



WHO / HAI Project on Medicine Prices and Availability

**Review Series on
Pharmaceutical Pricing Policies and Interventions**

Working paper 6:

**The Role of Health Technology Assessment in Medicine Pricing and
Reimbursement**



WHO / HAI Project on Medicine Prices and Availability

**Review Series on
Pharmaceutical Pricing Policies and Interventions**

Working paper 6:

**The Role of Health Technology Assessment in Medicine Pricing and
Reimbursement**

June 2013

Patricia Whyte and Cameron Hall
Deakin University, Australia

© **Health Action International 2013**

All rights reserved.

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of Health Action International concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by Health Action International in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

Health Action International do not warrant that the information contained in this publication is complete and correct and shall not be liable for any damages incurred as a result of its use.

The named authors alone are responsible for the reviews expressed in this publication.

Table of contents

Abbreviations.....	vii
Acknowledgements.....	ix
WHO/HAI Pricing Policy Working Group.....	ix
Foreword.....	xi
Executive summary.....	xiii
1. Introduction.....	1
1.1 Objectives.....	2
2. Methods.....	3
3. Results.....	5
4. Discussion.....	7
4.1 The role of health technology assessment.....	7
4.1.1 A summary of the history of health technology assessment.....	7
4.1.2 The role of health technology assessment in low and middle income countries... 8	
4.1.3 The role of health technology assessment in high income countries.....	10
4.1.4 What are the effects of applying health technology assessment?.....	12
4.2 Implementation of health technology assessment.....	13
4.2.1 Prerequisites for implementation of health technology assessment.....	13
4.2.2 Applying health technology assessment undertaken elsewhere.....	19
5. Conclusion.....	21
5.1 Recommendations.....	21
5.2 Limitations and areas for future research.....	22
Appendix 1:.....	
Summary of literature relevant to the use of HTA in low- and middle-income countries .	23
Appendix 2:.....	
Summary of available literature relevant to use of HTA in high-income countries.....	36
References.....	49

List of Tables

Table 1. Embase search strategy

Table 2. Cochrane Library search strategy

Table 3. Exclusion and consolidation process

Table 4. Prerequisites for implementation of Health Technology Assessment

Abbreviations

AHTAPol	Agency for Health Technology Assessment in Poland
CADTH	Canadian Agency for Drugs and Technologies in Health
CBA	Cost-benefit analysis
CDR	Common Drug Review (Canada)
CEA	Cost-effectiveness analysis
CMA	Cost-minimisation analysis
CUA	Cost-utility analysis
HAI	Health Action International
HIC	High-income countries
HTA	Health technology assessment
INAHTA	International Network of Agencies for Health Technology Assessment
LMIC	Low- and middle-income countries
MIC	Middle-income country
NICE	National Institute of Health and Clinical Excellence (UK)
OECD	Organization of Economic Co-operation and Development
PBAC	Pharmaceutical Benefits Advisory Committee (Australia)
PBS	Pharmaceutical Benefits Scheme (Australia)
PHARMAC	Pharmaceutical Management Agency (New Zealand)
QALY	Quality-adjusted life year
WHO	World Health Organization

Acknowledgements

The authors would like to thank members of the WHO/HAI Pricing Policy Working Group for providing guidance and for reviewing the paper.

WHO/HAI Pricing Policy Working Group

Alexandra Cameron, UNITAID; Abayneh Desta, WHO Regional Office for Africa; Jaime Espin, Andalusian School of Public Health, Spain; Margaret Ewen, Health Action International, The Netherlands; James Fitzgerald, WHO Regional Office for the Americas; Claudia Habl, Gesundheit Österreich GmbH (ÖBIG), Austria; Catherine Hodgkin, The Netherlands; Loraine Hawkins, United Kingdom; David Henry, University of Toronto, Canada; Kees de Joncheere, Department of Essential Medicines and Health Products, WHO; Panos Kanavos, London School of Economics, United Kingdom; Richard Laing, Department of Essential Medicines and Health Products, WHO; Zafar Mirza, Department of Public Health, Innovation and Intellectual Property, WHO; Anban Pillay, Department of Health, South Africa; Dennis Ross-Degnan, Harvard Medical School, USA; Joan Rovira, Andalusian School of Public Health, Spain; Budiono Santoso, formerly WHO Regional Office for the Western Pacific, Brenda Waning, UNITAID; Kris Weerasuriya, Department of Essential Medicines and Health Products, WHO.

Foreword

WHO/HAI Project on Medicine Prices and Availability

Since 2001, the World Health Organization (WHO) and Health Action International (HAI) have been working in partnership to collect reliable evidence on medicine prices, availability, affordability and price components in low- and middle-income countries. To date over 100 medicine price and availability surveys have been completed or are underway using the WHO/HAI methodology, with results publicly available on the HAI website (www.haiweb.org/medicineprices). While this work continues to expand, the WHO/HAI project has evolved from supporting research to using the results to effect positive changes in related policies and interventions.

The results of the surveys confirm that substantial opportunities exist to increase availability, lower prices, and improve the affordability of medicines in all regions of the world and at all levels of economic development. However, it can be challenging to identify and prepare suitable lines of response.

At the request of national policy-makers, WHO/HAI and a group of international experts have developed guidance on various policies and interventions to increase medicine availability and make medicines more affordable, with a focus on low- and middle-income countries. This guidance takes the form of a series of in-depth reviews on pharmaceutical pricing policies (generics policies, external reference pricing, mark-up regulation, health technology assessments, and cost-plus pricing) and other related issues including the role of health insurance in the cost-effective use of medicines, encouraging competition, and sales taxes on medicines. The reviews are not meant to recommend one policy intervention over another, but rather provide guidance to policy-makers on the design and implementation of various policy approaches. For each review, a policy brief will be published that highlights key points from the review.

The results of the policy reviews show that relatively little has been published about the use of pharmaceutical pricing policies and interventions in low- and middle-income countries. Therefore, the review papers are published as working drafts, to be developed as more becomes known on the use of these interventions in low-and middle-income countries. We welcome information and comments that will strengthen these reviews (please forward them to Margaret Ewen, Health Action International email marg@haiweb.org).

WHO and HAI would like to thank the authors of the papers, the reviewers, and all the national contributors who provided information on the use of the interventions in their country. We are also grateful to the members of the Pricing Policy Working Group who have shaped this work.

We hope these papers will be a useful resource, and encourage national policy-makers to tackle the challenge of developing and implementing policies and strategies that ensure universal access to affordable medicines.

Dr Kees de Joncheere
Director, Department of Essential
Medicines and Health Products
World Health Organization
Geneva

Dr Tim Reed
Director
Health Action International Global
Amsterdam

Executive summary

This review aims to identify and describe the role of health technology assessment (HTA) in the price-setting and reimbursement of pharmaceuticals with a focus on its use in low- and middle-income countries (LMICs). Additionally it aims to identify and describe the prerequisites necessary for the implementation of HTA, and to assess the evidence concerning the impact of HTA on pricing and access to medicines in developing countries.

These objectives are addressed by way of a systematic literature search. Searching the Embase database, the Cochrane Library and specific journals resulted in the retrieval of 113 articles relevant to the topic. These articles are summarized in the appendices to this review and discussed with reference to the objectives. The information retrieved is dominated by qualitative reviews, mainly within the setting of high income countries. There are few examples of comparative evidence available and this is also acknowledged in some of the literature.

An overarching theme throughout the published evidence is that there is great potential for HTA to be adopted in LMICs. But despite a strong need for the efficient allocation of relatively scarce health budgets, many LMICs have not adopted HTA processes. The evidence concurs readily that HTA could be used to meet this ‘value for money’ objective. There are numerous barriers and prerequisites identified for properly introducing HTA into a health system, and limitations to HTA; however, there are also solutions to these problems suggested and discussions of successful implementation of HTA in developed countries around the world. Further, there is some evidence to show that HTA, when combined with other tools such as restricting reimbursement to pharmaceuticals on a national formulary (access to which includes a cost-effectiveness hurdle), can be used to manage medicines expenditure growth effectively.

The assessment of the evidence has resulted in three key recommendations:

- Health technology assessment is a way to introduce value for money in health expenditure and adoption of HTA could be considered in LMICs given the high need for the most efficient allocation of scarce health resources.
- Capacity for health technology assessment in LMICs should be established early and supported; prerequisites and barriers are extensive but not insurmountable and must be considered as health technology assessment processes are developed.
- LMICs should learn from countries where health technology is well established and follow their lead. In turn, developed countries need to share guidance and expertise and be transparent at all times. There is potential for generalisability and transferability of health technology assessment results from developed countries to LMICs.

1. Introduction

Rapidly rising expenditure on healthcare is a growing concern for governments and healthcare providers around the world. Countries have employed a variety of approaches in an effort to keep pace with the latest health technologies while maintaining affordable access to healthcare for patients. The use of health technology assessment (HTA) in allocating healthcare resources is one common approach adopted and is the focus of this review.

Health technology in its broadest context includes pharmaceuticals, vaccines, medical devices, medical and surgical procedures, and the systems within which health is protected and maintained. In turn, HTA studies the medical, social, ethical, and economic implications of development, diffusion, and use of health technology, as defined by the International Network of Agencies for Health Technology Assessment (INAHTA).

More specifically, HTA can be used to determine the best course of action when there are multiple options available. Economic analysis conducted as part of HTA can address the question of whether a new health technology provides any incremental benefit compared with current practice, and at what incremental cost. When the incremental benefit to patients is high and the incremental cost is low, good value for money is observed. The information provided by HTA can be used to optimise the prioritisation of resources in healthcare: good value for money investments take precedent over poor value for money investments. Unnecessary or risky investments can thus be avoided. In this way, overall healthcare expenditure can be managed.

Within HTA there are several types of economic analysis which are commonly used: cost-benefit analysis (CBA), cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-minimisation analysis (CMA). These are briefly described below:

- CBA: An economic analysis that considers both the costs and benefits of investing in a particular health technology compared with an alternative strategy. Costs and benefits are typically measured in present value monetary terms.
- CEA: A form of analysis that considers both the costs and effectiveness of investing in a particular health technology. Effectiveness can be measured in a variety of ways such as number of falls, number of hospital visits, length of recovery time or an improvement of quality of life for instance. CEA returns a result in the form of cost per outcome.
- CUA: A sub-form of CEA that takes into account the incremental costs versus incremental utility provided of a new health technology. Utility gain is a measure of quality of life improvement that uses quality adjusted life years (QALYs) as units.
- CMA: The health technology under consideration has been deemed equivalent in efficacy to that of current practice and as such only the cost is of concern. The new technology will be adopted if the true cost of funding is equal or lower than the cost of current treatment.

Economic assessment of pharmaceuticals (pharmacoeconomic assessment) is a sub-discipline of HTA and describes the formal process of comparing the value of one pharmaceutical with

another. For medicines, HTA tends to be implemented after the requirements for quality, safety, and efficacy have been met. The procedures for assessing quality, efficacy and safety have largely been standardised across developed countries. However the application of HTA, and subsequently decisions about pricing and reimbursement of medicines, remains the realm of national policy makers and there is considerable variability across countries.

1.1 Objectives

This review has five main objectives:

1. To identify and describe the role of health technology assessment (HTA) in the price-setting and reimbursement of pharmaceuticals with a focus on its use in low- and middle-income countries;
2. To identify and describe the prerequisites necessary for implementation of HTA;
3. To consider issues relevant to the appraisal of HTA and how to use HTA undertaken by others;
4. To identify and describe the available evidence on the impact of HTA on pricing and access to medicines;
5. To assess the evidence concerning the impact of HTA on pricing and access to medicines in developing countries.

2. Methods

To meet the objectives of this review a systematic literature search has been conducted.

The Embase electronic database was searched in February 2012 for original studies and reviews published in English on the use of HTA in pharmaceutical pricing and reimbursement decisions in developing countries. The Embase database comprises Embase, Embase Classic, and Medline. A search of the Cochrane Library, primarily for relevant systematic reviews, was also conducted. While the current search was for only for English-language articles it is hoped that any future updates of the literature search will include other languages.

Additional literature was sourced by scanning the reference lists of selected articles as well as searching the contents of the journals *PharmacoEconomics* and *Value in Health*. A total of 20 relevant articles were identified outside of the Embase and Cochrane searches.

Table 1 below sets out the strategy and key terms used in the search of the electronic database of Embase.

Table 1. **Embase search strategy**

Search	Terms	Items
#1	'health technology assessment' OR 'health technology analysis' OR 'pharmacoeconomics'	174,810
#2	'policy' OR 'policy making' OR 'decision making' OR 'prioritisation'	494,285
#3	'pharmaceutical' OR 'medicine' OR 'drug'	12,400,616
#4	'pricing' OR 'price setting' OR 'reimbursement'	40,917
#5	#1 AND #2 AND #3 AND #4	1,816
#6	'review' OR 'systematic review' OR 'guidelines' OR 'comparative study'	3,565,046
#7	#5 AND #6	790
#8	#5 AND #6 NOT 'clinical trial' NOT 'randomised controlled trial'	666
#9	#5 AND #6 NOT 'clinical trial' NOT 'randomised controlled trial' NOT 'vaccine' NOT 'immunisation'	636

Note that there is no specific term included to narrow the literature search to evidence from, and related to, low- and middle-income countries only. Including the descriptor term: ['developing countries' OR 'low-income countries' OR 'middle-income countries' OR 'emerging economies'] results in 381 hits when combined with search #1 AND #2 AND #3 from the table above. However, after examination, this search was found to omit potentially useful information that could relate to the implementation and role of HTA within developing countries (often articles based on the experience of implementing HTA within a developed country). For this reason it was considered appropriate to exclude the term.

Table 2 details the search strategy applied using the Cochrane Library.

Table 2. Cochrane Library search strategy

Search	Terms	Items
#1	health technology assessment OR health technology analysis OR pharmacoeconomics	922
#2	policy OR policy making OR decision making OR prioritisation	16110
#3	#1 AND #2	146
#4	pharmaceutical OR medicine OR drug	362323
#5	pricing OR price setting OR reimbursement	11445
#6	#4 AND #5	7206
#7	#3 AND #6	11

The 665 results returned by the Embase, Cochrane, and manual searches were then combined and the publication titles assessed for inclusion in the analysis. Publication abstracts were only examined when it was unclear whether or not an article ought to be included from its title.

Table 3 outlines the exclusion process including the exclusion criteria applied and the number of items excluded.

Table 3. Exclusion and consolidation process

Reasons for Exclusion	Embase	Cochrane Library
Total number of articles retrieved before exclusion process	636	11
Exclusions after inspection of title	488	0
Exclusions after inspection of abstract	56	10
Total number of articles excluded	544	10
Total number of articles remaining	92	1
Total articles from Embase and Cochrane	93	
Duplicates excluded	0	
Additional articles included after manual search	20	
Consolidated total number of articles	113	

Owing to the broad scope of the literature search, a large number of items have been excluded from consideration after viewing of the title and abstract. The excluded items were judged to have little or nothing to contribute to the role of HTA on pharmaceutical reimbursement within developing countries. These items were often specific cost-effectiveness studies of health technologies or concerned with cost-effectiveness information within a narrow disease area.

3. Results

The 113 articles remaining after the exclusion process are divided loosely into two categories: those that potentially relate directly to the application of HTA on pharmaceuticals in LMIC; and those that focus on HTA as practised within a HIC setting. It is recognised that this is a rough distinction with many items potentially related to both categories but it serves purely as an aid to interpreting the results of the literature search. A very brief summary of the main themes of each of the articles identified in the Embase and Cochrane searches is presented in two tables (consistent with the category distinction) in Appendices 1 and 2. Note that some articles had English- language abstracts but the full text version appeared only in another language (for instance Dutch). In these cases the themes of the paper are captured from the abstract if possible and the language of the full text is noted in the relevant table in the annexes.

The Cochrane search did not find any systematic reviews addressing the role of HTA in regard to price setting and reimbursement. One article was returned by the search relative to the use of HTA in middle income countries.

4. Discussion

The discussion is split into two main themes addressed under the subheadings: ‘The role of health technology assessment’, and ‘Implementation of health technology assessment.’ The first section presents a succinct description of the history of HTA focussing on how HTA has come to be used in healthcare systems in developed and high-income countries (HIC). This is contrasted with the role of HTA in low- and middle-income countries (LMIC) drawing on the evidence identified in the literature search. A discussion of the findings of the literature on the various effects of incorporating HTA is also presented. The second section of the discussion focuses on the prerequisites for the successful interpretation and application of health technology assessment.

4.1 The role of health technology assessment

4.1.1 A summary of the history of health technology assessment

Since the early 1990s there has been a significant increase in the literature on health technology assessments of medicines.

Australia was the first country to require pharmaceutical companies to produce economic data in support of new pharmaceutical products through its pharmaceutical benefits scheme (PBS) (1). The first set of formal pharmacoeconomic guidelines were published in 1992 and the pharmaceutical industry saw it as an attempt to exert downward pressure on pharmaceutical prices in Australia. Some economists also expressed concerns about the policy and methodology (2, 3, 4).

Soon after the introduction of the Australian guidelines came initiatives in Canada through what became the Canadian Agency for Drugs and Technologies in Health (CADTH) (5), and in New Zealand by the Pharmaceutical Management Agency (PHARMAC). In 1999 it was reported that five additional countries (Denmark, Finland, the Netherlands, Portugal, and the UK) required or might require in the future that economic studies be done to obtain reimbursement for a new medicine (6).

France and Spain were also exploring the adoption of a formal requirement in 1999. In France, HTA is currently used to inform pricing decisions rather than to choose among alternative therapies. In Italy, Spain, Germany and Switzerland, economic evidence is only considered in certain circumstances. Japan has adopted a developmental approach; no HTA was required prior to 1992, but since 1994 companies have been required to submit HTA data in support of their pharmaceuticals (7).

In a study comparing pharmacoeconomic guidelines from Australia, Canada, and the UK (8), several differences between country guidelines were noted and it was suggested that there

should be standardisation of methods. However, it can also be argued that HTA is still a developing discipline and setting standards would be counter-productive (9).

A 1999 study of pharmacoeconomic research in 13 European countries (9) found that HTA was used most frequently for reimbursement decisions and the least common use was for price negotiations. Other uses included formulary decisions, development of clinical practice guidelines, and communication with prescribers.

Over a decade later, the majority of the countries that form the Organization of Economic Co-operation and Development (OECD) now require HTA as part of their reimbursement decisions and a number of developing countries have also introduced HTA as part of their reimbursement policy. The requirements, assessment and decision making criteria applied by each country vary based on the health system.

In 2004 the European Commission and Council of Ministers targeted HTA as ‘a political priority’, recognizing there was ‘...an urgent need for establishing a sustainable European network on HTA.’ In 2005, 35 organizations across Europe came together to establish the European network for HTA project (EUnetHTA) that ran from 2006 to 2008. The network continued with the establishment of the EUnetHTA Collaboration 2009, the EUnetHTA Joint Action 2010-2012 and the EUnetHTA Joint Action 2012-2015.

In 2010 fourteen HTA organisations from developed and developing countries were assessed against the key principles identified by an international working group (10). Most organisations supported timely assessments, consideration of evidence and outcomes, and transparency. Organisations were less compliant with the generalisability of findings, the transparency of the link between HTA outcomes and decision making, the consideration of the full societal perspective and the monitoring of the implementation of HTA findings.

4.1.2 The role of health technology assessment in low- and middle-income countries

The literature identified in the systematic search referred to the public sector, the private sector and a mix of both. It is predominantly descriptive and qualitative in nature but there are a number of relevant topics discussed that relate to the role of HTA in LMICs. A summary of the key themes of articles classified as potentially relevant to the application of HTA within LMICs appears in Appendix 1.

A consistent theme throughout the literature is that information on cost-effectiveness, and HTA more generally, has an important and influential role in reimbursement decision making (11, 12, 13). However, HTA has not yet found a firm footing in many developing countries especially those of the Asia Pacific region (14). The success of applying the cost-effectiveness approach in Asia will be dependent on two major factors: the technical competence of the end users and the transparency of the decision making process (15). Formal HTA programmes barely exist in middle-income countries in Europe despite the need for efficient allocation of scarce resources being greater than in the high-income European countries (16).

The role of cost-effectiveness analysis in pharmaceutical reimbursement is growing but there is a need for greater cooperation between stakeholders (regulators and payers) to improve the pharmaceutical evaluation process in the interests of patients (17). Growth in the use of HTA and pharmacoeconomic studies is often explained as being due to the need for an effective measure to control health spending and gain efficiency (or best value for money) within a health budget (13, 18, 19, 20, 21, 22). HTA is also increasing in popularity because it takes into account other factors important for decision making, such as cost, social and ethical values, legal issues, and factors such as the feasibility of implementation (23).

Further evidence of the influence of HTA information is provided from a review of HTA activity in Poland - now a high income country (24). A positive HTA pharmaceutical review by the Agency for Health Technology Assessment in Poland (AHTAPol) is very often linked to a decision for reimbursement. The review revealed 30 medicines with positive HTA recommendations were included on the reimbursement list and four with negative HTA recommendations. The primary aims of AHTAPol, when it was established in 2006, included the assessment of health technologies and the gathering and dissemination of information about HTA results, methodology and guidelines development, for the Minister of Health. Establishing and supporting a governmental organisation related to HTA development is one of most important lessons to be learned from the Polish experience (25).

Barriers to the successful use of HTA were identified in a number of articles and some proposed solutions.

In many instances, decision makers do not have the skills (or access to researchers with skills) to objectively assess the relevant economic evidence (26). But suboptimal technical competence could be overcome by making the data requirement initially less stringent to allow the build up of capacity both in the private and public sector (15).

The timing of information has consequences for the assessment process. For example, the cost-effectiveness information required by Canadian provinces was often not available at the time of their decisions about listing new medications and partly because of this, there was no collaboration in the assessment process between Canadian provinces leading to large differences between provinces in the decisions made (27). These points are also relevant to LMICs.

The timing of economic evaluations can thus act as a potential barrier to the uptake of HTA (26). One solution to this could be that if manufacturers identify key decision makers and their needs during the initial planning stages of pharmacoeconomic studies, the studies can be designed to meet those needs efficiently without expensive, lengthy appeals, retrospective data collection processes, and re-reviews (13). All stakeholders benefit when manufacturers provide the suggested or required data for the appropriate population at a product's initial review. Tripartite discussions between pharmaceutical companies, HTA agencies and regulatory bodies, have the potential to satisfy the informational requirements of both regulators and payers (28). Some companies have observed that the advice from HTA agencies shows far more similarities than differences across countries. Consequently, the clinical evidence requirements for both registration and for HTA evaluation could probably be achieved in a well designed Phase III programme, without increasing costs or development times significantly.

Reimbursement decisions often consider information other than just cost-effectiveness results but the full range of decision criteria leading to a reimbursement price is often not transparent (29). There is an argument for the patient to play a greater role within HTA (in the interests of personalised medicine) and that comprehensible transparent communication of HTA reports and decisions is necessary (30). This is reinforced in a review of how HTA has evolved in several European countries over the decade (31). Countries have generally strived to modify their methods and practices to improve the impact of assessments on policy and practice. They aim to meet national objectives, the various needs of stakeholders, and achieve greater transparency, legitimacy and relevance. Transparency is also a concern recognised in Poland (32). The recent major restructuring of AHTAPol and new pharmaceutical reimbursement decisions have aroused doubts about the transparency of the decision-making processes. However, transparency is vital for convincing stakeholders that a decision is made based on sound and consistent principles. This is of particular importance in Asia with the prevailing culture of ‘top-down’ decision making (15).

Other problems with introducing a requirement for HTA include: inadequate links between knowledge producers and decision makers; lack of receptor capacity; limited acceptance of external data; methodological barriers and limitations of economic guidelines; and providing incentives for use of economic evaluation (26). An innovative solution could be to introduce an international clearing house for economic evaluation, which would help to facilitate the transfer of knowledge between different settings (26).

Other articles collected in the literature search highlight the great potential for growth in the role of HTA particularly in developing countries. The prospects for future growth and development are quite good in Asia (33) and there are encouraging, although not yet significant, steps being taken to embed more pharmacoeconomics into the Chinese health care system (34). There is a great opportunity for HTA to become an important part of health reform in China, especially to help policy makers within the health sector to make difficult decisions (35). The potential for growth in the role of HTA in Croatia, the Czech Republic, Hungary, Poland, Slovakia, and Slovenia was studied in 2003 (36). In these countries, health economic information was used in reimbursement rather than in pricing processes but more systematic formal requirements for health economic data have been identified and are expected in these regions within a few years.

If a regulatory system is to be established and maintained, it needs to have the cooperation of interested parties. It also needs the political will to implement and maintain a system of evidence-based decision-making in the face of the inevitable pressures from those who stand to lose from individual decisions (37). A descriptive history of HTA in Argentina (38) concludes that although some signals from the national government and congress show that there are plans to formally incorporate HTA to inform reimbursement policies, these signals are still very weak. What is needed in Argentina, according to the authors, is clear political will to push forward for a national agency of HTA, similar to that in other developed countries, to advance regulation on the adoption of new health technologies that are not only designed to improve technical or allocative efficiency, but also health equity.

4.1.3 The role of health technology assessment in high-income countries

The literature relevant to HTA in high income countries is largely descriptive in nature, with the exception of three comparative analyses (Drummond et al. (6) discussed later in the review; Levy et al. (39); and Garattini et al. (40).

In 2009 the journal *Value in Health* published a series of articles describing HTA systems in a number of countries, including France, Belgium, Germany and Japan. These articles provided a history of HTA within each country together with characteristics of the system used. Other descriptive literature focuses on specific examples of HTA issues within an individual country, for example the reimbursement of oncology medicines in Canada (41). There are also a series of older articles from the 1990s, which describe the initial use of HTA in countries such as Australia and New Zealand (see Appendix 2).

The analysis by Levy et al. (39) used a literature review and interviews to form a comparison of HTA systems in Canada, Sweden, Scotland, the Netherlands and Australia. It was designed to inform the debate in the United States regarding the use of comparative effectiveness research. The analysis identified seven characteristics of HTA that are common across the countries studied which could serve as insights for the US: 1) the process must be responsive to stakeholders' interests; 2) the assessment of medical technologies other than pharmaceuticals, may present different challenges and is managed separately in other HTA organisations; 3) completion of the HTA process following regulatory approval can delay market access to new technologies because of the link between HTA and reimbursement decisions. Closer integration between regulatory approval and HTA processes is being explored; 4) there is a direct or indirect link to reimbursements. Without this link comparative effectiveness research in the US will remain advisory; 5) given the diverse multipayer environment in the US, comparative effectiveness research could usefully focus on generating comparative effectiveness evidence; 6) a common metric for assessing intended and unintended effects of treatment allows comparison across different technologies; 7) a stated focus of comparative effectiveness research is on therapeutic benefit among high priority populations. This will be difficult to achieve because few randomised trials have the power to detect effect modification.

The authors concluded that the distinctive features of the US healthcare system must be taken into account when assessing the transferability of insights from other countries. This conclusion also applies to low- and middle-income countries when considering the applicability of HTA issues, particularly those from high-income countries (see below on generalisability and transferability).

The analysis by Garattini et al. (40) covers the pricing and reimbursement procedures for new and innovative pharmaceuticals in seven European countries (Belgium, France, Germany, Italy, the Netherlands, Spain and the UK). The literature was reviewed and experts consulted. The authors concluded that a solution to reward real innovation could be to allow a premium price for very innovative medicines according to their estimated cost-effectiveness. New pharmaceuticals with modest improvement could be grouped in therapeutic clusters and submitted to a common reference price, despite patent expiry. Such a 'dual approach' could be a sensible compromise to restrict pharmaceutical expenditure while at the same time rewarding companies that invest in high-risk basic research. It does not appear that this type of approach has been employed within any countries that use HTA.

How clinical and cost-effectiveness evidence is used in coverage decisions is the focus of a retrospective review of data from the Common Drug Review (CDR) of Canada, the National

Institute of Health and Clinical Excellence (NICE) in the UK, and the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia (42). The analysis found that significant uncertainty around clinical effectiveness was a key issue in coverage decisions. The uncertainty resulted from inadequate study design, the use of inappropriate comparators, or non-validated surrogate endpoints. The authors concluded that the results of the evaluation process in different countries are influenced by the context, agency processes, ability to engage in price negotiation and perhaps differences in social values. It is expected that this would also apply in low- and middle-income countries.

How can regulators and HTA experts contribute to innovation and pharmaceutical development instead of being perceived as barriers? In considering the relationship between medicines regulation and HTA, there is potential for synergy particularly given that sponsors now collect cost and utility data alongside traditional regulatory information in clinical trials (43). This allows for the development of cost-effectiveness analyses and the authors suggest that while the two processes may differ, there is ample scope to ensure improved integration.

4.1.4 What are the effects of applying health technology assessment?

This brief assessment of the effects of HTA is taken from the (mainly descriptive rather than comparative) literature resulting from the systematic search.

The Drummond et al. (6) paper provides a comparison of internal reference pricing and HTA in four countries - Germany, The Netherlands, Sweden and the UK - with regard to the initial price and reimbursement status of innovative pharmaceuticals. It considers medicines for four diseases: hyperlipidaemia, diabetes, rheumatoid arthritis and schizophrenia. The paper provides the price of the medicines considered and their reimbursement status. The authors conclude that the impact of internal reference pricing is only substantial when there are large differences in the prices of medicines in a given group or cluster. No clear pattern of the impact of HTA on prices could be determined. However, given that recommendations based on HTA can be conditional or limited to certain indications or patient sub-groups, the recommendations following HTA potentially reward innovation while considering value for money. The paper indicates that reference pricing alone does not represent a viable policy for obtaining value for money from pharmaceuticals; HTA represents a much better approach given the reward for innovation and value for money consideration. The authors suggest that a dual policy may be emerging, in which the primary policy for obtaining value for money from new medicines is based on HTA and supported by internal reference pricing or another approach.

In a 2010 study of middle-income countries where HTA activities are evident, it was found that the role of HTA differed from country to country (22). In Argentina, Brazil, China, Colombia, Israel, Mexico, Philippines, Korea, Taiwan, Thailand, and Turkey, HTA is developing at uneven speeds and the reimbursement of pharmaceuticals is arranged differently ranging from the highly centralised (e.g. Turkey) to the fragmented (e.g. Argentina). The trend in all countries is toward public sector programmes covering the entire population but out-of-pocket expenses are common despite increasing government expenditures on health.

The most consistently raised argument in favour of HTA is that it contributes to improving the value for money of health expenditure. Increased worldwide cost-consciousness with regard to healthcare spending has resulted in a greater reliance on pharmacoeconomics as a tool for obtaining optimal value, better outcomes, and controlling spending (13). These themes are consistently echoed throughout the literature assessed (similar statements in 13, 18, 19, 20, 21, 22, 44).

Some articles highlight that HTA, or a combination of tools including HTA, can have a substantial effect on pharmaceutical prices in negotiations and national pharmaceutical budget expenditure. Pharmacoeconomic information can manage health expenditure when it is used in the negotiation mechanism and lead to lower overall pharmaceutical expenditures, according to a qualitative review (11).

This finding is solidly backed up in a review of the role and impact of New Zealand's Pharmaceutical Management Agency (PHARMAC) (44). PHARMAC manages the pharmaceutical budget and decides which medicines will (and will not) be funded by the government. PHARMAC uses a variety of tools including HTA to increase the value of New Zealand's expenditure on medicines. PHARMAC's impact on aggregate expenditure on pharmaceuticals in New Zealand is evident: there has been a noticeable slow down in the growth rate of expenditure compared with (the high rate) in the 1980s. From 1993 to 1998, the growth rate averaged 5%. More significantly, for the year ended June 1999, it fell by around 5%. There has also been a steady trend towards patients being prescribed newer, more expensive medicines rather than older, cheaper ones. PHARMAC has made dramatic strides to improve the value of the government's expenditure on pharmaceuticals and its actions have meant that more funds have been available for investment in other health services than would have occurred if previous policies had remained unchanged.

The wider implication of adopting HTA processes is that the general quality of HTA is likely to improve. A descriptive study reiterates the influential role of HTA with reference to the experience in the Netherlands (45). The paper finds that since cost-effectiveness evaluations have become mandatory, the analyses have increasingly adhered to the published guidelines for evaluations in the Netherlands although not all analyses were performed correctly.

4.2 Implementation of health technology assessment

4.2.1 Prerequisites for implementation of health technology assessment

The requirements for implementation of HTA are significant. They include establishing a medicines regulatory system, developing and enforcing legislation, employing appropriate technical expertise, and the allocation of sector-wide financial resources in accordance with the decisions of the organisation using the HTA. This section discusses the prerequisites for successful implementation of effective health technology assessment in a health system. The discussion is informed by the literature search and as such relates primarily to medicines rather than the broader definition of health technology although many of the principles are generalisable.

Table 4 below summarises the key features required for successful implementation of HTA in a health system.

Table 4. Prerequisites for implementation of health technology assessment

Feature	Detail
Health funds	A national medicines funding organisation must be able to control a proportion of the government health budget relating to medicines.
Medicines regulation	A medicine regulation organisation to ensure the efficacy, safety and quality of medicines. Medicines may be granted marketing authorization in a country when the requirements of pharmaceutical efficacy and safety are demonstrated as compared with placebo or other comparator in randomised controlled trials.
National formulary	An established national list of medicines that are reimbursed with public funds. There may be some clearly defined exceptions to the formulary and it may or may not include medicines used in hospitals.
National organisation for managing the formulary	An organisation established to manage the national formulary. It may or may not conduct the HTA in-house. If not in-house, it must be ensured that the HTA is undertaken independently from the pharmaceutical industry. The organisation must have appropriate funding to undertake the HTA or to pay for HTA from external sources.
National decision making committee	An expert committee with relevant clinical experience to make decisions on the acceptance of medicines to the formulary. The committee should be supported by sub-committees with specific expertise (such as health economics or particular medical knowledge) where necessary. The committee should use set decision criteria to operate consistently for each case. The legal power to de-list medicines from the formulary as necessary is also required for the committee.
Medical expertise	At all levels medical expertise must be available to inform decision making and HTA. Where possible this expertise can be drawn from the national medical community so as to provide country-specific and relevant information.
Health economics and statistical expertise	Those conducting the HTA must have relevant skills in health economics and statistics. Skills include appraisal of medical data (randomised clinical trials and the like), construction and manipulation of economic models, and knowledge of budget impact analysis among others. Statistical capability is required to interpret medical data and perform analyses as needed. These skills may be applied to the evaluation of pharmaceutical submissions from the pharmaceutical industry or elsewhere, or applied in the assessment of medicines for which no submission has been received.
Access to medical data	The most recent medical data must be available for use in HTA. Organisations conducting HTA must have access to online databases of medical information. Prescribing information should be available on request

Feature	Detail
	both to pharmaceutical companies in the process of making an application and to the national decision making agency when considering a medicine for listing.
Technology	Technology requirements potentially include the ability to track medicine prescription and reimburse accordingly, and the computing technology necessary for economic modelling. Professionals developing HTA must have skills with modelling software such as Microsoft Excel or TreeAge Pro.
Guidelines for pharmaceutical submissions	Submission guidelines outline to the industry what is required for a pharmaceutical to be considered for listing on the formulary. The aim of guidelines is to ensure all information is available for a decision to be made and that the information considered is consistent across all applications. Guidelines may request demonstrations of medicine cost-effectiveness along with the clinical evidence for effectiveness and the proposed price of the pharmaceutical.
Pharmaceutical industry	Engagement with the local pharmaceutical industry is vital to encourage submissions for medicine reimbursement and to forge professional relationships that aim to meet local needs.
Health professionals	Clinicians and others directly involved in the health industry know the local requirements best. Transparent communication and regular consultation will provide the basis for understanding and gaining the trust of healthcare providers.
Patients and patient groups; consumers and consumer groups	Transparent and comprehensible communication of decisions is necessary to patients (the end users of the medicines assessed with HTA) and consumers. Consultation will aid understanding of the relevant issues and how HTA can provide solutions.
Legislative support	The application of HTA must be supported by national legislature in order to maintain integrity within the system in order to ensure that all medicines are treated equitably and reimbursement is managed appropriately. HTA, and the decision criteria employed by the national decision making committee for listing products on the national formulary, must be mandated by law.

The local needs of each country must be taken into consideration with regard to the entries in Table 4 above. Each country will have its own reasons for adopting an individual approach to the themes discussed and the role of HTA will vary with local circumstances. Selected items from this table are discussed below but are simply suggestions or ideas to consider when developing a country-specific approach to the use of HTA information.

Medicines regulation

A sound system for medicine regulation needs to be in place prior to the introduction HTA to measure medicine cost-effectiveness. Medicine registration and regulation will ensure that the efficacy, safety and quality of medicines designated for national use are evaluated. The regulatory body examines the chemical composition of the medicine, the manufacturing process, efficacy versus placebo (or other comparator if mandated) and evaluates the safety profile as compared with all known data on the medicine. If standards are not met then the medicine will not be registered for use and the HTA process will not be initiated. This provides

a foundation for HTA in that it can be assumed, before other assessment, that the medicine is well represented by the available medical data.

National formulary

The national formulary (or regional formularies where they exist) is the foundation of the medicines system. HTA is used (often with other criteria) to determine which products are listed and which are not. The formulary must represent good value for money health investments as it is funded with public revenues. As an example, below are the nine decision criteria that the PHARMAC Board of Directors uses for listing a medicine on New Zealand's Pharmaceutical Schedule:

1. The health needs of all eligible people within New Zealand;
2. The particular health needs of Maori & Pacific peoples;
3. The availability and suitability of existing medicines, therapeutic medical devices and related products;
4. The clinical benefits and risks of pharmaceuticals;
5. The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health & disability support services;
6. The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Schedule;
7. The direct cost to health service users;
8. The Government's priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC's Funding Agreement, or elsewhere; and
9. Such other criteria as PHARMAC thinks fit. PHARMAC will carry out appropriate consultation when it intends to take any such "other criteria" into account.

HTA in the form of cost-effectiveness appears in criterion 4, however, all of the criteria are related to and inform HTA in some way.

National organisation and decision making committee

In order for HTA to consistently inform the reimbursement decision the national organisation must ensure that HTA is applied in all instances when a medicine is considered for public listing on the national formulary.

The majority of applications for public reimbursement are most likely to come from the pharmaceutical industry, however, this should not preclude requests from other sources such as patient groups, clinicians, or the general public, for the national organisation to actively pursue an application from a pharmaceutical company. The usual process would be that the manufacturer of a new medicine lodges a submission (ideally with reference to the guidelines on pharmaceutical submission for consideration for public reimbursement) outlining the benefits versus the costs of the new medicine relative to what is currently used. The national organisation responsible for managing the national formulary will then assign the submission for evaluation, which may or may not be in-house. A health economist will conduct the evaluation which is then presented to a committee of experts for discussion. The committee

will, after considering the application and the independent evaluation, recommend to accept or reject (or defer pending future data) the pharmaceutical for listing on the formulary. A summary of the decision should also be made available publically.

The resources required for establishing a HTA organisation may initially have to be sourced through the government. Operating costs, however, could be funded at least in part through a submission fee applied to manufacturers. Resources are required to support the personnel in the national organisation. Expertise in a wide range of medical areas including biostatistics, pharmacoepidemiology, and health economics are vital; developing countries may need to offer competitive salaries and other incentives to attract and retain staff.

In February 2001 a survey of the economic assessment of pharmaceuticals was conducted amongst eleven OECD member countries (Australia, Belgium, Canada, France, Italy, Japan, The Netherlands, Portugal, Sweden, Switzerland, UK and USA) (46). On the topic of personnel, the survey found that the head of the HTA agency is usually appointed by the Department of Health. Staffing levels were variable (5 to 23 full-time employees) depending on the number of economic assessments conducted and whether external consultants were involved. Most countries use external consultants for processing/conducting HTA but one of the concerns with the use of consultants was the potential conflict of interest; countries require that consultants have no pharmaceutical industry links.

Health economics, medical and statistical expertise

Health economics is the application of the principles and rules of economics in the area of health and health care. It includes the evaluation of health policy and the health system from an economic perspective; health system planning; the demand for, and supply of, health care; the economic evaluation of medical technologies and procedures; the determinants of health and its valuation, and analysis of the performance of health care systems in terms of equity and allocative efficiency (INAHTA definition).

The economic evaluation of pharmaceuticals is necessary within HTA. An economic evaluation can weigh up the value of an incremental benefit versus an incremental cost of a new treatment compared against current clinical practice. The proper application and interpretation of economic evaluations requires expertise in health economics linked with medical expertise and the ability to interpret and apply statistics.

Pharmaceutical industry and consultation

The pharmaceutical industry perceives HTA as a barrier to gaining market access. As a consequence, the industry is typically resistant to the introduction of HTA as a policy. Preparing a submission for a medicine or technology that incorporates HTA may require additional skills; a company must either train or employ new staff, or contract a consultant, which is a considerable additional expense. Public reimbursement of a medicine, however, tends to offer a lucrative incentive for industry and the skills requirement is then not insurmountable. Many pharmaceutical companies are multinational organisations with the skills to make submissions

for product listing in developed countries; the expertise needed to adapt pharmaceutical submissions for local circumstances is often available.

To facilitate applications from industry for public listing of pharmaceuticals, a national organisation can establish effective guidelines for submissions. There should be consultation with the industry on the guidelines (along with consultations with medical experts, patients, academics in the field of health economics, the general public and other relevant stakeholders) which should be weighed against the goals and mandates of the national funding organisation. An important element in a successful pharmaceutical listing system is regular workshops on the guidelines to aid interpretation and communication with the pharmaceutical industry.

The decision making process must be transparent but also pragmatic towards the pharmaceutical companies supplying the products for listing. Although the reasons for decisions should be publicly available, all possible measures should be taken to preserve the integrity of commercially sensitive information. A public summary of the reimbursement decision without disclosure of sensitive information would contribute to the transparency of the process and public understanding.

Health professionals, information and consultation

It is important that health professionals, particularly doctors and pharmacists, understand the purpose of health technology assessment and the decision making process. There is often the perception that the patient is provided with substandard care in order to save money when in reality the latest medicine or technology may not represent a cost-effective use of public funds compared with alternatives. The aim is to weigh up effectiveness with cost, and to enable comparisons across all potential health technology investments.

Medical specialists are usually keen to prescribe new medicines or to use new health technologies. A rejection for reimbursement of a new medicine may be interpreted as restricting the ability to pursue all possible courses of action for a patient. Early and effective consultation with specialists in the field before decision making is one way to address this issue.

Patient and consumer groups, information and consultation

Patient groups (and some consumer groups) monitor the entry of new medicines into the market particularly where these relate to the therapeutic area or disease that they represent. They can have both positive and negative impacts on the medicine reimbursement environment although the formation of patient groups ought to be encouraged. These groups often offer valuable support networks and can bring to public attention the views of certain patients. A group can thus provide a reasonable check or balance against a national funding organisation. Adequate consultation with patient groups can be an effective means of communicating key issues that underlie health technology resource allocation; the setting up of a forum will also enable the concerns of patients to be heard. However, as patient groups operate with a common goal and tend to source their funding from interested pharmaceutical companies, they can also be used to exert pressure on pharmaceutical funding organisations. To operate effectively, reimbursement organisations must not put the interests of a well-organised patient group ahead of other

patients. Health resources must be allocated equitably according to the preferences of society so as to avoid a situation where the ‘squeaky wheel gets the grease.’

Legislation

The introduction of HTA requires legislation to enforce the process. Enacting legislation can take several years if there are challenges from the pharmaceutical industry and other stakeholders. The legislation should clearly define what is expected in HTA by referencing guidelines: the evaluation and analysis process; decision making criteria; the roles and composition of various committees that should be established; whether the opportunity exists to appeal/reapply if unsuccessful; whether the findings of the evaluation will be made available to the public; the fees that would be levied for each application.

The decisions of the national organisation regarding the economic benefits of a particular product may be at odds with the applicant. The survey of eleven OECD countries (46) notes that some countries have an appeals procedure whereby an applicant can appeal against a government’s assessment decision. In other countries it is not possible to appeal the decision directly. Where there is no specific appeal process via government channels, applicants can always seek a review of the process in the courts of law. Legislation should allow for decisions of the national organisation to be challenged under certain circumstances and also recourse against pharmaceutical suppliers if they have not met contracted terms, for instance.

4.2.3 Applying health technology assessment undertaken elsewhere

The adaption of HTA across countries is a key concern, particularly for low- and middle-income countries which may be initiating HTA. If an analysis can be applied to another jurisdiction without adjustment, it has been defined as generalisable (47). It is transferable if it can be adapted to apply to another jurisdiction. A proposed adaption scale includes the following characteristics: no adaptation (transfer research); simple adaptation (e.g., perform exchange rate conversion of costs); more complex adaptation (replace all data inputs with appropriate data from the local jurisdiction); sophisticated adaptation (replace all data inputs and re-structure the analytical framework); and impossible adaptation (conduct new research specific to the jurisdiction) (48).

It has been argued that common HTA and economic evaluations across jurisdictions (i.e., countries) would contribute to a more cost-effective use of resources in regard to informing pricing and reimbursement decisions (49). In contrast, another commentary argues that despite common principles, the process of HTA, in particular the economic evaluation component, needs to be nationally-based (50). The results of an economic evaluation in one setting may not be applicable to another setting and consequently country-specific evaluations are needed which reflect the needs of decision-makers within a particular country. Nonetheless, there remains scope for collaboration between countries as each country can learn from the experiences of another country.

There is a need for high- income countries to provide technical assistance to middle-income countries in Europe in order to institutionalise HTA in decision making (16). Some HTA information will be relevant in every setting, for example, evidence from systematic literature reviews and evidence from randomised controlled trials regarding the efficacy and effectiveness of an intervention. However, factors such as the epidemiological profile of disease, models of clinical practice, relative prices and unit costs, the availability of healthcare resources and budget constraints, as well as the choice of health benefit, comparator, comparability of treatment patterns and populations, are more country-specific and hence may hinder the generalisability of results.

The transferability of results from one policy setting to another requires consideration of changes in resource implications, unit prices, and outcomes. The points made by Vale (50) tie in with the systematic review of the generalisability of pharmacoeconomic studies by Mason et al (51). Similarly, unit costs have been the factor most frequently cited as generating variability in economic results between locations. Regression analytic methods have indicated that some components of resource use are exchangeable across locations while others are not, and both cost and effectiveness aspects of decision analytic models may need to be adapted between locations (52).

It is reasonable to conclude that while the technical aspects of best practice within HTA, such as transparent reporting of methods and findings, are uncontroversial and can be applied across high-, middle- and low-income countries, other aspects of HTA are best developed specific to each setting. However, countries with limited HTA capacity can prioritise assessments based on the practice of high-income countries where HTA is well established. For example, if a high-income country finds that a particular technology is not cost-effective, it will likely not be cost-effective in a low- and middle-income setting either (16).

5. Conclusion

The results of the systematic literature search and the subsequent analysis and discussion have shown that there is little comparative and quantitative evidence on the effect of the application of HTA. This is especially true in the setting of low- and middle-income countries. However, much descriptive evidence was assessed which enables several conclusions to be drawn on the role of HTA and the likely impact that HTA would have if incorporated into health systems.

Many low- and middle-income countries have not adopted HTA processes and the ones that have are developing HTA processes at uneven speeds and have different informational requirements. A key theme of the evidence is that there is a great potential for HTA to be adopted in LMICs. These countries have the greatest need for efficient value-based allocation of their limited health funds. The literature identified that HTA is key to enabling this cost-effective allocation.

It can be concluded that there are many barriers to the introduction of formal HTA processes such as the potential shortage of expertise; timeliness of necessary information; linking the different parts of often fractured health systems including pharmaceutical companies, experts, researchers, and decision makers; and transparency of outcomes. These barriers are substantial but they can be overcome, and the evidence from the literature search addresses possible solutions in each case.

There is some evidence to show that HTA, when combined with other tools such as restricting reimbursement to pharmaceuticals on a national formulary (access to which includes a cost-effectiveness hurdle), can be used to manage medicines expenditure growth effectively. This is an important result as the evidence indicates that many aspects within HTA systems in developed countries are generalisable and transferable to low- and middle-income countries.

5.1 Recommendations

- Health technology assessment is a way to introduce value for money in health expenditure and adoption of HTA could be considered in low- and middle-income countries given the high need for the most efficient allocation of scarce health resources.
- Capacity for health technology assessment in low- and middle-income countries should be established early and supported; prerequisites and barriers are extensive but not insurmountable and must be considered as health technology assessment processes are developed.
- Low- and middle-income countries should learn from countries where health technology is well established and follow their lead. In turn, these countries need to share guidance and expertise and be transparent at all times. There is potential for generalisability and transferability of health technology assessment results from high-income countries to low- and middle-income countries.

5.2 Limitations and areas for future research

While this review has collected and assessed a large amount of literature relevant to the role of HTA in LMICs it is subject to some limitations that are briefly discussed below.

As the design of the review is based on a systematic literature search, there has been no direct contact with decision makers or representatives from LMICs. Information from LMICs where HTA is not well established can be difficult to obtain. Discussion on the role of HTA may not be published or available online; in this situation contact with representatives with firsthand experience with pharmaceutical reimbursement in LMICs would be ideal. The contacts may be able to share important and up to date insights on the key challenges faced by their country.

The objectives of the review are difficult to incorporate in a targeted search strategy within a literature database. The systematic search conducted yielded 636 hits but there is some concern that often relevant literature has not been captured in the search. Omitting the terms of ‘review’ OR ‘systematic review’ OR ‘guidelines’ OR ‘comparative study’ from the strategy results in more than 1800 potential hits. Due to time and resource constraints a thorough investigation of 1800 potential articles was not possible (the vast majority of these items would be excluded but it is very likely that the number of relevant articles to be analysed would increase considerably).

Owing to the results of the literature search being dominated by discussion pieces and descriptive articles, the conclusions generated are general and broad. This leads onto a possibility for future research. LMICs looking to develop the role of HTA in pharmaceutical reimbursement would likely benefit from targeted research that takes into account local circumstances. There is a need for research on individual LMICs and what is required for the development of HTA in that particular situation. This research could contribute focused and specific recommendations.

As was raised earlier in the review and reiterated here, there is a lack of quantitative evidence comparing the impact of HTA on prices and reimbursement in developed countries let alone developing countries (little can be expected when HTA is in very early stages of establishment). Future research must concentrate on the effect of HTA on pharmaceutical prices and reimbursement and medicine access. This could be performed in comparison with other price control measures such as reference pricing of medicines or pro-generics policy. The lack of studies on the impact of HTA constitutes an important gap in understanding the role and influence of HTA in health policy (31). As one commentator noted, whereas the previous 10 years have been well-spent on building the HTA infrastructure and evidence base, the next decade should focus on ascertaining outcomes.

Appendix 1: Summary of literature relevant to the use of HTA in low- and middle-income countries

Author	Type	Key Findings
Anis A.H. 1998 (53)	Review	<ul style="list-style-type: none"> All applications from drug manufacturers requesting Pharmacare (British Columbia government-funded drug insurance plan) coverage were evaluated by the Pharmacoeconomic Initiative (PI) of British Columbia. A total of 7 of the 21 products were recommended for formulary inclusion by the PI; 4 were full-benefit status and 3 were recommended under restricted use. Only 5 of 21 submissions, of which 4 had favourable reviews, complied with either the CCOHTA or the Ontario Ministry of Health guidelines. The results, based on actual experience from implementing HTA requirements, suggest that industry is slow to adapt and it may also be sceptical about the importance of cost effectiveness and guideline compliance in decision-making.
Augustovski 2009 (54)	Systematic review	<ul style="list-style-type: none"> Systematic review to determine to what extent health economic evaluations conducted in industrialised economies are generalisable to the Latin American and Caribbean region (LAC) and to other LAC countries. 72 studies, individual patient- and model-based health economic evaluations that involved at least one LAC country were identified in the literature search and included. Over one-third of the studies did not specifically report the type of economic analysis used. Cost-effectiveness and cost-consequence analyses comprised 78% of the studies. Authors state that overall reporting in the studies was poor and there was evidence of unfamiliarity with international guidelines. Reporting problems included issues related to sample representativeness, data collection and data analysis. Economic evaluation methodology was usually weak and less developed than the analysis of clinical data. There were a number of issues with the studies that precluded an assessment of their generalisability and transferability. Most studies had either general or specific 'knock-out criteria' such as a lack of acceptable quality or things like discount rate or perspectives which could not be assessed or were inadequate to allow for an assessment of generalisability.
Bending 2011 (12)	Systematic review	<ul style="list-style-type: none"> The search identified 12 quantitative studies and 23 qualitative studies on the influence of factors considered in the evaluation of pharmaceuticals on the reimbursement decisions of government funded bodies in OECD countries.

Author	Type	Key Findings
		<ul style="list-style-type: none"> • Cost-effectiveness was found to be consistently influential in reimbursement decision-making in Australia, England, Canada and The Netherlands. There was variation in the definition of clinical considerations and other factors in studies conducted in countries. • There is limited evidence on the influence of evaluation factors on reimbursement decisions in a few OECD countries with established reimbursement processes.
Bentkover 2002 (13)	Discussion	<ul style="list-style-type: none"> • Increased worldwide cost-consciousness with regard to healthcare spending has resulted in a greater reliance of health systems on pharmacoeconomics as a tool for obtaining optimal value, attaining better outcomes, and controlling spending. In such capacities, pharmacoeconomics is often used as a basis for pricing, purchasing, and reimbursement decisions. • If manufacturers identify key decision makers and their needs during the initial planning stages of pharmacoeconomic studies, the studies can be designed (with local physician input) to meet those needs efficiently without expensive, lengthy appeals, retrospective data collection processes, and re-reviews. All stakeholders benefit when manufacturers provide the suggested or required data for the appropriate population at a product's initial review.
Cai 2005 (34)	Descriptive review	<ul style="list-style-type: none"> • China must confront significant cost-containment in health care, as seen in every developing nation of the world. • Pharmacoeconomics is currently stagnating in China due to the lack of adequate academic research centres, pharmaceutical industry investment, and government coordination. • There are encouraging, although not yet significant, steps being taken to embed more pharmacoeconomics into the Chinese health care system.
Chen 2009 (35)	Discussion	<ul style="list-style-type: none"> • HTA is traced back to the early 1990s in China. HTA knowledge transfer and the establishment of HTA units were effective ways to develop HTA in China. • By the end of the 1990s, policy makers of the Ministry of Health made efforts to merge HTA with policy making to improve the quality and efficiency of health care. • There is a great opportunity for HTA to be an important part of health reform, especially to help policy makers within the health sector to make difficult decisions.
Delwel 2002 (55)	Review	<ul style="list-style-type: none"> • In the Netherlands, guidelines for pharmacoeconomic research have been published. These guidelines require a pharmacoeconomic study to contain a cost-effectiveness analysis and/or a cost-utility analysis and a budgetary impact analysis. • By 2005, all new drugs with therapeutic added value must supply a pharmacoeconomic evaluation in order to apply for reimbursement. • Full text in Dutch.
Doherty 2004 (33)	Review	<ul style="list-style-type: none"> • Pharmacoeconomics and outcomes research are being conducted mainly by academics. In addition, some pharmaceutical researchers are active and pharmaceutical companies are currently preparing to conduct more of

Author	Type	Key Findings
		<p>this research as part of their strategy for Asian pharmaceutical development.</p> <ul style="list-style-type: none"> Prospects for future growth and development in this field are quite good in Asia as rapid healthcare inflation, increasing rates of chronic conditions and aging populations, and increasing technology diffusion will underpin the need for greater awareness of the need to incorporate economic efficiency into health-care systems.
Filko 2010 (56)	Descriptive review	<ul style="list-style-type: none"> Evidence suggests that Slovak pharmaceutical expenditures do not result in the most cost-effective outcomes with several potentially not cost-effective pharmaceuticals reimbursed in Slovakia. Economic evaluations of medicines and medical devices are mandatory, but the quality of evaluations and critical appraisals are rather poor. Transparent methods of technology assessment can improve the consistency of reimbursement decision making on medicines and medical devices in Slovakia.
Glaeske 2008 (57)	Comment	<ul style="list-style-type: none"> Regulatory measures are trying to improve physicians' prescribing quality and efficiency based on the results of cost-effectiveness analysis. Full article is in German.
Goeree 2009 (23)	Review	<ul style="list-style-type: none"> HTA is increasing in popularity because it also considers other factors important for decision making, such as cost, social and ethical values, legal issues, and factors such as the feasibility of implementation. The HTA process adopted in Ontario, Canada is unique in that assessments are also made to determine what primary data research should be conducted and what should be collected in these studies.
Griffin 2008 (58)	Discussion	<ul style="list-style-type: none"> A formal decision analysis to inform reimbursement decisions allows those decisions to be made in a transparent manner when the available evidence and the assumptions used are reported. Transparency means that the methods may be criticized or challenged by those affected by the decision and helps to ensure that decisions made are defensible. By characterizing the decision uncertainty within a cost-effectiveness analysis, it can be used to inform both the reimbursement decision and decisions about acquiring additional evidence. This is a source of methodological challenges. Continued research to address the challenges advances the methodology of economic evaluation in health care.
Gulacsi 2009 (59)	Discussion	<ul style="list-style-type: none"> The main challenges for HTA in Hungary are partly similar to the ones in countries with a developed economy; cost-effectiveness analysis is needed; no questions asked. However, there are very important differences as well, that is why transferability and adaptability issues have to be considered. No HTA guidelines have been published in Hungary. The pharmaceutical coverage policy is very complicated; the ten different reimbursement categories make the whole system un-transparent and unmanageable. HTA results are not disseminated, and no dissemination strategy has been established. A mechanism to transfer HTA results into clinical practice guidelines is also missing. There are significant developments. The basic infrastructure, legal background, and training capacity for HTA are

Author	Type	Key Findings
		being established in Hungary. Successive HTAs and coverage decisions considerably increase the data available and trigger an accumulation of experience.
Harris 2001 (37)	Meeting report	<ul style="list-style-type: none"> • The use of economic evidence in decisions about medical technologies has become more widespread internationally in the past decade. The role of economic evaluation in the decision process varies from country to country. • The report discusses the role of economic evidence in reimbursement decisions in Australia, Canada, the Netherlands, and the UK. • A key lesson from the first few years of economic evaluation of medical technologies is that there is more to the implementation of cost-effectiveness analysis-based decision-making than the quality of the guidelines and the review itself. If a regulatory system is to be established and maintained, it needs to have the cooperation of interested parties. It also needs the political will to implement and maintain a system of evidence-based decision-making in the face of the inevitable pressures from those who stand to lose from individual decisions.
Hoomans 2010 (45)	Descriptive study	<ul style="list-style-type: none"> • Since pharmacoeconomic evaluations have become mandatory in the Netherlands, these evaluations increasingly adhere to guidelines for pharmacoeconomic research. This was particularly true of the perspective chosen, the relevant treatment comparator and the incremental and total analyses of costs and effects of the medicines under comparison. However, cost-effectiveness of new medicines was often inadequately validated by incorrect indications for use, and incorrect forms of evaluation or periods of analysis. In addition, costs and effects were not always correctly analysed. • Cost-effectiveness of new medicines and more valid pharmacoeconomic evaluations appear to play an ever more important role in reimbursement decision making and the pursuit of better and affordable health care.
Hutton 2006 (60)	Review	<ul style="list-style-type: none"> • To achieve a better understanding of the potential use of HTA an analytical framework was developed to describe and classify existing fourth hurdle systems. • Characteristics of the systems were grouped under four main headings: constitution and governance, objectives, use of evidence and decision processes, and accountability. • The analytical framework will help researchers and policy makers in individual countries to understand their own systems and will allow some preliminary sharing of experience between countries.
Johannesson 1995 (61)	Discussion	<ul style="list-style-type: none"> • Economic evaluations may be used as an aid to the development of treatment guidelines, decisions within healthcare organisations, and decisions relating to medicine approval, reimbursement and pricing. • It is argued that it is too early to introduce regulations that require the use of economic evaluations in, for example, reimbursement decisions. A more cautious approach might be preferred, where economic evaluations are used more selectively until the methodology and the field have developed further.
Kanavos 1999 (62)	Review	<ul style="list-style-type: none"> • Three categories of measures and their implications for pharmaceutical policy cost containment are analysed: supply-side measures (targeting manufacturers), proxy demand-side measures (targeting physicians and

Author	Type	Key Findings
		<p>pharmacists), and demand-side measures (targeting patients).</p> <ul style="list-style-type: none"> As part of the analysis of supply-side measures, the article examines the introduction of a fourth-hurdle (cost-effectiveness) requirement.
Kolasa 2011 (24)	Review	<ul style="list-style-type: none"> In terms of HTA activity, 63 negative and 83 positive HTA recommendations were issued. While clinical arguments were the most prevalent reason for negative HTA recommendations, major restrictions were most common in the positive guidance group. In terms of HTA impact, the results revealed 30 medicines with positive HTA recommendations and four with negative HTA recommendations were included in reimbursement lists. Most of AHTAPol's recommendations have a positive outcome for the product being appraised. The study revealed room for further enhancement of HTA impact.
Krol 2009 (25)	Discussion	<ul style="list-style-type: none"> AHTAPol was established in 2006 as a governmental organization whose aims are: assessment of health technologies, gathering and dissemination of information on HTA results, methodology and guideline development for the Minister of Health. Policy-makers, the public and clinicians mostly expect AHTAPol to be involved in the process of medicine and medical technology reimbursement through examination and discussion of evidence for the recommendations to be made by the Minister of Health (MoH). Establishing an organization on HTA development and supporting it is one of most important lessons learned from the Polish experience. International collaboration through exchanging experience, ideas, sharing knowledge or support in training staff is also important.
Kulkarni 2009 (18)	Discussion	<ul style="list-style-type: none"> Increasing health care cost is a major concern in the developing world and has increased individual economical burden. Pharmacoeconomics, a branch of health care economics, offers important guidance for the management of limited health care resources and medical practice.
Lenz 2011 (30)	Discussion piece	<ul style="list-style-type: none"> Some revisions to the traditional HTA approach are needed to assess the clinical, economic, ethical, legal and social issues and consequences specifically related to the field of personalized medicine. By providing the right therapy to each patient at the right time, patient outcomes can significantly improve, and so can the efficiency of the healthcare system. In this context it is of vital importance to give patients a more expansive role through comprehensible and transparent communication of HTA reports and decisions.
Li 2008 (15)	Discussion	<ul style="list-style-type: none"> Many Asian countries, such as Japan, Korea and China, spend a much higher percentage of their national healthcare budget on pharmaceuticals compared with the US and other countries within the Organization for Economic Co-operation and Development. The success of applying the cost-effectiveness approach in Asia will be dependent on two major factors: the first being the technical competence of the end-users and the second being the transparency of the decision making

Author	Type	Key Findings
		<p>process.</p> <ul style="list-style-type: none"> • Although the technical competence of end-users may currently be suboptimal, this may be overcome by making the data requirement less stringent at least initially to allow the build up of capacity both in the private and public sector. • Without an acceptable level of transparency, it is difficult to convince stakeholders that the decision made was based on sound and consistent principles. This is of particular importance in Asia due to the prevailing culture of ‘top-down’ decision making.
Liaropoulos 2000 (63)	Discussion	<ul style="list-style-type: none"> • Currently there are no efforts to control health technology in Greece. However, HTA has gained increasing visibility. • In 1997 a law provided for a new government agency responsible for quality control, economic evaluation of health services, and HTA. The hope is that the new law may introduce evaluation and assessment elements into health policy formulation and assure that cost effectiveness, quality, and appropriate use of health technology will receive more attention.
Liberti 2009 (28)	Descriptive review	<ul style="list-style-type: none"> • Facilitating tripartite discussions between pharmaceutical companies, HTA agencies and regulatory bodies has the potential to satisfy the informational requirements of both regulators and payers. • Some companies have observed that HTA and pricing and reimbursement agencies’ advice often shows far more similarities than differences across countries. Consequently, the clinical evidence requirements for both registration and for HTA evaluation could probably be achieved in a well designed phase III programme, and meeting the specific needs of these groups would not increase costs or development times significantly. • Early discourse among stakeholders will capture information that will support not only regulatory decision making regarding the safety and efficacy of a product, but will facilitate the HTA evaluation process, thus enabling decision makers to formulate pricing strategies that will meet needs. This will serve the goal of providing confidence to regulators and payers regarding their decisions while expediting patient access to medicine.
Liu 2009 (64)	Descriptive review	<ul style="list-style-type: none"> • The medicine approval criteria in China, Japan and Singapore are similar to those of the US FDA and many other countries, whose core measures are efficacy, safety, and quality, along with risk-based analyses in China and Singapore. • The cost-effectiveness is utilized for prioritization of new medicines listed in Singapore. Japan controls the price by government, whereas Singapore keeps market liberalism, and China maintains a mixture of both. • All three countries have established their own mechanisms, but cost-effectiveness requirements have not been fully introduced.
Maynard 2001 (21)	Comment	<ul style="list-style-type: none"> • Despite practical and methodological obstacles to the use of economic evidence in decisions, the logic of this development is evident: in order to maximise improvements in population health, scarce resources must be

Author	Type	Key Findings
		<p>targeted towards developing and applying technologies that deliver the greatest health gains per unit cost.</p> <ul style="list-style-type: none"> • The impact of this policy change on industry practice and profits will be considerable, and companies that fail to demonstrate the economic efficiency of their products will stumble at the fourth hurdle.
McDaid 2002 (26)	Review	<ul style="list-style-type: none"> • The use of economic evaluation knowledge in the policy making process is complex, and as yet there is little evidence to demonstrate that economic evaluation is used systematically in a decision making arena. • In many instances decision makers do not have the skills (or access to researchers with skills) to objectively assess this economic evidence. Barriers to the use of economic evaluation information include: <ul style="list-style-type: none"> ○ Inadequate links between knowledge producers and decision makers ○ Lack of receptor capacity ○ Limited acceptance of external data ○ Methodological barriers ○ Limitations of economic guidelines ○ Timing of economic evaluations ○ Providing incentives for use of economic evaluation • One possible vehicle for overcoming these difficulties may be the establishment of an international clearing house for economic evaluation, which would identify methodological differences and help to facilitate the transfer of such knowledge between different settings.
McGuire 2012 (29)	Editorial	<ul style="list-style-type: none"> • It is hardly controversial to state that price should be tied to value; the only difficulty is in defining value. • In France, Germany, and the UK, which account for approximately 20% of the world market but influences a much larger proportion of the world market, the value-based approach will form the basis of the main negotiation, although the negotiations will take account of a wider range of arguments to establish value. • In the most developed reimbursement regimes, it would appear that value is based on the degree of relative innovation associated with a new product around the time of launch. Yet, the reimbursement price will be established through a wider negotiation process, which is unlikely to be fully transparent.
Mota Pinto 2000 (65)	Discussion	<ul style="list-style-type: none"> • The Portuguese healthcare system is often portrayed as a National Health Service (NHS) model, characterized by universal coverage, comprehensive benefits, nearly free services, national tax financing, and public ownership or control of the factors of production. • However, in reality the system fails to accomplish these features in a complete way due to a number of problems. • This situation is encouraging interest HTA in Portugal, although activities are not yet very developed. Legislation requiring the presentation of economic evaluations for new pharmaceutical products was recently enacted. Present plans also call for the creation of a national agency for HTA.
Muller 2006 (66)	Perspective piece	<ul style="list-style-type: none"> • Several areas limit the usefulness of pharmacoeconomics. Lack of: (1) evidence-based data; (2) clinical endpoint data; (3) direct comparator studies. An impaired 'assay sensitivity' may cause uncertainty about the

Author	Type	Key Findings
		<p>appropriate value of a new medicine (4). Moreover situations with (5) incremental, small benefits, (6) lack of precedents in case of innovations or (7) obvious "efficacy-effectiveness gaps" may pose challenges in the pricing decision process for pharmaceuticals.</p> <ul style="list-style-type: none"> • Full article is in German.
Nellesen 2010 (67)	Editorial	<ul style="list-style-type: none"> • Better informed decisions based on superior evidence are to be expected, yet substantial barriers exist. • How will evidence from comparative effectiveness research (CER) be used in decision making by regulatory and reimbursement authorities, and by physicians? • How will effectiveness be evaluated in the context of other health technologies, given the significant challenges in conducting and interpreting CER other than drug-drug comparisons? • Will the application of results from CER appropriately address patient differences? • What will be the reaction to CER if it leads to increased costs (such as if the results of the research find that a specific medicine has a better efficacy/safety profile but is more expensive than its alternatives)? • How will CER impact on incentives for innovation? • And, most importantly, what will be the net impact on patient welfare?
Ngorsuraches 2012 (11)	Qualitative review	<ul style="list-style-type: none"> • Economic evidence, including budget impact and pharmacoeconomic evaluation, has also been very important for reimbursement decision-making in Thailand, China and South Korea. This evidence is sometimes used in negotiation mechanisms and leads to lower overall pharmaceutical expenditures. • Several common barriers, for example, human capacity and data availability, for obtaining economic evidence in all the three countries still exist. • Pharmaceutical reimbursement decision-making in Thailand, China, and South Korea is in its transition period. It seems to run in the same direction, for example, guideline development and pharmacoeconomic evaluation agency establishment. Pharmacoeconomic evaluation plays important roles in the efficiency of medicine reimbursement decision-making
Niankowski 2009 (32)	Discussion	<ul style="list-style-type: none"> • Several individuals and organizations have been involved in developing HTA, both from non-commercial and commercial standpoints. A goal to establish a national HTA agency appeared among the priorities of the Polish Ministry of Health in 2004 and was realized a year later. • The Agency for HTA in Poland published guidelines on HTA and established a sound and transparent two-step (assessment-appraisal) process for preparing recommendations on public financing of both medicines and technologies. The recommendations of the Agency's Consultative Council were warmly welcomed by the public payer. However, major restructuring of the Agency and new medicine reimbursement decisions aroused doubts on maintaining transparency of the decision-making processes.
Nuijten 2003 (36)	Systematic review	<ul style="list-style-type: none"> • The study covered Croatia, Czech Republic, Hungary, Poland, Slovakia, and Slovenia. In all countries health economic information was used in reimbursement decisions rather than in pricing processes.

Author	Type	Key Findings
		<ul style="list-style-type: none"> • Differences between the six countries were mainly variations in the relative importance of health economic data and the presence of explicit requirements and guidelines. • In most of the Central European countries it is more typical that authorities issue a brief list of required data for reimbursement submissions that includes health economic data. • More systematic formal requirements for health economic data are expected in the region within the next 3-5 years.
Oortwijn 2010 (22)	Review and survey	<ul style="list-style-type: none"> • The study selected middle-income countries where HTA activities are evident (Argentina, Brazil, China, Colombia, Israel, Mexico, Philippines, Korea, Taiwan, Thailand, and Turkey) to provide an overview of how HTA is used in these countries and its role in the process of pharmaceutical coverage. • Most of these countries have health care problems related to both equity and efficiency. The trend in all the countries is towards public sector programmes covering the entire population. • Out-of pocket expenses are common despite increasing government expenditures on health. • The market for pharmaceuticals in terms of the volume of sales for products is mostly dominated by generics. Branded imported pharmaceutical products tend to dominate the value of sales. • Most countries have a national formulary listing which pharmaceuticals can be reimbursed. However, the requirements (e.g. information on efficacy, safety, and pharmacoeconomic data) to be included in the formulary differ by country. Also the reimbursement of pharmaceuticals is arranged differently by country ranging from the highly centralized (e.g. Turkey) to the fragmented (e.g. Argentina). • In all the countries under study the use of HTA was relatively undeveloped; however, the increasing establishment of HTA organisations indicates that HTA is gaining interest and attention. It seems that increased health care spending and the resulting demand for access to modern technology gives a strong impetus to HTA. • A first priority area is to promote the concept of HTA by sharing of expertise and experiences in middle-income countries among professionals, policy-makers, academia, industry, health insurance sector, patients, consumer organizations, and people. Another priority is capacity building: a need for trained and experienced personnel for carrying out, interpreting, and using the results of HTA.
Pausjenssen 1998 (68)	Review	<ul style="list-style-type: none"> • We are aware of only two guidelines that are directly linked to purchase review: The Ontario Guidelines and the Australian Guidelines. Each of these is linked to a review process performed by a committee appointed by government to provide advice about the purchase of outpatient pharmaceutical products. • Published literature suggests that the textbook-type guidelines have not yet had significant impact (in the adherence of researchers to six basic principles of economic analysis), nor have they reached a broad enough audience. • Whether the decision-making process finds the guideline information useful is still unknown.
Perez	Conference	<ul style="list-style-type: none"> • In many countries within the Organization for Economic Co-operation and Development (OECD) health

Author	Type	Key Findings
Izquierdo 2009 (19)		<p>coverage is not complete and the state is not able to assume this responsibility.</p> <ul style="list-style-type: none"> • For Latin American and Caribbean countries it is important to maximise health while taking into the account the availability of resources. Regulatory agencies are required.
Rubinstein 2009 (38)	Discussion	<ul style="list-style-type: none"> • Argentina is an upper-middle income country with major healthcare problems related to both equity and efficiency. • In the past decade, Argentina, like many other Latin American countries, has undergone a profound reform of its healthcare system. • Although some signals from the national government and congress show that there are plans to formally incorporate HTA to inform reimbursement policies, these signals are still very weak. • What is needed in Argentina is a clear political will to push forward for a national agency of HTA that, similar to other developed countries, advance the regulation on the adoption of new health technologies to improve not only technical or allocative efficiency, but also health equity.
Rutten 1994 (69)	Review	<ul style="list-style-type: none"> • It can be argued that certain requirements for the design and execution of economic evaluation studies have to be met for these studies to play a relevant role in health policy. • In Europe, countries differ widely in the extent to which economic evaluation is supporting actual decisions on reimbursement and control.
Sansom 2010 (17)	Descriptive	<ul style="list-style-type: none"> • Internationally, there is a growing use of cost-effectiveness analysis as part of the decision-making process for the subsidy of pharmaceuticals. • As the costs increase, the capacity of the individual patient to pay for these medicines becomes limited and new medicines will generally not have a market unless they are subsidized. • There seems to be a divide between regulators and payers. All stakeholders need to work together to improve the efficiency of pharmaceutical evaluation processes to ensure that patients have timely access to safe and effective medicines at a price they and their nations can afford.
Shih 2009 (70)	Retrospective review	<ul style="list-style-type: none"> • Assessment of the use of data from an electronic health information system in Taiwan to assess cost-effectiveness of chemotherapy use among breast cancer patients. • A cohort of patients in the National Health Insurance Research Database in Taiwan who had been diagnosed with breast cancer and received chemotherapy following surgical tumour removal were identified and data from these patients were used to conduct a cost-effectiveness analysis comparing two different chemotherapy regimens. • Analyses indicated that cyclophosphamide, epirubicin, fluorouracil (CEF) was not cost effective compared to cyclophosphamide, methotrexate, fluorouracil (CMF), with CEF more costly and less effective than CMF. Sensitivity analyses indicated that CEF could have been more cost effective than CMF had the optimal dosage level for CEF been established for breast cancer patients in Taiwan. • The authors concluded that a population-based, fully integrated health information system provides useful data to

Author	Type	Key Findings
		<p>assess the cost-effectiveness of competing treatments and interventions in clinical practice and that such information may potentially inform policy makers of modifications that can be instituted to improve cost effectiveness of a new therapy.</p>
Shillcutt 2009 (71)	Editorial	<ul style="list-style-type: none"> • Discussion of pharmaceutical expenditure within South Africa and means of controlling expenditure, with the indication that the implementation of pharmacoeconomic analysis will take 2 to 5 years. • Editorial indicates that there would have to be sufficient capacity before pharmacoeconomic analysis could be implemented, which would require capacity-building for both the Department of Health and for industry.
Simoens 2010 (49)	Descriptive	<ul style="list-style-type: none"> • HTA and economic evaluation across jurisdictions could contribute to a more cost-effective use of resources with a view to informing pricing and reimbursement decisions. Such an approach would support jurisdictions with restricted resources or limited expertise in conducting and evaluating such exercises. • The customization of guidelines across jurisdictions raises the costs of gaining pricing and reimbursement approval. As a result, companies sometimes develop global decision-analytic models that are specifically designed to be adapted from jurisdiction to jurisdiction. A move toward more uniform evidence requirements between jurisdictions would facilitate the process of generating data during the research and development process, and would decrease costs of gaining pricing and reimbursement approval. • The development of a core model for HTA also shows that an approach across jurisdictions can take into account jurisdiction-specific guidelines.
Sivalal 2009 (14)	Review	<ul style="list-style-type: none"> • Although HTA has been well established in all developed countries, it has not found a firm footing in any developing countries. This is especially true of the Asia Pacific region, which covers much of the world population. • There are two broad categories of countries in the region: Australia, Malaysia, Singapore, New Zealand, China, Philippines, Korea, Thailand, and Taiwan, which have formal HTA programs, and others for which informal mechanisms or related activities exist, which includes Bangladesh, Bhutan, Brunei, Cambodia, India, Indonesia, Laos, Maldives, Mongolia, Nepal, Pakistan, Sri Lanka, and Vietnam. • Once HTA is established, it is important that it is used effectively. Perseverance and dedication is needed to ensure the success of an HTA programme.
Sorenson 2012 (31)	Review	<ul style="list-style-type: none"> • This paper reflects upon the development and evolution of HTA in Europe over the last decade, with a focus on England, France, Germany and Sweden. • While HTA in Europe has evolved differently across jurisdictions over the last 10 years, it is evident that countries have generally strived to modify their methods and practices to improve the impact of assessments on policy and practice, meet national objectives and the various needs of stakeholders, and achieve greater transparency, legitimacy and relevance. • In order to better link decision makers' needs with research agendas and account for the growing sophistication

Author	Type	Key Findings
		<p>of health technologies, increased attention will be placed on developing and considering different kinds of evidence and ways to generate such information.</p> <ul style="list-style-type: none"> • While HTA is often applied to coverage and reimbursement decisions, its influence in other areas of policy making seems set to grow (for instance in the case of value-based pricing). • Discussion around the disinvestment of existing, ineffective interventions is mounting to achieve greater health system efficiency. • In light of existing hurdles to use or implement HTA at the local level, a potential area for future work is how to better localise evidence-based decision making. • The lack of studies on the impact of HTA constitutes an important gap in understanding the role and influence of HTA in health policy. As one commentator noted, whereas the previous 10 years have been well-spent on building the HTA infrastructure and evidence base, the next decade should focus on ascertaining outcomes.
Sullivan 2010 (72)	Review	<ul style="list-style-type: none"> • Decision-making structures and review processes for reimbursement were developed for the selected countries including: Austria, Demark, Hungary, Ireland, France, Germany, Denmark, UK, Sweden, Australia, Canada, Taiwan, United States, and others. • Decision structures for reimbursement (e.g., coverage, coding, and payment) vary according to the type of product (e.g., pharmaceutical, medical device, diagnostic), the individual country and in some instances, by regions within the country.
Tantivess 2009 (73)	Descriptive review	<ul style="list-style-type: none"> • A description of the establishment and characteristics of the Health Intervention and Technology Assessment Program (HITAP) in Thailand. • Contextual background information about the development of HITAP and information about its structure, financing, staffing, management and the contribution of cost-effectiveness analysis to policy was reviewed. • HITAP only had 2 years of data when the paper was published so it was unclear what role HITAP research and associated recommendations have played in policy decisions. • The authors hoped that information based on the creation of HITAP as well as information on its strategies and management structure would be helpful for other resource-constrained countries when considering how to strengthen their capacity for conducting economic appraisals.
Taylor 2004 (20)	Review	<ul style="list-style-type: none"> • Licensing of medicines has traditionally been based on quality, safety, and efficacy. • Faced with increasing healthcare costs, many countries are now also requiring evidence of cost-effectiveness; the fourth hurdle. • The limited evidence available suggests fourth hurdle policies have contributed to more cost-effective use of medicines. • Increasing international harmonisation and greater openness could improve the operation of fourth hurdle systems.

Author	Type	Key Findings
Thatte 2009 (74)	Descriptive review	<ul style="list-style-type: none"> • In India, the Philippines, Malaysia, and Pakistan the Ministries of Health are generally responsible for the approval of health technologies through various agencies. • Reimbursement: A mix of social, voluntary private and community-based health insurance plans are available in India while the Philippine Health Insurance Corporation is responsible for reimbursement of medicines and medical devices in the Philippines. In Malaysia there is no formal reimbursement system, and in Pakistan the government reimburses medical claims of its employees. • One of the priority areas that the national regulatory agencies in the region would benefit from is human resource development to facilitate the process of evidence based assessment of health technologies.
Vuorenkoski 2008 (75)	Review	<ul style="list-style-type: none"> • Six separate studies analysing a decision-making process as a whole were identified. According to the studies, the most important groups in decision-making were experts and administrative persons. • The decision-makers had an explicitly or implicitly defined set of criteria that were considered in decision-making, with clinical evidence on the benefit and the costs being the main criteria used. However, formal pharmacoeconomic analyses were given a rather small role.
West 2002 (27)	Discussion from survey response	<ul style="list-style-type: none"> • Cost-effectiveness information required by the Canadian provinces is not available at the time of decision-making about listing new medications. • Efficacy information is generated in a scientifically rigorous manner, whereas effectiveness and cost data are estimates potentially subject to biases and evaluated by expert opinion alone. • There is no collaboration in the assessment process between Canadian provinces, leading to large differences between provinces in the decisions made. • Establishing a single national scientific review committee, with re-evaluation of each medicine's cost-effectiveness after a suitable period of monitored use, is recommended
Zikopoulos 2003 (76)	Systematic review	<ul style="list-style-type: none"> • Pharmacoeconomics is analysed as a part of decision processes at several stages of drug development and drug marketing. • It is expected that within Europe, the pharmacoeconomic function will continue to grow in importance in the pharmaceutical industry in the coming years and will have at least a moderate commercial impact on pharmaceutical manufacturers through the pricing and reimbursement mechanism.

Appendix 2: Summary of available literature relevant to use of HTA in high-income countries

Author	Type	Summary
Anis 2000 (77)	Systematic review	<ul style="list-style-type: none"> Assesses compliance of pharmacoeconomic studies submitted to Pharmacoeconomic Initiative of British Columbia Assesses methodological quality of individual submissions. Demonstrates importance of submitting guidelines-compliant analyses. 25 cost-comparison analyses, 14 cost-effectiveness, 11 cost-minimisation, 9 cost-utility and 29 budget impact analyses. 65 of 88 (74%) of submissions failed to comply with the guidelines. 80% of non-compliant analyses were cost-comparison or budget impact analyses. 74% of all submissions were not recommended for listing as a provincial drug plan benefit. 80% of non-compliant submissions were not recommended. 13 of 64 (20%) of non-compliant analyses were recommended for coverage while 10 of 24 (42%) of compliant analyses received a positive recommendation. An association between the type of analysis and type of recommendation was found, $p=0.03$ with cost-comparison and budget impact analyses less likely to be recommended.
Assiff 1999 (78)	Survey	<ul style="list-style-type: none"> Telephone and face-to-face interviews with members of the health economic units and chief executive officers of the top 21 Canadian pharmaceutical companies. Survey responses indicate that pharmaceutical companies are having difficulty justifying the importance of the health economic department because of inconsistencies in the interpretation of economic evaluations by healthcare payers.
Bae 2009 (79)	Review	<ul style="list-style-type: none"> Discussion of the process and content of pharmacoeconomic guidelines in South Korea. Lack of local data and limited availability of human resources has been identified as barriers for economic evaluation in South Korea.

Author	Type	Summary
Barry 2007 (80)	Review	<ul style="list-style-type: none"> • Description of pricing and reimbursement in Ireland. • Use of external reference pricing came into effect in 2006. • In some cases new technologies may be subjected to pharmacoeconomic assessment. • A cost-effectiveness threshold of €45,000/QALY was adopted.
Bos 2000 (81)	Review	<ul style="list-style-type: none"> • Description of the healthcare system in the Netherlands. • In 1988 a special national fund for HTA was set up. • In 1993 the government stated that enhancing effectiveness in health care was one of its prime targets and that HTA would be a prime tool for that purpose.
Braae 1999 (44)	Review	<ul style="list-style-type: none"> • Description of the Pharmaceutical Management Agency (PHARMAC) in New Zealand. • The role of PHARMAC is to manage pharmaceutical subsidies. It has taken a proactive approach by selecting the pharmaceuticals that are to be subsidised and declining to subsidise others. • Tools used to increase the value of New Zealand's pharmaceutical expenditure include HTA, reference pricing, encouraging competition amongst pharmaceutical companies, and developing innovative commercial arrangements. • PHARMAC's impact on aggregate expenditure on pharmaceuticals is evident: there has been a noticeable slow down in the expenditure growth rate compared with the high rate in the 1980s. From 1993 to 1998, the growth rate averaged 5%. More significantly, for the year ended June 1999, it fell by around 5%. There has also been a steady trend towards patients being prescribed newer, more expensive medicines rather than older, cheaper ones. • PHARMAC has made dramatic strides to improve the value of the New Zealand government's expenditure on pharmaceutical subsidies and its actions have meant that more funds have been available for investment in other health services, than would have occurred if previous policies had remained unchanged.
Breckenridge 2010 (43)	Comment	<ul style="list-style-type: none"> • Discussion of the relationship between pharmaceutical regulation and HTA, with a focus on how reliable evidence on efficacy and safety, as well as clinical and cost-effectiveness, can best be provided to allow patients access to new medicines; and how can regulators and HTA experts contribute to innovation and drug development instead of being perceived as barriers? • Authors suggest that there is potential for synergy across regulation and HTA that may be beneficial to all parties in regard to evidence for safety and efficacy and clinical and cost-effectiveness. In particular, sponsors now often collect cost and utility data alongside traditional regulatory information in clinical trials, assisting the development of a dossier on cost-effectiveness.

Author	Type	Summary
		<ul style="list-style-type: none"> • It is likely that the contribution of HTA will become increasingly important in determining access to new medicines and while the methods used in drug regulation and HTA may differ there is ample scope to ensure the two processes are better integrated.
Caro 2010 (82)	Review	<ul style="list-style-type: none"> • Description of methods used in Germany to inform German decision makers of the net cost and benefits of interventions. • Uses an efficiency plot with costs on the horizontal axis and benefits on the vertical axis. • Authors confirm this approach informs decision makers about the efficiency of interventions, conforms to the mandate, and is consistent with basic economic principles.
Chabot 2010 (41)	Review	<ul style="list-style-type: none"> • Assessment of the reimbursement of sunitinib for renal cell carcinoma in Canada. • Economic evaluation resulted in an ICER of \$144,000/QALY for sunitinib compared to interferon alfa. The medicine is reimbursed in all Canadian provinces, indicating the high ICER was not an insurmountable barrier to reimbursement. Payers were receptive to immature survival data but substantial progression-free gains for a relatively rare cancer with few treatment options. • Authors conclude this demonstrates that an ICER is only one of many factors that affect access decisions in oncology.
Cleemput 2009 (83)	Review	<ul style="list-style-type: none"> • Overview of the history of HTA in Belgium. • Principle of evidence-based medicine was introduced in 2001 with the establishment of the Drug Reimbursement Committee (DRC). • In 2003 the Belgian Healthcare Knowledge Centre (KCE) was established. Its mission was to perform policy preparing research in the healthcare and health insurance sector and to give advice to policy makers about how they can obtain an efficient allocation of limited healthcare resources that optimizes the quality and accessibility of health care. KCE is independent from the policy maker. Its HTAs contain policy recommendations that may inform policy decisions but are not binding. • Authors conclude the impact of HTA in Belgium is increasing.
Cleemput 2000 (84)	Review	<ul style="list-style-type: none"> • Description of the healthcare system in Belgium with a focus on government measures to control costs. • Belgium has no formal national programme for HTA and that the future of HTA in Belgium depends on a changing perception by providers and policy makers that a stronger scientific base for health care is required.
Clement 2009 (42)	Retrospective review	<ul style="list-style-type: none"> • Descriptive analysis of retrospective data from the Common Drug Review (CDR) of Canada, the National Institute of Health and Clinical Excellence (NICE) in the UK and the Pharmaceutical

Author	Type	Summary
		<p>Benefits Advisory Committee (PBAC) in Australia, with a focus on how clinical and cost-effectiveness evidence is used in coverage decisions.</p> <ul style="list-style-type: none"> • Significant uncertainty around clinical effectiveness, usually due to inadequate study design, the use of inappropriate comparators or unvalidated surrogate endpoints, was a key issue in coverage decisions. The authors concluded that the results of the evaluation process in different countries are influenced by the context, agency processes, ability to engage in price negotiation and perhaps differences in social values.
Dalton 2001 (85)	Review	<ul style="list-style-type: none"> • Overview of the pharmaceutical reimbursement system in Australia. • Description of the decision framework, sections of pharmaceutical submissions as indicated by the Pharmaceutical Benefits Advisory committee (PBAC) Guidelines, and methodological and applications issues.
Drummond 2011 (6)	Review	<ul style="list-style-type: none"> • Comparison of the use of reference pricing and HTA for pricing and the reimbursement status of pharmaceuticals in Germany, the Netherlands, Sweden and the UK. • The impact of reference pricing is only substantial when there are large differences in the prices of pharmaceuticals in a given group or cluster. • As soon as one of the pharmaceuticals becomes generic, reference pricing can have a major impact. • No clear pattern of the impact of HTA on prices could be determined. • The focus of reference pricing is setting the reimbursement level for the cluster, however, in the absence of a generic, it is unclear how this level is set. In contrast, with HTA reimbursement can be conditional or limited to certain indications of the pharmaceuticals or certain patient sub-groups. • The authors concluded that reference pricing alone does not represent a viable policy for obtaining value for money from pharmaceuticals, and HTA represents a much better approach, given the reward for innovation and value for money. A dual policy, in which the primary policy for obtaining value for money from new pharmaceuticals is based on HTA, supported by reference pricing or another approach, may be emerging.
Drummond 1992 (2)	Review	<ul style="list-style-type: none"> • Assessment of the methodological principles behind the new Australian guidelines for assessing pharmaceuticals. • Author concludes the new guidelines place as many demands on the funders (the government) as on the suppliers (pharmaceutical industry).
Fleurette 2000 (86)	Review	<ul style="list-style-type: none"> • Description of the French healthcare system. • In 1989 the National Agency for the Development of Medical Evaluation was established, and in

Author	Type	Summary
		<p>1996 it was expanded to include hospital accreditation and renamed the National Agency for Accreditation and Evaluation in Health. In 1999 the National Agency for Health Products was established, which controls the safety of medical products and evaluates medical benefits before reimbursement decisions are made.</p> <ul style="list-style-type: none"> HTA is now related to virtually every health policy process in France and its role will increase.
Fricke 2009 (87)	Review	<ul style="list-style-type: none"> Description of HTA in Germany, including information about the organisations involved in HTA and their processes as well as current issues for the assessment and use of HTA.
Fuhrlinger 2006 (88)	Review	<ul style="list-style-type: none"> Discussion of the use of pharmacoeconomic analyses in Austria. When deciding on whether a pharmaceutical is listed in the Code of Reimbursement or not, pharmacoeconomic studies are obligatory in two cases: for real innovations with substantial therapeutic benefit and for applications for inclusion in the Yellow Box, when there are no alternatives listed in the Yellow Box. A pharmacoeconomic study is always only one aspect among others deciding on reimbursement and price. Even though the pharmaceutical applied for is not included in the Code of Reimbursement, reimbursement is possible in special cases if there is no adequate pharmaceutical listed in the Code of Reimbursement and the pharmaceutical is absolutely needed for therapeutic reasons. In these cases prior approval from a chief medical officer is required. Studies performed in countries other than Austria may be subject to different health care systems, general conditions, therapeutic alternatives and costs and have therefore to be adapted to Austrian conditions. Pharmacoeconomic studies are a key factor for assessing new pharmaceuticals and represent an important contribution to reimbursement and price decisions in Austria.
Garattini 2007 (40)	Review / comparative analysis	<ul style="list-style-type: none"> Assessment of the regulations applied by EU governments to reward potentially innovative medicines, with a focus on 7 EU countries: Belgium, France, Germany, Italy, the Netherlands, Spain and the UK. Pricing and reimbursement procedures for new and innovative medicines were investigated, with a focus on the use of economic evaluations. Literature was reviewed and experts consulted. A solution to reward real innovation could be to admit a premium price for very innovative medicines according to their estimated cost-effectiveness. New medicines with modest improvement could be grouped in therapeutic clusters and submitted to a common reference price, despite patent expiry.

Author	Type	Summary
		Such a "dual approach" could be a sensible compromise to restrict pharmaceutical expenditure while at the same time rewarding companies that invest in high-risk basic research.
Greene 2009 (89)	Comment / opinion	<ul style="list-style-type: none"> • Description of the issues surrounding the development of comparative effectiveness research in the US, including a description of the history of therapeutic evaluation in the US.
Henry 1999 (90)	Review	<ul style="list-style-type: none"> • Overview of the use of pharmacoeconomic analysis in the process that determines pharmaceutical reimbursement in Australia. • Description of the types of pharmacoeconomic data submitted to support reimbursement, the methods and standards used to assess the data, the more commonly encountered flaws in the submitted data and how the different types of data influence reimbursement decisions.
Hill 2003 (91)	Review	<ul style="list-style-type: none"> • Description of the processes involved in the Australian pharmaceutical benefits scheme, with a focus on the methods used to assess evidence.
Hisashige 2009 (92)	Review	<ul style="list-style-type: none"> • Description of the history of HTA in Japan. • HTA became visible when several committees were set up in the late 1990s. • HTA has not developed as expected, with the most important failure being that the application of HTA to health policy has been neglected by the Ministry of Health, Labor and Welfare in Japan. • Without a central organisation for HTA several researchers continue to do HTA studies, but most have moved into diverse, related areas. • Reconsideration and reorganisation of HTA, which covers not only healthcare services but also the healthcare system as a whole is becoming an urgent matter for healthcare reform in Japan.
Ikeda 1996 (93)	Comment	<ul style="list-style-type: none"> • The quality of pharmacoeconomic data submitted to the Japanese government is poor and heavily biased. • Guidelines are required so that appropriate comparisons of the cost-effectiveness of new medicines can be made. • The Ministry of Health and Welfare should clarify how pharmacoeconomic data are to be used to aid policy decisions; and the publication of pharmacoeconomic data should be mandated.
Jorgensen 2000 (94)	Review	<ul style="list-style-type: none"> • Description of HTA in Denmark, prior to the year 2000. • A national institute for HTA (DIHTA) was established. • Authors note the increasing awareness of evidence-based healthcare among health professionals and a general acceptance of health economic analyses as a basis for health policy decision making.
Laupacis 2006	Review	<ul style="list-style-type: none"> • Discussion of the most common challenges faced by the Canadian Common Drug Review (CDR).

Author	Type	Summary
(95)		<ul style="list-style-type: none"> The challenges include: determining the effectiveness of a pharmaceutical; a massive rise in cost of new medicines which does not seem to be accompanied by a massive increase in effectiveness; interpreting complex pharmacoeconomic evaluations; prescription creep, use of pharmaceuticals in patients who were not studied in clinical trials; ethical and societal issues, particularly reimbursement of expensive pharmaceuticals for rare diseases.
Laupacis 2005 (96)	Review	<ul style="list-style-type: none"> Description of the organisation and decision-making processes of the Drug Quality and Therapeutics Committee and the Canadian Expert Drug Assessment Committee.
Lee 2005 (97)	Review	<ul style="list-style-type: none"> Review of published economic evaluations of healthcare technologies in the Korean market. Assess whether published economic evaluations in the Korean context have been performed according to international standards and whether their results are useful for decision making. 14 (31%) cost-effectiveness analyses, 14 (31%) cost-benefit analyses, 5 (11%) cost-utility analyses and 12 (27%) other analyses, including cost-of-illness and cost comparison studies. 20 evaluations (44%) used discounting and 20 (44%) performed sensitivity analyses. 52% of studies used a time horizon of less than one year and 11% of studies did not clearly specify the time horizon. 64% of evaluations stated a societal perspective was used, but this perspective was not always taken consistently, completely or appropriately. Misunderstandings were found of what type of analysis was actually performed, i.e. some analyses were presented as cost-effectiveness analyses however they were actually cost analyses or cost comparisons. The authors concluded that many studies did not meet international standards.
Levy 2010 (39)	Review / comparative analysis	<ul style="list-style-type: none"> Literature review and interviews to compare HTA systems in five jurisdictions – Canada, Sweden, Scotland, the Netherlands and Australia. Review identified 7 characteristics that are shared across the jurisdictions and may potentially serve as insights for the US: 1) the process must be responsive to stakeholders’ interests; 2) the assessment of medical technologies other than pharmaceuticals may present different challenges and is managed separately in other HTA organisations; 3) because of the link between HTA and reimbursement decisions, completion of the HTA process following regulatory approval can delay market access to new technologies, thus closer integration between regulatory approval and HTA processes is being explored; 4) there is a direct or indirect link to reimbursements and without this link comparative effectiveness research in the US will remain advisory; 5) given the diverse multipayer environment in

Author	Type	Summary
		<p>the US, comparative effectiveness research in the US may usefully focus on generating comparative effectiveness evidence; 6) a common metric for assessing intended and unintended effects of treatment allows comparison across different technologies; 7) a stated focus of comparative effectiveness research is on therapeutic benefit among high priority populations, however this will be difficult to achieve because few randomised trials have power to detect effect modification.</p> <ul style="list-style-type: none"> • The authors conclude that the distinctive features of the US healthcare system must be taken into account when assessing transferability of insights from other countries.
Levy 2002 (98)	Review	<ul style="list-style-type: none"> • Description of the policies and review processes in each Canadian province for formulary decisions. • 6 of the 10 provinces require manufacturers to submit economic evaluations, however, the full integration of their results into the decision-making process is unclear.
Mason 2006 (51)	Systematic review	<ul style="list-style-type: none"> • Update of 1997 systematic review of generalisability of pharmacoeconomic studies • Generalisability is comprised of 3 aspects – technical merit, applicability and transferability • Technical elements of best practice are uncontroversial, and these include choosing relevant alternatives, transparent reporting of methods and findings, accessing and using the best-quality evidence, using the best methods to synthesize data, using deterministic sensitivity analysis to explore systematic bias and probabilistic sensitivity analysis to explore influence of random error at the whole model level. • Applicability of economic evaluation findings within original policy context can be determined assuming best practice guidelines for economic modelling are adhered to. • Transferability of results from one policy setting to another requires consideration of changes in resource implications, unit prices, outcomes. • Limitations remain for economic analyses because of opaqueness of method, failure to reflect opportunity cost of decisions and lack of societal mandate. • The authors conclude that making health economic findings accessible to patients, clinicians and society, in the form of relevant narratives will expose assumptions underlying economic analysis to broader critical inspection.
Menon 2009 (99)	Review	<ul style="list-style-type: none"> • Description of the methods and use of HTA in health care decisions in Canada, including a description of the history of HTA in Canada. • Description of current issues in HTA in Canada, including transferability of economic information, use of real-world data, timeliness, transparency in decision making and QALY thresholds.
Morland 2009	Review	<ul style="list-style-type: none"> • Description of the Norwegian contribution to international HTA history.

Author	Type	Summary
(100)		<ul style="list-style-type: none"> • Norwegian HTA was set up rather late compared to the Swedish unit. • Norwegian HTA agency is regarded as highly successful in involving clinical experts and responding to questions arising from macro- and micro-levels of decision makers. • Over 10 years HTA has become a well-established activity in Norway.
Neumann 2009 (101)	Review	<ul style="list-style-type: none"> • Review and critical evaluation of published cost-utility analysis pertaining to pharmaceuticals over the past 30 years. • 51.2% of cost-utility analyses had a US perspective (although economic evaluation is generally not required for formulary submissions or health technology assessments in the US), 15.6% a UK perspective and 6.9% a Canadian perspective. • 41.4% of the cost-utility analyses were industry-funded, 33.0% were non-industry funded and 25.6% did not disclose funding source. • There has been an improvement in adherence to recommended methods over time (clearly stated perspective, discounted costs and QALYs, time horizon stated, year of currency stated, incremental analyses conducted correctly), with 90% of cost-utility analyses in 2005-2006 adhering to the 5 criteria stated above compared to 60-85% adherence from 1976-1998. • ICERs from industry-sponsored studies are more favourable than other ratios.
Park 2008 (102)	Comment	<ul style="list-style-type: none"> • Description of the systems and processes used for reimbursement decisions in South Korea, including the establishment of the New Health Technology Assessment Committee (NHTAC) which will conduct reviews of new technologies.
Pelc 1994 (103)	Review	<ul style="list-style-type: none"> • Description of the current French price reimbursement scheme, including a description of the present status afforded pharmacoeconomic studies in the price reimbursement scheme.
Perleth 2009 (104)	Review	<ul style="list-style-type: none"> • Overview of the history of HTA in Germany since the 1990s. • HTA became part of several healthcare reform laws since 1997, and in 2004 the Institute for Quality and Efficiency in Health Care (IQWiG) was formed. • There is an aim to use evidence in decision-making processes for coverage and other decisions. • There is considerable impact of HTA in Germany.
Rocchi 2008 (105)	Review	<ul style="list-style-type: none"> • Assessment of the impact of economic evidence to Canadian pharmaceutical reimbursement decisions – whether an explicit or implicit threshold has been identified; is the impact of the threshold different for oncology medicines? • Review used a literature search, a review of publicly available Canadian reimbursement decisions and a one-day key informant roundtable with 13 individuals.

Author	Type	Summary
		<ul style="list-style-type: none"> • Despite the formal requirement for structured economic evidence, limited public information suggests that its uptake in the Canadian decision-making process has been tentative. • Based on reviews of reimbursement recommendations, thresholds specific to oncology medications may be higher than for non-oncology medications in Canada and elsewhere. • Canadian reimbursement recommendations can appear inconsistent with respect to clinical evidence, economic evidence, and nonevidentiary factors, possibly because of a lack of transparency or context-sensitive interpretations. • Roundtable participants suggested the following improvements: transparency of processes and decisions, dynamic formularies that can adapt with evolving treatment practices and clinical data, broader representation of expertise on review panels, greater use of ethics to resolve conflicts arising from different perspectives, and the development of an explicit Canadian weighting system for evidence and values.
Rohrbacher 2005 (106)	Comment / opinion	<ul style="list-style-type: none"> • Discussion of the role of modelling and economic evaluations in Australian and Canadian pharmaceutical reimbursement decisions. • For reimbursement decisions in Canada, the authors concluded that unit price and budget impact have a larger impact on decision-making than any other pharmacoeconomic information.
Sculpher 2004 (52)	Systematic review	<ul style="list-style-type: none"> • 3 systematic reviews and a series of case studies to review and develop the methods used to assess and increase the generalisability of economic evaluation studies. • Review of methods literature on generalisability to identify factors causing variability in cost-effectiveness between locations and over time. • Review of methods literature relating to available methods to assess variability between locations and over time. • Review of applied economic evaluation studies undertaken alongside multi-location trials to describe how studies have assessed and reported generalisability and variability in results between locations. • Case studies to explore the use of multi-level modelling to assess variability in cost-effectiveness between locations. • Review of economic evaluations based on decision analytic models in osteoporosis to describe how studies have made analyses relevant to decision-makers. • Case study of decision analytic model to illustrate methods to estimate cost-effectiveness for NHS using data collected in non-UK locations. • Unit costs were the factor most frequently cited as generating variability in economic results between

Author	Type	Summary
		<p>locations.</p> <ul style="list-style-type: none"> • No studies were identified which considered factors causing variability in results over time. • Evidence of variation between locations in volume and cost of resource use and in cost-effectiveness. • Regression analytic methods have indicated that some components of resource use are exchangeable across locations while other are not. • Both cost and effectiveness aspects of decision analytic models may need to be adapted between locations. • Weaknesses in some aspects of the reporting of cost-effectiveness analyses may limit decision-makers ability to judge relevance of a study for their location. • Multi-level modelling can facilitate correct estimates of uncertainty in cost-effectiveness results and also provide a means of estimating location-specific cost-effectiveness. • Few studies were explicit about their target decision-makers/jurisdictions. • Generally more effort is made to ensure cost inputs were specific to their jurisdiction than effectiveness parameters.
Shemer 2009 (107)	Review	<ul style="list-style-type: none"> • Description of HTA in Israel based on the knowledge of the authors and literature. • HTA in Israel is increasingly a decentralised activity conducted by a variety of institutions and Israeli health policies are increasingly based on the results of HTA.
Spoorendonk 2001 (108)	Review	<ul style="list-style-type: none"> • Description of the commencement of the use of pharmacoeconomic evaluations in the Netherlands.
Tilson 2010 (109)	Editorial	<ul style="list-style-type: none"> • Description of the use of pharmacoeconomic assessment in Ireland. • Since 2006 high-cost products and those with a significant budget impact have been subjected to formal pharmacoeconomic assessment. In 2009 the National Centre for Pharmacoeconomics (NCPE) in collaboration with the Health Service Executive (HSE) began to consider the cost-effectiveness of all new medicines following applications for reimbursement. • Brief description of the characteristics of Ireland’s system are provided, including use of rapid reviews, a dynamic cost-effectiveness threshold and consideration of budget impact assessment.
Towse 2010 (110)	Comment / opinion	<ul style="list-style-type: none"> • Comment on price setting in the UK • States that instead of adding uncertainty the institutional arrangements for assessing value should seek to be predictable and science based, building on NICE’s current arrangements. • Increasing uncertainty in the UK market through government price setting will reduce incentives for research and development and for early UK launch of products.

Author	Type	Summary
Vale 2010 (49)	Comment	<ul style="list-style-type: none"> • Discussion of the fact that despite the common principles across HTA, the process of HTA, and most particularly its economic evaluation component, needs to take a country-specific approach toward evaluation. • In some cases results of economic evaluations are transferable. • Countries need to consider their national decision-making requirements when considering the relevance of economic evaluations. • HTA and economic evaluations should be tailored to fit national circumstance.
van Oostenbruggen 2005 (111)	Review	<ul style="list-style-type: none"> • Description of the use of pharmacoeconomic analyses in the Netherlands pharmaceutical reimbursement system.
Walker 2011 (112)	Review	<ul style="list-style-type: none"> • Determine the impact of comparative effectiveness (in the US) and value based pricing (in the UK) on the price and market access of new pharmaceuticals for treating depression. • Both comparative effectiveness and value based pricing take indirect costs into account. Because depression has high indirect costs this is likely to lead to increased value of new agents, and should enable better access to new agents.
Weill 2009 (113)	Review	<ul style="list-style-type: none"> • Description of the history of HTA in France. • The Agence Nationale de l'Evaluation Medicale (ANDEM) was established in 1989. • In the mid 1990s the mandate of ANDEM was extended to hospital accreditation and the name changed to Agence Nationale d'Accreditation et d'Evaluation en Sante (ANAES). • In 2005 the National Authority for Health (HAS) consolidated efforts to centralise the programmes of HTA, with the aim of helping decision making regarding reimbursement and pricing. • HTA has become a strong influence in the healthcare system in France.
Williams 2006 (114)	Review	<ul style="list-style-type: none"> • Assessment of use (or lack of use) of research evidence relating to economic analyses in healthcare decision-making • To what extent, and in what ways, is health economic information used in health policy decision-making in the UK? • What factors are associated with use, or non-use, of such research findings? • At the local level it was found that it is an exception for economic evaluation to inform technology coverage decisions. Main sources of cost-effectiveness information were manufacturers of the product and NICE guidance. Local respondents were receptive to making greater use of health economic information, but levels of understanding and expertise in the subject were low.

Author	Type	Summary
		<ul style="list-style-type: none"> • At the national level the use of economic analysis is highly integrated into the decision-making process of NICE’s technology appraisal programme. Attitudes toward economic evaluation varied among committee members and there was significant disagreement between members around economic evaluations. • The authors conclude that the most fundamental challenges relate to the overall design of the health system and structure of health care organisations, beyond attempts to make cost-effectiveness studies easier to obtain and understand.
Xie 2011 (115)	Review	<ul style="list-style-type: none"> • Description of the current application of HTA in Canada, in particular how academic researchers collaborate with decision-makers in the Canadian federal and provincial systems. • Description of issues and challenges with the use of HTA.

6. References

1. Henry, D. Economic Analysis as an aid to subsidisation decisions: The development of Australian guidelines for pharmaceuticals. *PharmacoEconomics*, 1992, 1(1):54-67.
2. Drummond, M. Australian guidelines for cost-effectiveness studies of pharmaceuticals: The thin end of the boomerang? *PharmacoEconomics*, 1992, 1(Suppl. 1):61-69.
3. Johannesson, M. The Australian guidelines for subsidization of pharmaceuticals: The road to cost-effective drug prescribing? *PharmacoEconomics*, 1992, 2 (5):355-362.
4. Langley, PC. The role of pharmacoeconomic guidelines for formulary approval: The Australian experience. *Clinical Therapeutics*, 1993, 15(6):1154-1176.
5. Detsky, A. Guidelines for economic analysis of pharmaceutical products: A draft document for Ontario and Canada. *PharmacoEconomics*, 1993, 3(5):354-361.
6. Drummond M, Jonsson B, Rutten F, Stargardt T. Reimbursement of pharmaceuticals: reference pricing versus health technology assessment. *The European Journal of Health Economics*, 2011, 12:263-71.
7. Hisashige, A. Healthcare technology assessment and the challenge to pharmacoeconomics in Japan. *Pharmacoeconomics*, 1997, 11(4):319-333.
8. Jacobs P, Bachynsky J, Baladi JF. A comparative review of pharmacoeconomic guidelines. *PharmacoEconomics*, 1995, 8(3):182-189.
9. Drummond, M et al. Current trends in the use of pharmacoeconomic and outcomes research in Europe. *Value in Health*, 1999, 2(5):323-332.
10. Neumann PJ, Drummond MF, Jönsson B et al. Are key principles for improved health technology assessment supported and used by health technology assessment organizations? *International Journal of Technology Assessment in Health Care*, 2010, 26(1):71-78.
11. Ngorsuraches S, Meng W, Kim BY, Kulsomboon V. Drug reimbursement decision-making in Thailand, China, and South Korea. *Value in Health*, 2012, 15(suppl. 1): S120-S125.
12. Bending MW, Hutton J, McGrath C, Glanville J. What influences pharmaceutical reimbursement decisions? A systematic review of factors reported to influence decisions in OECD countries. *Value in Health*, 2011, 14(3):A22.
13. Bentkover JD, Corey R. Effective utilization of pharmacoeconomics for decision makers. *Disease Management and Health Outcomes*, 2002, 10(2):75-80.
14. Sivalal S. Health technology assessment in the Asia Pacific region. *International Journal of Technology Assessment in Health Care*, 2009, 25(suppl. S1):196-201.

15. Li SC. Can pharmacoeconomic guidelines be implemented successfully in Asia? *Journal of Medical Economics*, 2008, 11(2):341-343.
16. Moran, V. Health technology assessment in Europe: Communicating and applying lessons learned from high-income countries to middle-income countries. *Journal of Management & Marketing in Healthcare*, 2010, 3(2):141-149.
17. Sansom L. Assessing the value of medicines. *Pharmaceutical Medicine*, 2010, 24(2):89-92.
18. Kulkarni U, Dalvi K, Moghe VV, Deshmukh YA. Pharmacoeconomics: An emerging branch in health sciences for decision making. *African Journal of Pharmacy and Pharmacology*, 2009, 3(8):362-367.
19. Perez Izquierdo V, Alvarez Muniz M. 3rd Latin American and Caribbean congress on health economics. *Expert Review of Pharmacoeconomics and Outcomes Research*, 2009, 9(1):33-35.
20. Taylor RS, Drummond MF, Salkeld G, Sullivan SD. Inclusion of cost effectiveness in licensing requirements of new drugs: The fourth hurdle. *British Medical Journal*, 2004, 329(7472):972-975.
21. Maynard A, Cookson R. Money or your life? The health-wealth trade-off in pharmaceutical regulation. *Journal of Health Services Research and Policy*, 2001, 6(3):186-189.
22. Oortwijn W, Mathijssen J, Banta D. The role of health technology assessment on pharmaceutical reimbursement in selected middle-income countries. *Health Policy* 2010; 95:174-84.
23. Goeree R, Levin L, Chandra K, Bowen JM, Blackhouse G, Tarride JE, Burke N, Bischof M, Xie F, O'Reilly D. Health Technology Assessment and Primary Data Collection for Reducing Uncertainty in Decision Making. *Journal of the American College of Radiology*, 2009, 6(5):332-342.
24. Kolasa K, Schubert S, Manca A, Hermanowski T. A review of Health Technology Assessment (HTA) recommendations for drug therapies issued between 2007 and 2009 and their impact on policymaking processes in Poland. *Health Policy*, 2011, 102(2-3):145-151.
25. Krol ZJ, Matuszewicz W, Musialowicz A. HTA procedures in drug reimbursement process in Poland. Evolution of recognition the role of agency of health technology assessment (AHTAPOL) by policy makers. *Value in Health*, 2009, 12(3): A202-A203.
26. McDaid D, Mossialos E, Mrazek MF. Making use of economic evaluation. *International Journal of Risk and Safety in Medicine*, 2002, 15(1-2):67-74.
27. West R, Borden EK, Collier JP, Rawson NSB, Tonks RS. "Cost-effectiveness" estimates result in flawed decision-making in listing drugs for reimbursement. *Canadian Journal of Public Health*, 2002, 93(6): 421-425.
28. Liberti LE, Pichler F, Walker SR. Preparing for regulatory review and reimbursement decisions: A case for cooperation between regulatory authorities, sponsors and health technology assessment agencies. *Pharmaceutical Medicine*, 2009, 23(5-6):263-267.

29. McGuire A. The European value-pricing game. *Expert Review of Pharmacoeconomics and Outcomes Research*, 2012, 12(1):5-6.
30. Lenz C, Girek O, Schmitt D. Advancing health technology assessment (HTA) and reimbursement processes to promote access to personalized medicine. *Journal fur Pharmakologie und Therapie*, 2011, 20(5):150-152.
31. Sorenson C, Chalkidou K. Reflections on the evolution of health technology assessment in Europe. *Health Economics, Policy and Law*, 2012, 7(1):25-45.
32. Niankowski R, Wilk N. From idealistic rookies to a regional leader: The history of health technology assessment in Poland. *International Journal of Technology Assessment in Health Care*, 2009, 25(suppl. 1):156-162.
33. Doherty J, Kamae I, Lee KK, Li H, Li SC, Liu GG, Tarn YH, Yang BM. What Is Next for Pharmacoeconomics and Outcomes Research in Asia? *Value in Health*, 2004, 7(2):118-132.
34. Cai Q, Salmon JW. What role may pharmacoeconomics play in pharmaceutical pricing and reimbursement in China? *Journal of Pharmaceutical Finance, Economics and Policy*, 2005, 14(1):51:75.
35. Chen Y, Banta D, Tang Z. Health technology assessment development in China. *International Journal of Technology Assessment in Health Care*, 2009, 25(suppl. S1):202-209.
36. Nuijten MJC, Szende A, Kosa J, Mogyorosy Z, Kramberger B, Nemecek K, Tomek D, Oreskovic S, Laskowska M. Health care reform in six Central European countries: A focus on health economic requirements in the drug pricing and reimbursement processes. *European Journal of Health Economics*, 2003, 4(4):286-291.
37. Harris A, Buxton M, O'Brien B, Rutten F, Drummond M. Using economic evidence in reimbursement decisions for health technologies: Experience of 4 countries. *Expert Review of Pharmacoeconomics and Outcomes Research*, 2001, 1(1):7-12.
38. Rubinstein A, Pichon-Riviere A, Augustovski F. Development and implementation of health technology assessment in Argentina: Two steps forward and one step back. *International Journal of Technology Assessment in Health Care*, 2009, 25(suppl. S1):260-269.
39. Levy AR, Mitton C, Johnston KM, Harrigan B, Briggs AH. International comparison of comparative effectiveness research in five jurisdictions: Insights for the US. *Pharmacoeconomics*, 2010, 28(10):813-830.
40. Garattini L, Cornago D, De Compadri P. Pricing and reimbursement of in-patent drugs in seven European countries: A comparative analysis. *Health Policy*, 2007, 82(3):330-339.
41. Chabot I, Rocchi A. How do cost-effectiveness analyses inform reimbursement decisions for oncology medicines in Canada? The example of Sunitinib for first-line treatment of metastatic renal cell carcinoma. *Value in Health*, 2010, 13(6):837-845.

42. Clement FM, Harris A, Li JJ, Yong K, Lee KM, Manns BJ. Using effectiveness and cost-effectiveness to make drug coverage decisions. A comparison of Britain, Australia and Canada. *JAMA*, 2009, 302(13):1437-1443.
43. Breckenridge A, Woods K, Walley T. Medicines regulation and health technology assessment. *Clinical Pharmacology & Therapeutics*, 2010, 87(2):152-54.
44. Braae R, McNee W, Moore D. Managing pharmaceutical expenditure while increasing access: the Pharmaceutical Management Agency (PHARMAC) experience. *PharmacoEconomics*, 1999, 16(6):649-660.
45. Hoomans T, Van der Roer N, Severens JL, Delwel GO. Cost-effectiveness of new drugs impacts reimbursement decision making but room for improvement. *Nederlands tijdschrift voor geneeskunde*, 2010, 154(30):A958.
46. Dickson M, Hurst J, Jacobzone S. Survey of Pharmacoeconomic Assessment Activity in Eleven Countries. OECD health working papers No.4, 16 May 2003.
47. Drummond M, Barbieri M, Cook J, Glick HA, Lis J, Malik F, Reed SD, Rutten F, Sculpher M, Severens J. Transferability of Economic Evaluations Across Jurisdictions: ISPOR Good Research Practices Task Force Report. *Value in Health* 2009; 12(4): 409-18.
48. O'Sullivan A, Thompson D, Bekker D. Country-to-country adaptation of pharmacoeconomic research: methodologic challenges and potential solutions. *ISPOR Connect* 2009; 15:6-8.
49. Simoens S. Health technology assessment and economic evaluation across jurisdictions. *Value in Health*, 2010, 13(6):857-859.
50. Vale L. Health technology assessment and economic evaluation: Arguments for a national approach. *Value in Health* 2010, 13(6):859-61.
51. Mason JM, Mason AR. The generalisability of pharmacoeconomic studies: Issues and challenges ahead. *Pharmacoeconomics* 2006; 24(10):937-45.
52. Sculpher MJ, Pang FS, Manca A, Drummond MF, Golder S, Urdahl H, Davies LM, Eastwood A. Generalisability in economic evaluation studies in healthcare: a review and case studies. *Health Technology Assessment*, 2004, 8(49):1-207.
53. Anis AH, Rahman T, Schechter MT. Using pharmacoeconomic analysis to make drug insurance coverage decisions. *PharmacoEconomics*, 1998, 13(1 Pt. 2):119-126.
54. Augustovski F, Iglesias C, Manca A, Drummond M, Rubinstein A, Marti SG. Barriers to generalizability of health economic evaluations in Latin America and the Caribbean region. *Pharmacoeconomics*, 2009, 27(11):919-29.
55. Delwel GO, Sprenger MJW. Pharmaco-economic evaluations of new drugs: Potential key to a more efficient allocation of the health care budget. *Nederlands Tijdschrift voor Geneeskunde*, 2002, 146(23):1068-1071.
56. Filko M, Tesar T. Quality assurance of fourth hurdle within the Slovak Republic. *Value in Health*, 2010, 13(3):A97.

57. Glaeske G. More safety and justice in treatment decisions. Cost-benefit analysis in the healthcare system with special considerations for oncology. *Der Onkologe*, 2008, 14(7):660-668.
58. Griffin S, Claxton K, Sculpher M. Decision analysis for resource allocation in health care. *Journal of Health Services Research and Policy*, 2008, 13:23-30.
59. Gulacsi L, Brodszky V, Pentek M, Varga S, Vas G, Boncz I. History of health technology assessment in Hungary. *International Journal of Technology Assessment in Health Care*, 2009, 25(suppl.S1):120-126.
60. Hutton J, McGrath C, Frybourg JM, Tremblay M, Bramley-Harker E, Henshall C. Framework for describing and classifying decision-making systems using technology assessment to determine the reimbursement of health technologies (fourth hurdle systems). *International Journal of Technology Assessment in Health Care*, 2006, 22(1):10-18.
61. Johannesson M. Economic evaluation of drugs and its potential uses in policy making *PharmacoEconomics*, 1995, 8(3):190-198.
62. Kanavos P. Financing pharmaceuticals in transition economies. *Croatian Medical Journal*, 1999, 40(2):244-259.
63. Liaropoulos L, Kaitelidou D. Health technology assessment in Greece. *International Journal of Technology Assessment in Health Care*, 2000, 16(2):429-448.
64. Liu GG, Fukuda T, Lee CE, Chen V, Zheng Q, Kamae I. Evidence-based decision-making on medical technologies in China, Japan, and Singapore. *Value in Health*, 2009, 12(suppl. 3):S12-S17.
65. Mota Pinto M, Ramos F, Pereira J. Health technology assessment in Portugal. *International Journal of Technology Assessment in Health Care*, 2000, 16(2):520-531.
66. Muller M. Limitations of pharmacoeconomics from a clinical-pharmacological point of view. *Wiener Medizinische Wochenschrift*, 2006, 156(23-24):619-621.
67. Nellesen D, Birnbaum HG, Greenberg PE. Perspectives on comparative effectiveness research: Views from diverse constituencies. *PharmacoEconomics*, 2010, 28(10):789-798.
68. Pausjenssen AM, Detsky AS. Guidelines for measuring the costs and consequences of adopting new pharmaceutical products: Are they on track? *Medical Decision Making*, 1998, 18 (suppl. 2):S19-S22.
69. Rutten FFH, Van Hout BA. Economic evaluation and the reimbursement of drugs: Current policies and future trends. *European Journal of Clinical Research*, 1994, 6:186-194.
70. Shih YCT, Pen IW, Tsai YW. Information technology facilitates cost-effectiveness analysis in developing countries. *Pharmacoeconomics* 2009, 27(11):947-61.
71. Shillcutt SD, Walker DG, Goodman CA, Mills AJ. Cost-effectiveness in low- and middle-income countries: A review of the debates surrounding decision rules. *Pharmacoeconomics* 2009, 27(11):903-917.

72. Sullivan N, Szeinbach S, Seoane-Vazquez E, Matuszewski K, Mayo K, Holmstrom S. Developing global road maps for reimbursement processes used in health technology assessment: Pharmaceuticals, medical devices, and diagnostics. *Value in Health*, 2010, 13(3):A97.
73. Tantivess S, Teerawattananon Y, Mills A. Strengthening cost-effectiveness analysis in Thailand through the establishment of the health intervention and technology assessment program. *Pharmacoeconomics*, 2009, 27(11):931-45.
74. Thatte U, Hussain S, De Rosas-Valera M, Malik MA. Evidence-based decision on medical technologies in Asia Pacific: Experiences from India, Malaysia, Philippines, and Pakistan. *Value in Health*, 2009, 12(suppl. 3):S18-S25.
75. Vuorenkoski L, Toiviainen H, Hemminki E. Decision-making in priority setting for medicines-A review of empirical studies. *Health Policy*, 2008, 86(1):1-9.
76. Zikopoulos A. Pharmacoeconomics for the pharmaceutical industry in Europe: A literature review. *International Journal of Pharmaceutical Medicine*, 2003, 17(5-6):201-209.
77. Anis AH, Gagnon Y. Using economic evaluations to make formulary coverage decisions. *PharmacoEconomics*, 2000, Jul 18(1):55-62.
78. Assiff L, Pollock MR, Manzi P, Faienza B, Menon D. Health economics in the Canadian pharmaceutical industry. *PharmacoEconomics*, 1999, 16(6):669-678.
79. Bae EY, Lee EK. Pharmacoeconomic guidelines and their implementation in the positive list system in South Korea. *Value in Health*, 2009, 12 (3):S36-S41.
80. Barry M, Tilson L. Recent developments in pricing and reimbursement of medicines in Ireland. *Expert Review of Pharmacoeconomics and Outcomes Research*, 2007, 7(6):605-611.
81. Bos M. Technology assessment in the Netherlands. *International Journal of Technology Assessment in Health Care*, 2000, 16(2):485-519.
82. Caro JJ, Nord E, Siebert U, Mcguire A, Mcgregor M, Henry D, De Pouvourville G, Atella V, Kolominsky-Rabas P. The efficiency frontier approach to economic evaluation of health-care interventions. *Health Economics*, 2010, 19(10):1117-1127.
83. Cleemput I, Van Wilder P. History of health technology assessment in Belgium. *International Journal of Technology Assessment in Health Care*, 2009, 25(suppl. S1):82-87.
84. Cleemput I, Kesteloot K. Health technology assessment in Belgium. *International Journal of Technology Assessment in Health Care*, 2000, 16(2):325-346.
85. Dalton A. Australia's pharmaceutical benefits system: flawed but improving, and better than anywhere else. *Australian Health Review*, 2001, 24(2):7-14.
86. Fleurette F, Banta D. Health technology assessment in France. *International Journal of Technology Assessment in Health Care*, 2000, 16(2):400-411.

87. Fricke FU, Dauben HP. Health technology assessment: A perspective from Germany. *Value in Health*, 2009, 12(Suppl. 2):S20-S27.
88. Fuhrlinger S. Relevance of pharmacoeconomic analyses to price and reimbursement decisions in Austria. *Wiener Medizinische Wochenschrift*, 2006, 156(23-24):612-618.
89. Greene JA. Swimming upstream: Comparative effectiveness research in the US. *PharmacoEconomics*, 2009, 27(12):979-982.
90. Henry D, Lopert R. Pharmacoeconomics and policy decisions: The Australian Health Care System *Clinical Therapeutics*, 1999, 21(5):909-915.
91. Hill S, Henry D, Stevens A. The use of evidence in drug selection: The Australian pharmaceutical benefits scheme. *Japanese Pharmacology and Therapeutics*, 2003, 31(7):615-628.
92. Hisashige A. History of healthcare technology assessment in Japan. *International Journal of Technology Assessment in Health Care*, 2009, 25(suppl. S1):210-218.
93. Ikeda S, Ikegami N, Oliver AJ, Ikeda M. A case for the adoption of pharmacoeconomic guidelines in Japan. *PharmacoEconomics*, 1996, 10(6):546-551.
94. Jorgensen T, Hvenegaard A, Kristensen FB. Health technology assessment in Denmark. *International Journal of Technology Assessment in Health Care*, 2000, 16(2):347-381.
95. Laupacis A. Economic evaluations in the Canadian common drug review. *PharmacoEconomics*, 2006, 24(11):1157-1162.
96. Laupacis A. Incorporating economic evaluations into decision-making: The Ontario experience. *Medical Care*, 2005, 43(Suppl II):II15-II19.
97. Lee KS, Brouwer WBF, Lee SI, Koo HW. Introducing economic evaluation as a policy tool in Korea: Will decision makers get quality information? A critical review of published Korean economic evaluations. *PharmacoEconomics*, 2005, 23(7):709-721.
98. Levy AR, Gagnon YM. Canadian formulary decisions: Does pharmacoeconomics matter? *Pharmaceutical News*, 2002, 9(1):47-55.
99. Menon D, Stafinski T. Health technology assessment in Canada: 20 years strong? *Value in Health*, 2009, 12(suppl. 2):S14-S19.
100. Morland B. The history of health technology assessment in Norway *International Journal of Technology Assessment in Health Care*, 2009, 25(suppl.S1):148-155.
101. Neumann PJ, Fang CH, Cohen JT. 30 years of pharmaceutical cost-utility analyses: Growth, diversity and methodological improvement. *PharmacoEconomics*, 2009, 27(10):861-72.
102. Park SH, Lee SM. Evidence-based decision-making and health technology assessment in South Korea. *Value in Health*, 2008, 11(suppl. 1):S163-S164.

103. Pelc A, Castan JP. New developments in pricing and drug reimbursement in France. *PharmacoEconomics*, 1994, 6(suppl. 1):28-35.
104. Perleth M, Gibis B, Gohlen B. A short history of health technology assessment in Germany. *International Journal of Technology Assessment in Health Care*, 2009, 25(suppl. S1):112-119.
105. Rocchi A, Menon D, Verma S, Miller E. The role of economic evidence in Canadian oncology reimbursement decision-making: to lambda and beyond. *Value in Health*, 2008, 11(4):771-783.
106. Rohrbacher R. The role of modelling in reimbursement decisions: An international perspective. *Gesundheitsökonomie und Qualitätsmanagement*, 2005, 10(suppl. 2):S45-S51.
107. Shemer J, Shani M, Tamir O, Siebzeiner MI. Health technology management in Israel: HTA in action. *International Journal of Technology Assessment in Health Care*, 2009, 25(suppl. S1):134-139.
108. Spoorendonk PAR. Panacea or new hurdle? Pharmacoeconomic evaluation in the Netherlands. *Pharmaceutisch Weekblad*, 2001, 136(19):674-679.
109. Tilson L, Barry M. Recent developments in pharmacoeconomic evaluation in Ireland. *Expert Review of Pharmacoeconomics and Outcomes Research*, 2010, 10(3):221-224.
110. Towse A. Value based pricing, research and development, and patient access schemes. Will the United Kingdom get it right or wrong? *British Journal of Clinical Pharmacology*, 2010, 70(3):360-366.
111. Van Oostenbruggen MF, Jansen RB, Mur K, Kooijman H. Penny and pound wise: Pharmacoeconomics from a governmental perspective. *PharmacoEconomics*, 2005, 23(3):219-226.
112. Walker R, Ng-Haing J, Koruth R, Sparrowhawk K. What is the impact of comparative effectiveness and value based pricing on a product's value and market access? *Value in Health*. 2011, 14(3):A22.
113. Weill C, Banta D. Development of health technology assessment in France. *International Journal of Technology Assessment in Health Care*, 2009, 25(suppl. S1):108-111.
114. Williams I, Bryan S, McIver S. The use of economic evaluations in NHS decision-making: A review and empirical investigation. NHS final report 2006.
115. Xie F, Bowen JM, Sutherland SC, Burke N, Blackhouse G, Tarride JE, O'Reilly D, Goeree R. Using health technology assessment to support evidence-based decision-making in Canada: An academic perspective. *Expert Review of Pharmacoeconomics and Outcomes Research*, 2011, 11(5):513-521.