its role in the future development of the Indian healthcare sector", *Perspectives in Clinical Research*, 3(2), 2012.
- 188 Gabbay et al., "Workshop on the Potential for HTA in India", 2011. South Asia Network for Chronic Disease; Sharma, "Presentation on HTA in India: Roles and Goals of practice", ISPOR India, 2013.
- 189 "UK and India to work together on evidence-informed healthcare policy and practice", British High Commission New Delhi, 2013.
- 190 Vorobiev, "Health Technology Assessment in Russia", ISPOR – RSPOR, 2012.
- 191 Pigorov, "Procedure for clinical and economic evaluation of drug lists that are submitted for reimbursement coverage from public healthcare budget. Decision-making criteria", ISPOR, 2010.
- 192 "2013 Activities", ISPOR HTA Russia Regional Chapter 2013; "International Forum: Europe and Russia development vector harmonization: I and II session", Russian Academy of Sciences and WHO, 2012.

In this updated Comparison report we used the methodology developed in 2011 to include additional metrics, included a diffusion analysis, widened the set of stakeholder perspectives, undertook a therapy-specific analysis and introduced a distinction between metrics that focus on system design and system operation. There are areas that could be improved further:

- It could be useful to go through the principles and set out metrics that capture design and operation more consistently (as we have largely used the 2011 metrics to maintain comparability).
- Given the two datasets (2013 and 2011) there is opportunity for statistical analysis of HTA decisions. There is a range of analyses that could be undertaken using the dataset developed for this project, but this is beyond the scope of this assignment.
- In terms of the diffusion analysis, it would be interesting to develop a statistical analysis to see if HTAs have any significant effect on delays of market entry or on the speed of uptake of innovative drugs.