The Use of Health Economic Analysis in OECD Countries' Pharmaceutical Reimbursement Systems and its Contribution to Decision-making

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Abstract

Developed countries' publicly funded health care systems all share the similar task of deciding which pharmaceuticals should be reimbursed. OECD countries' pharmaceutical reimbursement systems achieve this task through a number of institutions some of which use Health Technology Assessment (HTA) including health economic analysis to inform decision-making. The reimbursement decisions influence the health outcomes of patients, produce signals of the demand curve to manufacturers and may have political consequences. The overall aim of this thesis is to examine the use of health economic analysis in OECD countries' reimbursement systems and the contribution of health economic analysis and other factors to decision-making. Chapter 2 provides a literature review of previous quantitative and qualitative studies examining the factors contributing to reimbursement decision-making in OECD countries. The review identified limited evidence for comparisons across OECD countries and outlined the methodological limitations of identifying influence. Chapters 3 and 4 categorise OECD reimbursement systems using a published framework. Application of the framework identified that Health Economic analysis is used by agencies operating in heterogeneous reimbursement systems with respect to the objectives, other institutions, processes, guidelines, interpretation and other factors considered alongside health economic analysis. Chapter 5 uses regression analysis to examine decisions by those agencies that similarly use clinical evidence and health economic analysis, and identifies common factors across four countries. Chapter 6 uses a qualitative methodology to match decisions for an agency using health economic analysis in comparison to one not and found evidence of the influence of health economic analysis alongside other evidence and process factors. Finally, chapter 7 concludes by outlining the differential contribution of health economic analysis depending on how it is used by the systems. The limitations are discussed and recommendations provided for further research.

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Author Declaration

I confirm that the work presented in this thesis is to the best of my knowledge, original, except as acknowledged by references in the text. The thesis contains no material previously published or written by other people in whole or in part, for a degree at this university or any other university.

The research outlined in Chapters 2, 5 and 6 were presented at Health Technology Assessment International and ISPOR conferences. The research outlined in Chapter 6 has been accepted for publication in an academic peer reviewed journal:

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Chapter 1: Introduction

1.1 Pharmaceutical market and its structure

Developed countries' health care systems typically aim to provide universal and equitable access to health care in order to improve the health of their populations. Each country's public health system must decide which treatments to provide and pay for, with or without conditions, given the limited resources available to meet their objectives. Pharmaceuticals are one form of treatment option to meet these requirements and are produced by manufacturers located globally. Pharmaceutical global sales were reported by IMS Health to be $875bn US dollars in 2010, representing growth of 4.1% since 2009. The US is the largest market with 38% of sales, followed by Europe with 29% and Asia, Africa and Australasia with 15% of sales (IMS Health, 2011). Pharmaceutical research and development is complex, risky and highly regulated by governments. It takes between 12 to 13 years (EFPIA, 2011) to bring a pharmaceutical to market for which the latest estimates of costs per product to reach market are around $1.2 billion for a biopharmaceutical and $1.3 billion US Dollars for traditional pharmaceuticals (DiMasi and Grabowski, 2007).

There has been speculation on whether pharmaceuticals influence mortality and some evidence that the relationship between pharmaceutical innovation and mortality may have declined over time (Weisbrod, 1991, Beltrán-Sánchez et al., 2008). Other studies report an association between new medicines and mortality and the quality of life of societies. A recent US study based on 40 years of data demonstrates that there is a significant relationship between pharmaceutical innovation and yearly fluctuations in life expectancy at birth, which is robust to controls for income as well as other forms of medical spending (Schnittker and Karandinos, 2010). In an earlier study, the impact of new medicines launches on life expectancy in 52 countries during the period between 1986 and 2000 demonstrated important positive impacts upon health. The analysis demonstrated a relationship between the number of New Chemical Entities (NCEs) introduced and the impact on life expectancy. The period showed that life expectancy increased by almost two years across the sample of countries, of which 40% (3 weeks per year) may be accountable to the introduction of the NCEs during this period (Lichtenberg, 2005). These analyses do not take into account the fact that scientific advances result in both new medicines and changes in behaviour. Behavioural changes such as reduced smoking rates and other innovations may be just as important in explaining the association.

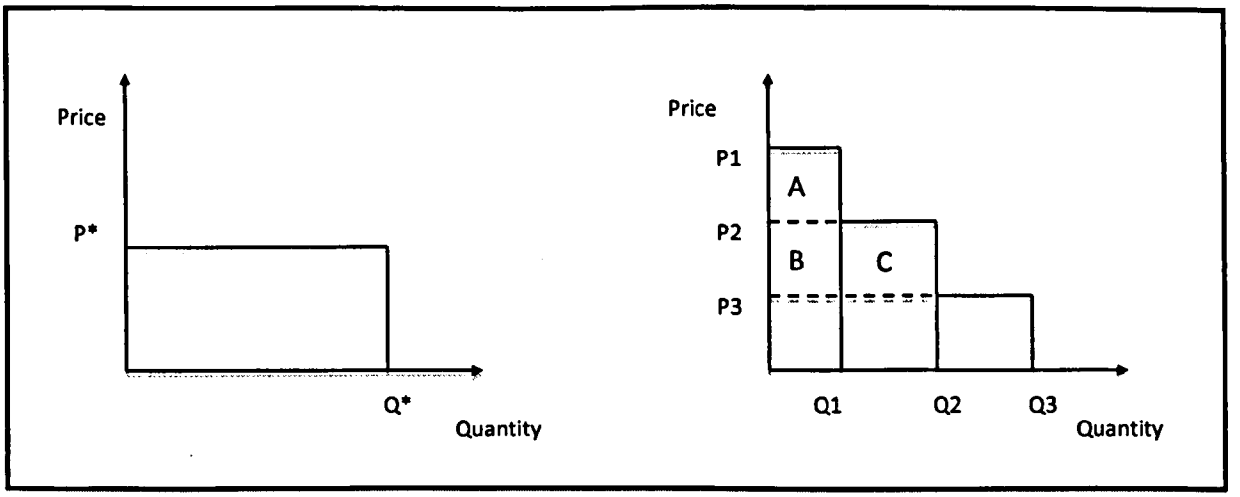
The pharmaceutical market is highly regulated and requires manufacturers to make large sunk costs. Governments provide pharmaceutical manufacturers with incentives to innovate by the use of patents. A patent provides protection for the invention of a new medicine for a limited period of time, commonly 20 years. Patents are necessary to provide pharmaceutical manufacturers with legal protection to achieve a price sufficient to recover Research and Development (R&D) costs and provide incentives for the creation of new and innovative medicines. The pharmaceutical manufacturer is assumed to maximise global profits. The patent system guarantees the monopoly status of the manufacturer for a set period of time but the final value is determined by consumers, which in the case of the public reimbursement system is usually a single reimbursement or payer body which can be referred to as a monopsony buyer (Puig-Junoy, 2005).

A market characterised by a single seller (monopoly) and a single buyer (monopsony) is known as a bilateral monopoly, where the buyer will tend to drive for a lower price and the seller a higher price. The price is indeterminate within a wide range of prices which may take the extreme values set between the price set by a single manufacturer where there are a number of competitive purchasers (where the manufacturer retains all the benefit) and the price that a monopsonist buyer would impose on a number of competitive manufacturers (where the health system retains all the benefit), (Scherer, 1970). The price indeterminacy problem can be overcome using game theory (Nash, 1950, Rubinstein, 1982). The situation between the monopoly manufacturer and the monopsony reimbursement institution represents a bargaining game and the price and reimbursement coverage will be determined by their relative bargaining power (Hawkins and Scott, 2011). There are different decision processes in countries' reimbursement systems that set the rules for bargaining.

Claxton argues that reimbursement institutions that use health economic analysis can provide clear signals of the 'demand curve' by being explicit about the threshold range (the opportunity cost or value of displaced health service activities) and where possible considering cost-effectiveness by subgroups within indications where there is elastic demand rather than average cost-effectiveness of the entire population (Claxton, 2007, Claxton et al., 2008). If the manufacturer is able to price at the average cost effectiveness all the benefit will be accrued to the manufacturer, assuming that price has been set in accordance to the threshold. This is represented as P*/Q* in the diagram reproduced from (Claxton, 2007) where the demand curve is perfectly price elastic. If subgroups have differential effectiveness within the indication, an elastic demand curve can be specified as in Figure 1.1 (diagram b). The manufacturer can choose a price for which they would be prepared to supply the market taking into account their average costs

and the impact on the local market profit and influence on prices in other countries reimbursement systems (either P1, P2, or P3). Restrictions on reimbursement in relation to the marketing authorisation can then be read off the demand curve in relation to the manufacturers choice of price, i.e. higher prices result in more restrictive decisions when there is evidence of the medicines differential effectiveness across subgroups (as illustrated by P1/Q1, P2/Q2 and P3/Q3), (Claxton, 2007). The final reimbursement decision and price will depend on the ability of the system to ensure marginal pricing by subgroup where appropriate and the pricing process followed within each country (prices are set freely by the manufacturer, statutory pricing or negotiated prices).

Figure 1.1: Demand curve reproduced from figure 1 (Claxton, 2007)



1.2 The journey from laboratory bench to reimbursement (fourth hurdle)

Following a patent application a new medicine will have gone through approximately ten years of research and development which includes pre-clinical testing (Pharmacology, acute and chronic toxicity) and clinical research (Phase I, Phase II and Phase III trials) (EFPIA, 2011). A new medicine must gain a regulatory licence/marketing authorisation before it can be considered by the reimbursement system. The manufacturer must obtain a new licence by providing evidence of the medicine's quality, safety and efficacy. This is not sufficient in many countries to obtain reimbursement of the medicine in the public system and the manufacturer must provide evidence in a further step called the 'fourth hurdle'. The 'fourth hurdle' is a term used by many stakeholders to describe the stage by which the system judges whether the medicine should be reimbursed by the public system after obtaining a regulatory licence (Hutton et al., 2006). This is recognised by many stakeholders to refer to this stage but the term is sometimes used to describe different analytical techniques or methods used by countries systems such as Health Technology

Assessment (HTA) (Maynard and McDaid, 2003, Hutton et al., 2006), comparative effectiveness (Honig, 2011) or economic analysis (Hill et al., 1997, Drummond, 2003, Taylor et al., 2004) to inform reimbursement decisions.

There is a belief that the formal use of evidence and analytical methods to inform the decisions for reimbursement improves decision-making for pharmaceutical reimbursement (Culyer and Lomas, 2006). There is currently a lack of evidence across international reimbursement systems of whether such evidence improves decision-making. The practical use of evidence in decision-making has been criticised on a number of occasions because of the divergence between theory and use in real life practice (Birch and Gafni 2002, Birch and Gafni 2006 & Birch and Gafni 2007). In particular the health economic analysis framework has been criticised on the basis of its theoretical assumptions, whether empirical studies can truly identify the opportunity cost and the practical problems of the opportunity cost varying across different parts of the health system. A central theoretical focus has been with respect to the maximisation of health and improvements in allocative efficiency where improvements in health are defined as the welfare maximand. Allocative efficiency is the situation in which resources are allocated so as to maximise the welfare (health) of the community or in other words achieving the right mixture of healthcare programmes to maximise the health of society (Palmer and Torgerson, 1999). The examination of whether such evidence improves decision-making requires convergence between theory and practical application, alongside evolution of the explicit criteria important for each system in which the economic analysis is used. The uncertainty over many of these practical difficulties means that it is difficult to assess whether the use of such analysis leads to improvements in allocative efficiency and other criteria deemed important by each system. An examination of whether such evidence improves decision-making requires study firstly of the factors driving decisions in each country, consideration of the desirability of each of these factors and the improvement in welfare resulting from better decisions by using such analysis.

Most developed countries health systems have established national reimbursement agencies that appraise and make decisions on the availability of new medicines in their health systems (Hutton et al., 2006). An appraisal is defined as the activity of judging on the basis of the current information and a variety of analytical methods according to stated criteria, the value of the medicine prior to the medicines use (ex ante) and proposing recommendations (either mandatory or advisory) for its future use. The analytical methods referred to in this thesis are similar to those broadly described in (Dowie, 1997) for which evaluation (ex post) was said to include intuitive judgement, Randomised Controlled Trials (RCTs), observational studies and decision analytic

models. The term evaluation will only be used to refer in this thesis to those medicines that are judged using analytical methods, evidence and other factors after being in use for a period of time. There are five common process stages which each fourth hurdle system can be observed to broadly follow such as identification of the question and definition, evidence generation, evidence synthesis, deliberation and the decision (Hutton et al., 2008).

HTA has been an increasingly prominent source of information considered amongst other factors/criteria when reimbursement agencies appraise medicines for use in developed countries (Banta, 2003, Neumann, 2009, O'Donnell et al., 2009, Sorenson et al., 2008). HTA was first introduced in the US with the formation of the US Office of Technology Assessment (OTA) in 1972, (Banta and Luce, 1993). The seminal report written by the Committee for Evaluating Medical Technologies in Washington defined HTA as "any process and reporting of properties of a medical technology used in health care such as safety, efficacy, feasibility and indication of use, cost, cost-effectiveness as well as social, economic and ethical consequences whether intended or unintended", (Mosteller et al., 1986). There have been a number of other broadly similar definitions published since then (Facey et al., 2006, Banta and Luce, 1993). The definition adopted by Health Technology Assessment International (HTAi) is "The systematic evaluation of properties, effects, and/or impacts of health care technology. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care. HTA is conducted by interdisciplinary groups using explicit analytical frameworks drawing from a variety of methods." (HTAi, 2011). HTA is therefore a scientific field, which seeks to inform decision-making on the use of technologies and broadly covers five main areas; clinical effectiveness, cost-effectiveness, social, ethical and legal aspects. A recent study aimed to clarify the definition of HTA because of the lack of consistency of the use of terms across jurisdictions and distinguish the activity from Evidence Based Medicine (EBM) and Comparative effectiveness research (CER). Luce and colleagues proposed more specific terminology for HTA and state that it answers the question of "is it worth it?" and they define this as "a method of evidence synthesis that considers evidence regarding clinical-effectiveness, safety, cost-effectiveness and, when broadly applied, includes social, ethical and legal aspects of the use of technologies. The precise balance of these inputs depends on the purpose of each individual HTA. A major use of HTAs is informing reimbursement and coverage decisions, in which case HTAs should include benefit-harm assessment and economic evaluation.", (Luce et al., 2010).

There is variation across countries national reimbursement agencies with regards to either requiring a full HTA or partial HTA and this may be provided by the manufacturer, a third party independent group or by both of these groups. The term HTA agency is used to describe a range of bodies, which may apply full HTA or use a range of components of HTA assessing different technologies for different purposes. The International Network of Agencies for Health Technology Assessment (INAHTA) has 54 member agencies from 26 countries and organisations can become members if they assess technologies in health care and are non-profit public organisations relating to regional or national governments. Health economic analysis is an important component of HTA and many systems use this formally in their relevant process to consider the consequences of a decision.

1.3 Health economic analysis (appraisal and evaluation)

In order to understand the importance of heath economic analysis and other factors, a clear definition of what is meant by the term health economic analysis is required. Health economic analysis (economic evaluation or appraisal) aims to provide a framework for organising and addressing as many of these consequences as possible and providing justification of the explicit value judgements in decision-making. In a recent bibliometric tour of the past 40 years of health economics, 'Economic Evaluation in Health care' represents the second largest topic with respect to the Top 300 most highly cited articles in Health Economics (Wagstaff and Culyer, 2011). The Google Ngram viewer shows the use of the term 'health economic evaluation' begun to appear in books in the late 1990s. Drummond *et al.* provides the distinguishing characteristics of health care evaluation and differentiates between full economic evaluation and partial evaluation. Partial evaluation includes efficacy, effectiveness evaluation, cost-analysis and cost outcome description. The term economic evaluation with respect to health was defined as the "the comparative analysis of alternative courses of action in terms of both their costs and consequences." (Drummond et al., 1987). This includes four types of health economic analysis, cost-minimisation analysis, cost-effectiveness analysis, cost-utility analysis and cost-benefit analysis.

The definition of health economic evaluation does not include a time dimension for the analysis with respect to the technology or programs implementation and therefore does not directly distinguish between appraisal and evaluation. The UK Treasury Green Book defines appraisal as the assessment and judgement of whether a proposal is worthwhile before the implementation of a project proposal. In contrast evaluation uses similar techniques (economic analysis) to appraisal but uses data directly after the implementation of the proposal and can feedback for improving the assessment of new proposals (HM Treasury, 2011). The differentiation between

health economic appraisal and health economic evaluation are often not made clear and the terms are used interchangeably to mean those aspects of full evaluation as described by Drummond et al. data available at appraisal may provide different results to that available at an evaluation stage. The term health economic appraisal will be used in this thesis to refer to whether a medicine *will be* cost-effective in practice whereas health economic evaluation will refer to whether a medicine *has been* cost-effective in practice. However, the same techniques of economic analysis are used in health economic appraisal and health economic evaluation which include cost-minimisation analysis, cost-effectiveness analysis, cost-utility analysis and cost-benefit analysis. These types of analysis may be required by reimbursement agencies to provide the economic case for a new or existing medicine.

Cost-benefit analysis is the cornerstone of the Welfare Economists approach to addressing problems in public policy (Brouwer et al., 2008). The origins of cost-benefit analysis can be traced back to Jules Dupuit in 1849 in his theoretical study of toll bridges (Ekelund, 1968) and the concept was then formalised in economics by Alfred Marshall in 1890, (Marshall, 1920). Cost-benefit analysis was defined by Sugden and Williams as: 'requiring the identification of all the effects of the project on the individual welfare of all members of the community. It then requires these effects to be measured in some common units so that aggregate benefits can be compared with aggregate costs.' (p89 (Sugden and Williams, 1978)). It therefore compares whether the monetised benefits of a medicine exceed the monetised costs. Cost-benefit analysis is grounded in welfare economics and the Pareto improvement criterion – if the reallocation makes at least one individual better off and no one worse off, *ceteris paribus*, this represents a Pareto improvement. The benefits of a project can be measured in terms of the changes in individual's welfare through a monetary valuation of the health effects.

There are three approaches to assigning a monetary valuation to health outcomes either through the human capital approach, revealed preferences (value of a statistical life year) or stated preferences through a contingent valuation approach (willingness-to-pay survey). The political undesirability of measuring health benefits in monetary terms made way for the growth in a second approach called cost-effectiveness analysis which measures the benefits in some other units. The first cost-effectiveness analysis in health appeared in the 1960's (Backhouse et al., 1992, Elixhauser et al., 1993, Warner and Hutton, 1980, Culyer et al., 1977). The first published cost-effectiveness analyses were on the economics of syphilis control programs, (Klarman, 1965) and the cost-effectiveness of contraceptives with respect to population growth (Enke, 1966).

Cost-effectiveness analysis in its broadest sense is a method designed to assess the comparative impact of expenditures on different health expenditures (Gold et al., 1996) assuming that for any given level of resources society aims to maximise the total health benefit of the population (Weinstein and Stason, 1977). The analysis produces a cost per unit of health effect (effectiveness data but new medicines often rely on efficacy data and assumptions on potential effectiveness) from a medicine when compared to an alternative (per life year, per natural unit treatment specific), otherwise known as an Incremental Cost-effectiveness Ratio (ICER). The use of cost-effectiveness analysis may be treatment specific and may not allow comparisons between different treatments for different diseases but cannot address the issue of opportunity cost of funding a new medicine across diseases.

In contrast, cost-utility analysis allows various different outcomes to be combined into one single composite outcome and allows comparisons across different diseases areas and treatment programmes. Cost-utility analysis is a method where the costs are identical to cost-effectiveness analysis but the units of health effect differ and are measured in quality-adjusted life-years (QALYs) gained (effectiveness). Cost-utility analysis was first used in a study of the treatment of patients with chronic renal disease where those patients on dialysis were given a quarter of a life year reduction in life year gained in comparison to those patients with an effective transplanted kidney (Klarman et al., 1968). This study at the time did not refer to this as the QALY. The formal definition of cost-utility analysis is 'a form of evaluation that focuses on the quality of the health outcome produced or forgone by health programmes or treatments (Drummond et al., 1997). The incremental cost effectiveness estimates (ICER) using this approach are expressed in the form of a cost-per QALY gained. This value must then be compared against a cost-effectiveness threshold which may be established through empirical data and the method for establishing this will depend upon the system (opportunity cost of the least efficient funded treatment or willingness to pay).

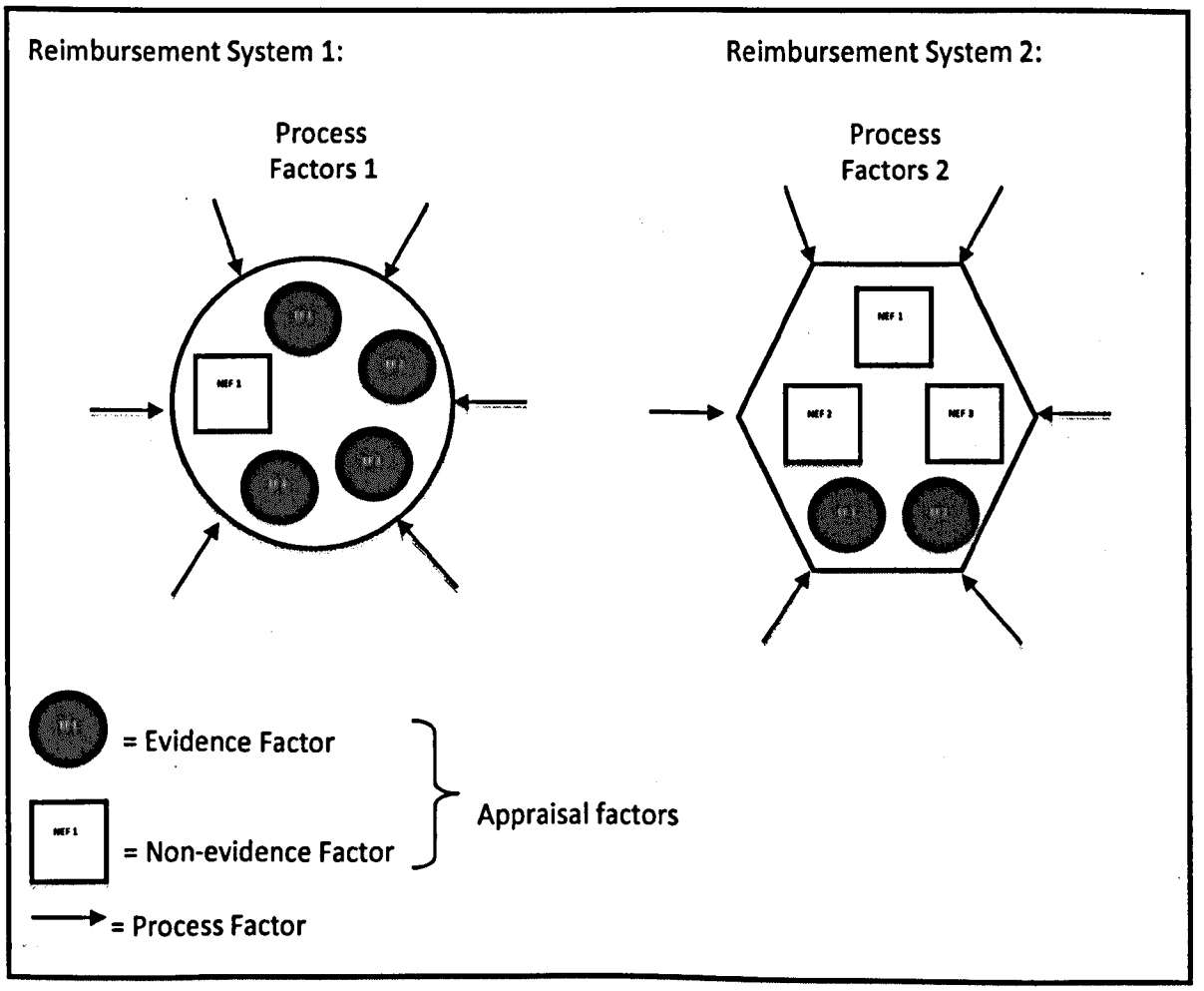
Cost-minimisation analysis concerns the analysis of two treatments that have equivalent efficacy by a trial finding no statistically significant difference or effectiveness (where data available) and involves a comparison of the costs of the two treatments. A cost-analysis may become a cost-minimisation analysis if there is evidence that the treatments are equivalent in their consequences (Drummond et al., 1997). In the third edition of the book Drummond dropped cost-minimisation as a form of full evaluation technique because of uncertainty around determining whether two treatments are broadly equivalent with respect to either costs or effects. Cost-minimisation is not a study design that can be determined in advance and the authors suggest that the type of analysis is only justifiable when the technologies are near identical (Drummond et

al., 2005). A recent study has demonstrated that when CMA is used it is likely to bias estimates of uncertainty and leads to overestimate or underestimates of the probability that the treatment is cost-effective. The study suggests cost-effectiveness analysis is almost always required to guard against biased estimates of the uncertainty (Dakin and Wordsworth, 2011).

1.4 The contribution of health economic analysis and other factors in heterogeneous reimbursement systems

Only a few, on average, of every 10,000 substances synthesised in research laboratories, will successfully pass all the research and development stages to become a medicine marketed to patients (EFPIA, 2011). Manufacturers require stability and predictability to develop successful new medicines. Public reimbursement systems need to provide clear signals of their demand for medicines so that manufacturers can make efficient investment decisions in the light of the uncertainty.

Figure 1.2: Diagram of reimbursement system factors



Reimbursement agencies can provide stability and predictability by clearly communicating the process and requirements, the main decision factors and details of their deliberations so that manufacturers and other stakeholders can understand the determinants of the decisions. The factors or determinants of medicine reimbursement decisions can be investigated within countries and across countries when such details are provided. A factor can be considered either as an evidence or non-evidence factor that are important in the appraisal or a factor with respect to technology assessment process. An 'evidence factor' - a characteristic of the medicines evidence (safety, clinical efficacy, clinical effectiveness and cost-effectiveness), 'non-evidence factor' - other value judgement applied because of a characteristics of the medicine that influences the decision (medicine treats severe illness, end of life medicine, orphan medicine, innovative medicine). These factors are potentially not backed by evidence but are a form of value that Williams referred to as postulated by the decision-maker in the political process (Williams, 1972). The third category is a 'process factor' - characteristic of the process of assessment or appraisal (Within countries: different committees, time period, different processes and across Countries: Differences in categorisation of the reimbursement system) that the medicine undergoes which effects or influences the reimbursement decision (Figure 1.2).

An understanding of the similarities and differences of the influence of factors on decisions is important for manufacturers as it enables them to select new molecules, develop medicines with appropriate clinical strategies and produce effective and profitable medicines with the correct evidence requirements for each reimbursement system. An understanding of the relative importance of the factors within and across countries is important for policy makers to help to identify the desirability of differences in their system with respect to the overall operation and objectives of the system. This enables the policy makers to legitimately communicate the rationale for decisions to patients to enable patients to understand any differences in decisions for medicines that may occur across public reimbursement systems.

The definition of what constitutes the influence of a factor on the reimbursement decision is important because there are many potential interpretations of the term 'influence'. Buxton considered this issue and the problem of the 'missing counterfactual' to determine the influence of economic evaluation on health policy in the United Kingdom. 'The consistency of a subsequent health policy with the conclusions of the study does not necessarily indicate that the study has influenced the policy. The consistency may be a happy coincidence, with the evaluation used rather as a drunken man may use a lamp post – more for support than illumination' (Buxton, 2006). With respect to the influence of factors on reimbursement decisions in countries reimbursement systems this can be interpreted to mean:

1. The observation that reimbursement system states that the factor is considered, regardless of the reimbursement decision. Or;
2. Influence may be considered where a factor (cost-effectiveness considered) is found consistently to be attributable to a certain decision outcome (correlate influence). Or;
3. Influence maybe considered with respect to the causal influence of a factor on the decision, in the situation where the counterfactual is evident where the factor is not present (not considering cost-effectiveness evidence) and the reimbursement decision and compared with the decision where the factor is considered (considering cost-effectiveness evidence) and the reimbursement decision, ceteris paribus.

The second and third will be used to define what constitutes influence in this study, with preference for the third definition of the causal influence. However, the third definition is impossible to observe in practice. This requires a study with experimental design such as a randomised trial or statistical analysis that can correct for the counterfactual. A randomised trial at country level would not be possible and a study assessing the influence of the use of health economic analysis would require two "identical twin reimbursement agencies" operating with identical reimbursement systems in which health economic evidence would be considered by one of the agencies for the medicine and would not be considered by its twin. The influence could then be assessed by the differences in reimbursement decisions between the two.

The literature acknowledges that HTA and economic analysis supports and informs reimbursement decisions (Oliver et al., 2004, Drummond et al., 2008, Annemans et al., 2010). However, few empirical studies have been conducted to discover the relative influence of the evidence and other factors in reimbursement decisions within countries and comparisons of these between countries. An initial search of the literature reveals a focus has been made on the use of evidence in reimbursement decisions within Australia, Canada and England. Factors may have similar effects in some countries, differential effects in some and have no influence in other countries on reimbursement decisions. Cross-country comparisons of the similarities and differences in the determinants of reimbursement decisions are scarce. One study focuses on a comparison of the clinical and cost-effectiveness evidence used in reimbursement decisions for Australia, Canada and England that there are a limited number of common medicines across countries and concludes some of the variation in reimbursement decisions may be explained by differences in process (Clement et al., 2009).

The empirical literature appears to focus on the influence of evidence. Evidence covers a number of factors in the appraisal of medicines for reimbursement but other non-evidentiary factors that

may influence reimbursement (Berg et al., 2004, Neumann, 2009). Every reimbursement system operates in the social and political priorities of the country, decision structures and resources available. These are complex systems and other characteristics of the systems such as the objectives; processes and other factors may be influential upon the reimbursement decisions. There is considerable variation in the processes and types of institutions involved within the systems that incorporate HTA in the appraisal of medicines (Hutton et al., 2008). Of the few studies available, many focus on categorising a small number of selected reimbursement systems and considering these with respect to the influence of differences in the use of evidence to inform reimbursement (Belgian Health Care Knowledge Centre, 2010).

The process differences across countries may have considerable influence in explaining differences between countries reimbursement decisions and the relative importance of factors. For example, consider the hypothetical scenario where two systems are similar on all characteristics and the manufacturer presents the same evidence but they differ in an aspect of process, two separate committees conduct assessment and appraisal in one system and by a single committee in the other, it is conceivable that these two systems may reach different decisions because of differences in the committees representatives. The process may also modify the effect of other factors. The evidence maybe revised by a third party independent assessment of the cost-effectiveness which results in different cost-effectiveness estimates leading to a difference in the relative influence of the cost-effectiveness evidence in comparison to a system without such third party assessment. The third party assessment provides a further perspective on the evidence.

The first stage in examining the influence of differences in process on decisions requires considering the characteristics of reimbursement systems. It is not anticipated that any of the systems will be identical with respect to all characteristics of the reimbursement system but it is expected that some will share more similarities than others. Where countries share similarities it would be expected that there would be more convergence in decisions than those that were dissimilar, assuming similar evidence. An understanding of the importance of process requires comparison of decisions across countries of the decisions and factors important within each respective country. This thesis will focus on the use of evidence and the specific contribution of health economic evidence, accounting for differences in reimbursement process across systems. This will be undertaken by considering the similarities and differences in reimbursement systems, the differences and similarities in the use of economic evidence and the empirical contribution of economic evidence alongside other factors in reimbursement decision-making.

1.5 Aims and objectives

Reimbursement systems are complex and the literature describes differences in the use of evidence within countries but has not focused on the influence of differences in other factors within countries and in process within and across countries on reimbursement decisions. The overall aim of the thesis is to examine the influence of health economic analysis and other factors on medicine reimbursement decisions within and across countries. In order to recognise this it is necessary to categorise OECD reimbursement systems to understand the similarities and differences across systems. Each reimbursement system produces decisions on medicines that are paid for by the public health system. An understanding of the influence of the broad factors affecting reimbursement decisions for pharmaceuticals will help to understand the role of health economic evidence in countries that share similarities and differences in processes and the information used in decision-making. This aim will be investigated by considering the following research questions (objectives):

1. What factors have been considered in empirical studies assessing the influence upon reimbursement decisions? What is the influence of these factors on decisions in these countries?

2. What are the similarities and differences in reimbursement systems in OECD countries and what are the stated criteria in the appraisal of medicines in these systems?

3. What is the common influence of health economic analysis and other factors in countries with broadly similar reimbursement systems that use health economic analysis?

4. What is the influence of health economic evidence in a country using cost-effectiveness evidence in comparison to a system using solely clinical effectiveness evidence?

Research Question 1: What factors have been considered in empirical studies assessing the influence upon reimbursement decisions? What is the influence of these factors on decisions in these countries?

The influence of factors in reimbursement decisions maybe considered through either a qualitative or quantitative study. A systematic review will be performed in chapter four to identify empirical studies that have analysed the impact of factors on reimbursement decisions in OECD countries. This will consider the factors that have been considered across countries and the

resulting influence of these factors within countries. A comparison will be made against the stated criteria provided by the reimbursement systems in the appraisal of medicines identified in chapter 4. This will identify countries that have not been studied and the opportunity to conduct useful cross-country comparisons where sufficient information is available on the reimbursement decisions

Research Question 2: What are the similarities and difference in reimbursement systems in OECD Countries and what are the stated factors in the appraisal of medicines in these systems?

Chapter 3 and 4 will provide a categorisation of the entire reimbursement system using the framework for classifying fourth hurdle systems (Hutton et al., 2006). The framework considers the establishment, objectives, implementation and accountability of the system (policy implementation level) as a distinct set of characteristics of the entire system from how decisions are made with the systems for individual technologies (individual technology decision level). The chapters aim to consider the similarities and differences between OECD countries processes and stated criteria in the appraisal of medicines. It is anticipated that some systems will be more transparent than others and provide details of the characteristics of the system and details of the deliberations for the decisions. This will also inform the feasibility of conducting an empirical analysis of the factors influencing decisions in OECD countries.

Research Question 3: What is the common influence of health economic analysis and other factors in countries with similarities in reimbursement systems that use health economic analysis?

Countries sharing broad similarities with the reimbursement system will be investigated through the categorisation of systems and the previous empirical research in this area. Those agencies providing similar evidence requirements and use of health economic evidence and similarities in the reimbursement system will be studied alongside other factors to establish whether there are common factors that can be identified regardless of potential variation in the process. A quantitative regression analysis will be considered introducing new factors by providing variables to account for factors previously studied in countries and new factors. The study will aim to investigate whether there are common factors that are influential over and above any differences in process observed across the countries. This will require sufficient reporting of the evidence assessment and appraisal within countries and there will be a trade off between more information on factors in a smaller sample of countries and including as many countries as possible with less information or no information on factors where health economic analysis is used in decision-making.

Research Question 4: What is the influence of health economic evidence in a country using cost-effectiveness evidence in comparison to a system using solely clinical evidence?

Health Economic evidence can be used by the reimbursement agencies to provide an indication of the demand curve for medicines and the manufacturer can select or propose a price. The rules of the game are different in countries that do not use health economic analysis where other criteria are set to appraise the medicine and decide reimbursement. A comparison of reimbursement decisions will be performed between a reimbursement system that uses health economic evidence and one that only considers clinical evidence, where sufficient documentation of the assessment and deliberations are publically available. A qualitative study will be performed on the influence of health economic analysis alongside any observed variation in other factors in the decision-making. This will identify common medicines assessed between the agencies and consider whether health economic analysis can explain these differences or whether other factors may explain the differences in decisions between the two systems.

1.6 OECD reimbursement systems

The study focuses on countries reimbursement systems in the Organisation for Economic Co-operation and Development (OECD). The OECD was established in 1961 and provides information to help government's foster prosperity and fight poverty through economic growth and financial stability. There are 34 (36 including the countries of the United Kingdom, Scotland, Wales and England) member countries of the OECD as of July 2011.

The OECD countries which will be considered within this research are listed below:

1. Australia
2. Austria
3. Belgium
4. Czech Republic
5. Canada
6. Chile
7. Denmark
8. Estonia
9. Finland
10. France
11. Germany
12. Greece

13. Iceland
14. Ireland
15. Israel
16. Italy
17. Japan
18. Hungary
19. Korea
20. Luxembourg
21. Mexico
22. Netherlands
23. New Zealand
24. Norway
25. Poland
26. Portugal
27. Slovak Republic
28. Slovenia
29. Spain
30. Sweden
31. Switzerland
32. Turkey
33. United Kingdom – England and Wales
34. United Kingdom – Scotland
35. United States of America

1.7 Summary

This chapter has outlined the importance of understanding the influence of health economic analysis and other factors within and across countries to explain similarities and differences in access to medicines reimbursed by the public health system. Chapter 2 will provide a systematic review of the current evidence of the influence of factors internationally. Chapter 3 and 4 will identify the impact of system and process differences on the use and interpretation of health economic analysis and other factors. Two further chapters will provide two empirical analyses of the use of health economic analysis in different countries. Chapter 5 will explore the common factors for decisions using a multinomial regression analysis in systems using both clinical-effectiveness and cost-effectiveness evidence. Chapter 6 will consider the contribution of formal

health economic analysis on decisions in a process using such analysis in Scotland in comparison to a process not routinely using such analysis in France. The final chapter will provide a discussion of the use and influence of health economic analysis in heterogeneous reimbursement systems and provide the limitations and some ideas for further research.

Chapter 2: Systematic Review of Factors Influencing Pharmaceutical Reimbursement Decisions in OECD countries'

Abstract

Objective: Chapter 1 introduced examples of the many factors that influence pharmaceutical reimbursement decisions. This chapter aims to determine the factors considered in empirical studies and the influence of these factors on the reimbursement decisions of government funded reimbursement bodies in OECD countries'.

Methods: A search of MEDLINE, EMBASE, EconLit, Health Management Information Consortium, NHS EED and REPEC Economic working papers until July 2010 was conducted. A hand search of the International Journal of Technology Assessment in Health Care was undertaken (1990-2010). A citation search was undertaken for one highly cited article. The following study designs were eligible: experimental, quasi-experimental, retrospective, prospective, case series and surveys or questionnaires design. The influential factors were reviewed across and within OECD countries and the validity of study findings critically appraised.

Results: The search identified 13 quantitative studies and 19 qualitative studies. The quantitative studies considered the correlation between factors and decisions either through regression analysis of retrospective decisions or discrete choice experiments. Cost-effectiveness was found to be consistently influential for 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. This limited comparability within and across countries. Studies reported mixed evidence of the influence of the quality, quantity and type of clinical evidence, appropriate economic analysis, economic analysis uncertainty, lack of alternative therapy and severity of disease on reimbursement decisions. Qualitative studies reported narrative descriptions, case studies and interviews with decision-makers. These studies supported the influence of cost-effectiveness found in the quantitative evidence. Additional factors were described to influence decisions in the qualitative studies, namely, the composition of the decision panel, committee deliberations, stakeholder involvement and lobbying upon decisions.

Conclusion: There is limited evidence of the influence of factors on reimbursement decisions in a few OECD countries with established reimbursement processes and qualitative evidence highlights some potential factors that have not been included in quantitative studies. Wider investigation of the factors influential in other countries would allow comparison of the similarities and differences across OECD countries.

2.1 Introduction

Developed countries' health care systems typically aim to provide universal and equitable access to health care. In the last 30 years, a rise in the diffusion of new medicines and resulting pressure on healthcare budgets has led countries with public systems to explicitly decide which medicines should be funded. Some countries have developed explicit procedures and established national reimbursement agencies using formal HTA (or elements of HTA) along with other factors to make such decisions. The introduction of evidence requirements and the resulting emergence of HTA have improved the transparency of countries reimbursement decision-making. Examples of some established reimbursement agencies using elements of HTA are contained in Table 2.1.

Table 2.1: Examples of reimbursement agencies and institutions

Country	National Reimbursement Institute/agency/entity
England and Wales	National Institute for Health and Clinical Excellence (NICE)
Australia	Pharmaceutical Benefits Advisory Committee (PBAC)
Scotland	Scottish Medicines Consortium (SMC)
Canada	Canadian Agency for Drugs and Technologies in Health (CADTH)
Germany	Joint Federal Committee (G-BA) and IQWIG
France	Haute Autorité de santé (HAS)
Sweden	Pharmaceutical Benefits Board (TLV)
Netherlands	Dutch Health Insurance Boards (CVZ)
New Zealand	Pharmaceutical Management Agency (PHARMAC)

The objectives of different systems vary but all aim to make evidence informed recommendations or mandatory decisions on whether a medicine should be included on each country's formulary or list of medicines for reimbursement by their respective government funded schemes. The reimbursement processes include an assessment of the evidence provided by the manufacturer or other source, followed by an appraisal of the evidence by experts. The appraisals involve judgements regarding the evidence and analysis of the value of a new medicine in comparison with the available alternatives. The countries reimbursement processes vary with respect to the extent by which the assessment phase of the process can be distinguished from the appraisal. There is variation in the factors considered by reimbursement agencies (Hutton et al., 2006) and this may explain the variation in reimbursement recommendations for the same medicines across countries (Clement et al., 2009).

The first chapter identified that the influence of health economic appraisal/evaluation can only be identified in countries reimbursement systems by controlling for all factors influencing the appraisal and final decision of the reimbursement agency. The previous chapter broadly categorised these factors into evidence factors, non-evidence factors and process factors. The evidence factors included clinical evidence factors, economic evidence factors and the other

economic evidence factors such as budget impact and productivity savings. Studies may explore these factors through the consideration of a single reimbursement system or by comparing the decisions and factors in cross country comparisons. This chapter aims to consider the factors that have already been studied with respect to factors influencing the reimbursement decisions within and across national government funded medicine reimbursement systems.

An understanding of the factors studied within and across OECD countries will be important for identifying current international comparisons of reimbursement systems, the challenges of constructing factors across countries and potential solutions, the weight of evidence and other factors to explain differences in reimbursement decisions across countries and the limitations of the different methodologies currently available to consider the question of factors influencing reimbursement decisions. Further to this the identification of differences between appraisal components and the influence of process factors would help to clarify certain differences between agencies and establish the respective importance and desirability of specific combinations in methods, processes and procedures for reimbursement agencies in different health systems. This would help to understand how the procedures influence the decisions arrived at for new drugs and further understand the dynamics and evolution of these system The review will help to identify further research to understand the similarities and differences between the factors internationally.

2.1.1 Previous relevant systematic literature reviews

An initial search was conducted of the Cochrane CENTRAL database and the International Journal of Technology Assessment in Health Care to identify any previous systematic reviews on this topic. The search did not identify any systematic reviews that consider the use of factors in the appraisal of medicines on reimbursement decisions. There have been two systematic reviews and one intervention protocol, which consider the influence of methods and factors on pharmaceutical reimbursement systems.

Williams et al. performed a study, which identified the ways, and extent to which economic analysis is used in health policy decision-making through a systematic review and qualitative data collection of heath policy decisions broader than pharmaceuticals (Williams et al., 2008). The review also considered the factors associated with the utilisation of economic evaluation findings. The search strategy for this systematic review considered evidence between 1966 and 2002 for England and Wales. The review considered the use of economic evaluation in policy-making, health and non-health literature on the use of economic analysis in policy-making and studies that

have considered the actual and perceived barriers to economic analysis. There were few systematic reviews of the evidence for this question and the primary studies identified suffered from methodological concerns. The review identified a number of factors limiting the emphasis on economic analysis that included the lack of a clear objective for the committees and their relationship with the structures and process, satisfying a number of interests in an explicit political decision-making process and the absence of a specifically defined budget. The study illustrated that more primary studies are required to identify the extent of which economic analysis informs health policy decision-making. The study also suggested that a formal process should be set out to clarify the objectives of the healthcare system/reimbursement system seeks from investments in healthcare.

Eddama and Coast conducted a systematic review with the objective of understanding the use of economic evaluation at a local level (Eddama and Coast, 2009). The study identified a total of 40 empirical studies and found that there has been an increase in the use of economic evaluation overtime, especially in the UK. The review highlighted that there is little known of the influence of economic evaluation at the local level. The authors suggested that further qualitative research may be helpful in understanding further the impact of economic evaluation. The perspective of this chapter will be from the national level rather than local or regional level.

2.2 Literature review methodology

2.2.1 Objective

To determine the formal appraisal and process factors in empirical studies considering the influence of these factors on medicine reimbursement decisions in OECD countries and the influence of these factors on reimbursement decisions in these countries.

The objective has been split into two sub-objectives with a number of respective questions to be addressed:

1. To determine the formal appraisal and process factors that have been considered to influence reimbursement decisions or recommendations in OECD countries.
    a. What methodologies are used to consider the influence of factors on decisions?
    b. What is the definition of influence within studies?
    c. What factors are included in studies considering influence?

2. To determine the influence of formal appraisal and process on the reimbursement in OECD countries government funded reimbursement bodies.

2.2.2 Types of studies

A review of systematic reviews was conducted to identify whether this topic is original and to identify other studies to include in this review.

Influence is defined in Oxford Online Dictionary as "the capacity to have an effect on the character, or behaviour of someone or something, or the effect itself", (Oxford Online Dictionaries, 2011). In the context of reimbursement decision-making the term influence refers to the extent by which appraisal factors within a country or process factors within or across countries effect a medicines reimbursement decision outcome. Influence maybe identified by:

1. Influence may be considered where a factor (cost-effectiveness estimate) is found consistently to be attributable to a certain decision outcome (correlate influence). Or;
2. Influence maybe considered with respect to the causal influence of a factor on the decision, in the situation where the counterfactual is evident where the factor is not present (not considering cost-effectiveness evidence) and the reimbursement decision and compared with the decision where the factor is considered (considering cost-effectiveness evidence) and the reimbursement decision, *ceteris paribus*.

In development of the review methodology the reviewer did not expect to find RCTs studies because of the difficulties pragmatically in randomising different appraisal factors and processes between different national reimbursement systems. In the light of this a variety of research designs were included to address the research questions:

1. Experimental study designs;
2. Quasi-experimental study designs using statistical approaches to identify the impact of factors;
3. Retrospective study designs;
4. Prospective study designs;
5. Case series;
6. Survey or questionnaire based studies in relation to a number of countries' reimbursement decisions.

A study with a single reimbursement recommendation or decision (case report) was not considered in this review because this type of study does not allow the identification of the relationship between factors and may not be representative of the general decisions made by a reimbursement body at a particular period of time/over decision periods.

2.2.3 Study population

The study population includes national institutions, bodies or entities that consider elements of HTA evidence to produce formal reimbursement recommendations or decisions for medicines. The term "reimbursement" is defined as the payment for new medicines under a government funded scheme. This may include studies that investigate the influence of factors on reimbursement decisions within single countries or cross-country comparisons. The study population would not include studies of reimbursement decisions of privately funded agencies or those HTA reports produced for information only and do not have a practical reimbursement purpose.

2.2.4 Types of intervention

A factor can be described as a component of appraisal or relevant characteristic of the decision-making process that influences the medicine reimbursement decisions within or across countries.

2.2.4.1 Formal appraisal factors

Many reimbursement systems include one or more committees that judge the characteristics of a medicine with respect to criteria. The criteria may or may not be explicitly stated. Appraisals factors can either be evidence based or non –evidence based. Evidence based appraisal factors include the elements of formal identification, gathering, synthesis and analysis of the evidence that are judged by a committee for the purpose of reaching a reimbursement recommendation or decision for a new medicine. The evidence includes those elements of HTA such as clinical evidence, economic evidence and budget impact. The non-evidence based factors judged by a committee include social value judgements, respective patient information, public perceptions of the decisions, political considerations such as location of industry and other economic considerations.

2.2.4.2 Process factors

The reimbursement decision for individual medicines may be influenced by the characteristics of the process by which a medicine is assessed and appraised. Variation in process may impact upon how a medicine is viewed by the committee or individuals tasked with appraising a medicine for reimbursement. Process factors may vary within countries for each medicine appraised such as the time taken to complete the decision, type of process followed (e.g. Single Technology Appraisal (STA) or Multiple Technology Appraisal (MTA) in the case of NICE) or decision appealed by stakeholders or processes may only vary at the country reimbursement level such as freedom to set price, independent assessment, number of reimbursement process stages and number of committees informing the decision. The influence of country level process factors on decisions can only be completely investigated within studies including a comparison of countries.

2.2.5 Types of outcome measures

A study was included if it reported the following details:

A description of appraisal factors considered by the reimbursement body/institution/entity AND:

A quantitative report of the factors involved in the appraisal/evaluation for the reimbursement or recommendation of medicines. Such as:

- The number of decisions, percentage or proportion influenced by each of the factors used by the reimbursement body.

OR:

A qualitative report of the factors involved in the appraisal/evaluation for the reimbursement or recommendation of medicines. Such as:

- A ranking or more detailed analysis of data from a questionnaire or survey of the influence of factors on reimbursement decisions or recommendations.

2.2.6 Study exclusion

A study inclusion and exclusion form was completed for each of the studies and the template is included in Box A2.1. The following studies were excluded:

1. Editorials or discussion papers were excluded if they did not report a data analysis.
2. Studies that consider factors at the local or regional decision-making level

3. Studies that explain or report one pharmaceutical reimbursement decision.
4. Studies conducted before 1990.

2.2.7 Critical appraisal of included studies for validity of results and risk of bias

2.2.7.1 Quantitative studies validity and reliability (risk of bias)

Buxton describes the influence of an economic evaluation on decision-making and discusses what constitutes influence (Buxton, 2006). In order to assess the influence of a factor on a reimbursement decision an understanding of the counterfactual is required. For example, the counterfactual would be the policy or decision if the factor had not been present. The gold standard study design would be an experimental study where all factors are quantifiable and measurable and the effect of changes can be observed. This can theoretically be achieved through either an RCT or through an observational study using advanced statistical methods (instrumental variables and propensity score matching) to overcome the issues of confounding/endogeneity. A confounding variable is related both to the outcome variable (reimbursement decision) and to the independent variable of interest (factors such as economic evaluation) and is not part of the causal pathway between them (Bowling and Ebrahim, 2008). An understanding of the counterfactual allows consideration of whether the observed association between a factor and the reimbursement decisions are causal or spurious and therefore related by an underlying separate factor.

The Cochrane handbook suggests that a focus should be made on the risk of bias in the results rather than the methodological quality of quantitative studies included (Higgins and Green, 2011). The Cochrane framework will be used for an assessment of risk of bias for those studies that are of an experimental design. The framework applied by the Cochrane collaboration using the assessment of risk of bias tools which consider selection bias, performance bias, attrition bias, detection bias and reporting bias. The purpose of the tool is for consideration of risk of bias in healthcare interventions and the tool will be tailored to consider the risk of bias for the purpose of this thesis.

The potential value for using the risk of bias tool for those studies that are non-experimental is more of a contested issue, especially for those studies of a qualitative nature. The quantitative non-experimental studies will be critiqued separately from the qualitative studies. The validity of the results of observational studies using econometrics techniques will be reviewed with respect to a number of criteria.

The key characteristics of a good regression model are summarised in Essential Econometrics (Gujarati, 1999). Gujarati states that a model can be critically appraised by considering the following general criteria:

- Parsimonious: A regression model can never completely capture the decision-making environment. The regression model should be kept as simple as possible;
- Goodness of fit: The regression analysis should explain as much of the variation in the dependent variable as is possible by the included explanatory variables (factors);
- Theoretical consistency: The model should have a theoretical underpinning to the inclusion and construct of the factors in the regression analysis;
- Predictive power: The models predictions should be borne out by the actual experience in reimbursement decision-making.

These criteria can be used to consider the validity of the results provided by the regression analysis. The robustness of the quantitative observational studies will be assessed with respect to the following specific criteria and regression diagnostic tests such as (Greene, 2003, Gujarati, 1999):

- Reporting of the definition of influence and appropriate statistical methods;
- Regression model specification:
    - Dependent variable and construct of independent factors: Data and construct of methods justified (attempts to minimise subjectivity and measurement error);
    - Sample size: are there sufficient reimbursement decisions given the number of factors to provide robust evidence of the association or causal impact of the factor on the reimbursement decision;
    - Model Goodness of fit: The measure will depend on the type of statistical analysis used in the regression model;
    - Omitted relevant variables (under-fitting the model) are a type of specification error;
    - Sample selection bias in which there are missing data for the dependent variable (selected sample of decisions for medicines);
    - Testing of regression model assumptions used in each of the studies.
- External validity of the results to other reimbursement decisions made by the agency.

2.2.7.2 Qualitative studies validity and reliability:

The application of quality guidelines to qualitative studies is controversial because no one set of guidelines can be definitive for these types of studies (Mays and Pope, 2000, Centre for Reviews and Dissemination, 2009). A descriptive critique will be made of the qualitative studies included with respect to the validity and reliability of the results. The suggested questions proposed by (Mays and Pope, 2000) will be considered when assessing the validity of the qualitative studies:

- Clarity of research question on influence;
- Appropriateness of study design;
- Sampling;
- Data collection and analysis;
- Reflexivity of the account given by the researchers undertaking the study.

2.2.8 Data extraction

The data will be extracted for experimental studies and non-experimental studies through a data collection form. A formal data collection form was used to capture the characteristics and results of the studies and the template is included in Table A2.1. The data was extracted by MWB for each of the included studies and the definition of the factors and results were double checked by MWB to minimise errors in recording and interpretation of the data from each study. The data extraction form included the following elements:

- Study details
    - Study ID;
    - Report ID;
    - Review author ID;
    - Citation and contact details.
- Methods
    - Quantitative/ Qualitative study;
    - Agencies compared;
    - Study design;
    - Analysis type/Statistical/narrative/interviews/focus groups;
    - Methods relating to either experimental study design or non-experimental study design.
- Reimbursement decisions

- Total number of reimbursement decisions;
- Characteristics of reimbursement decisions.

- Interventions
  - Types of factors considered;
  - Definition of the variables for each factor (quantitative studies);
  - Definition of influence (quantitative studies).
- Outcomes
  - Decision outcome and date decision made.
- Results
  - Factors influencing decisions.

2.2.9 Data analysis

The studies will first be grouped by quantitative and qualitative studies by country or by country comparison. A textual description of each of the studies included in the review and the characteristics systematically assessed in a table so that the same information is extracted on each of the studies.

2.2.9.1 Quantitative studies:

The quantitative studies will be categorised and the results reported separately for country comparisons and within country analyses of decisions and factors in reimbursement systems (Table 2.2):

- A consideration of the definition of factors and variables assessed for each country by type of factor;
- Definition of influence;
- Number of decisions assessed by each study;
- The statistical methods for assessing influence;
- Decision outcome.

The description of influence of each factor will be described within and across the countries in a separate section.

Table 2.2: Example of the quantitative extraction for the definition of factors

	[Study name]
Institutions (Year)	[Name]
Decision outcome (Number of decisions or responders)	[Categorical type]
Influence (Methods)	[Definition of medicines]
Sample of medicines/responders	[Types of medicines considered in sample]
Clinical evidence definition	
Clinical evidence factor 1	[Definition]
Clinical evidence factor 2	[Definition]
Economic evidence definition	
Economic evidence factor 1	[Definition]
Economic evidence factor 2	[Definition]
Non-evidence factors definition	
Non-evidence factor 1	[Definition]
Non evidence factor 2	[Definition]
Process factors definition	
Process factor 1	[Definition]
Process factor 2	[Definition]

2.2.9.2 Qualitative studies:

The qualitative studies will be categorised and the results reported separately for country comparisons and within country analyses of decisions and factors in reimbursement systems:

- A description of the factors considered by type of factor;
- Number of decisions for each study;
- Methodology used;
- Description of the influence of the factor.

A comparison will be made across the quantitative and qualitative studies to assess consistency of findings within and across countries.

2.2.10 Search methods for identification of studies

An initial broad search of evaluative approaches informing pharmaceutical recommendations was performed.

2.2.10.1 Resources to search:

- Medline;
- EMBASE;
- EconLit;
- HMIC Health Management database;
- NHS EED;
- REPEC Economic Working Papers;

- HTAi conferences abstracts;
- WHO;
- OECD reimbursement bodies' websites (e.g. NICE);
- EUnetHTA website.

2.2.10.2 Key journals search

The following key journal was searched between 1990 and 2010:

- International Journal of Technology Assessment in Health Care (IJTAHC).

2.2.10.3 Identification of reimbursement institutions/bodies/entities

Table 2.3: Country and Reimbursement Institution and abbreviation

OECD Country	Reimbursement Institution/Body/Entity	Abbreviation
Australia	Pharmaceutical Benefits Advisory Committee	PBAC
Austria	Pharmaceutical Evaluation Board	HEK
Belgium	Committee for Drug reimbursement (CRM)	CRM
Canada	CADTH Common Drug Review (CDR) decision at a provincial level	CADTH CDR
Chile	Not identified	-
Czech Republic	Ministry of Finance	-
Denmark	Danish Medicines Agency Laegemiddel stryrelsen	DMA
Finland	Ministry of Social Affairs and Health Pharmaceutical Pricing Board (PPB)	PPB
France	Haute Authorité de santé French National Authority for Health	HAS
Germany	IQWIG Institute for Quality and Efficiency in Health Care Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen Federal Joint Committee	IQWIG/GBA
Greece	Reimbursement and Medicinal Products	EDAF
Hungary	National Health Insurance Fund Administration	NHIFA
Iceland	Ministry of social affairs and health Tryggingastofnun rikisins (Icelandic Health Insurance)	-
Ireland	National Centre for Pharmacoeconomics	NCPE
Italy	Italian Medicines Agency (Agenzia Italiana del Farmaco)	AIFA
Japan	Ministry of Health, Labour and Welfare	MHLW
Korea	Health Insurance Review Agency	HIRA
Luxembourg	Direction de la santé Health Directorate	-
Mexico	Council Centro Nacional de Excelencia Tecnológica en Salud National Center of Excellence in Health Technology	CENETEC
Netherlands	National Insurance Health Boards (CVZ) college voor zorgverzekeringen	CVZ
New Zealand	Pharmaceutical Management Agency	PHARMAC
Norway	Norwegian Medicines Agency Statens legemiddelverk	-
Poland	Health Technology Assessment Agency	AOTM/AHTAPol
Portugal	National Institute for Pharmacies and Medicines Instituto Nacional da farmacia e do medicamento	INFARMED
Slovak Republic	Ministry of Health	-
Spain	Ministry of Health Agència d'Avaluació de Tecnologia i Recerca Mèdiques de Catalunya	-
Sweden	Dental and Pharmaceutical Benefits Board	TLV
Switzerland	Federal Office of Public Health	FOPH
Turkey	Social insurance agency	-
United Kingdom (England, Wales, Scotland)	National Institute for Health and Clinical Excellence (NICE), Scottish Medicines Consortium (SMC)	NICE, SMC
United States	Medicare evidence development and coverage advisory committee	-
Israel (joined September 2010)	Not included (Became an OECD country after search strategy conducted)	-
Estonia (joined December 2010)	Not included (Became an OECD country after search strategy conducted)	-
Slovenia (joined July 2010)	Not included (Became an OECD country after search strategy conducted)	-

There were 33 OECD countries when the search strategy was undertaken. Since 2010, 3 new countries gained membership of the OECD and as of September 2011 there are 36 OECD countries. Table 2.3 identifies the reimbursement institution/body/entity that is involved in appraising evidence for reimbursement decisions. These details were included in the search strategy in the next section.

2.2.11 Search strategy

The identification of the reimbursement agencies informed the search strategy for the systematic review to identify the population and intervention (Table 2.4).

Table 2.4: Population and Intervention

Population	Intervention
Reimbursement	Decision$
Payer	Allocation$
Drug coverage	Advice
Reimbursement mechanisms/	List
Pharmaceutical benefits advisory committee	Lists
Pbac	Recomend$.ti,ab
Committee for drug reimbursement	Recommend$
Danish medicines agency	Apprais$
haute autorit$ de sant$.	Drug approval/
french national authority for health	
reimbursement and medicinal products	
edaf	
ministry of social affairs and health	
italian medicines agency	
agenzia italiana del farmaco	
aifa	
health insurance review agency	
national cent$ of excellence in health technology	
centro nacional de excelencia tecnologica en salud	
cenetec	
pharmaceutical management agency	
pharmac	
health technology assessment agency	
aotm	
ministry of health adj20 slovak republic	
dental adj6 pharmaceutical benefits board	
pharmaceutical adj20 tlv	
social insurance agency adj20 turkey	
medicare adj20 coverage advisory committee	
Institute for Quality and Efficiency in Health Care	
Institut fur Qualitat und Wirtschaftlichkeit im Gesundheitswesen	
iqwig	
national health insurance fund administration adj20 hungary	
national centre for pharmacoeconomics	
ncpe	
ministry of health adj5 labour and welfare adj20 Japan	
direction de la sant$.	
national insurance health boards	
college voor zorgverzekeringen	
cvz adj20 netherlands	
norwegian medicines agency (statens legemiddelvern)	

Table 2.4 Continued..../

national institute for pharmacies and medicines	
instituto nacional da farmacia e do medicamento	
agencia d'Avaluacio de tecnologia i recerca mediques de catalunya	
federal office of public health adj20 switzerland	
national institute adj6 clinical excellence	
scottish medicines consortium	
Nice	
smc	

A preliminary search strategy was run and the first 100 studies from 2010 and 100 for 2009 were taken to identify new search terms from the studies selected. The final search strategies for Medline, Embase, Econlit, HMIC, NHSEED and REPEC are reported in the Box A2.3.

2.2.12 Grey literature searches

Table 2.5 documents the websites searched and Table 2.6 displays the results (21July 2010).

Table 2.5: Websites searched (21July2010)

International Health Economics Association IHEA	http://eche2010.abstractbook.org/presentations/
National Institute for Health and Clinical Excellence (NICE)	http://www.nice.org.uk/
REPEC	http://ideas.repec.org/
Google Scholar search	http://scholar.google.co.uk/
ISPOR	http://www.ispor.org/
HTAI	http://www.htai.org
EUnetHTA	http://www.eunethta.net/

Table 2.6: Website search results

Internet Search	Website
IHEA	1
REPEC	0
Scholar	2
Total	3

2.2.13 Citation searches

A citation search was conducted for one of the seminal quantitative regression studies of NICE decision-making that has been highly cited (Devlin and Parkin, 2004). The search identified the following two additional studies:

(Raftery, 2006) and (Williams and Bryan, 2007).

2.3 Literature review results

Table 2.7 identified the databases searched and the number of hits and Table 2.8 provides details of the number of studies finally included.

Table 2.7: Database searches conducted (July 2010)

Database Search	Number of Hits
Medline Search hits (06/07/2010)	3,423
Medline within database duplicates	83
Medline hits	3,340
Embase Search hits (06/07/2010)	3,837
Embase within database duplicates	27
Embase hits	3810
EconLit Search hits (06/07/2010)	401
Econlit within database duplicates	6
Econlit hits	395
HMIC Search hits (06/07/2010)	749
HMIC within database duplicates	25
HMIC hits	724
NHSEED REPEC Search hits (06/07/2010)	101
NHSEED within database duplicates	1
NHSEED hits	100
Total combined database hits	8369

Table 2.8: Studies included and reference list searches

	Hits
Database search hits	8369
Internet search	3
Citation list search	2
Total hits	8374
Duplicates across database	2468
Exclude title/abstract	5850
Full Text	56
Full text retrieved	56
Not Retrieved (Not English language)	4
Full Text excluded	21
Full Text included	31
Total included	**31**

Figure 2.1: Study selection flow diagram

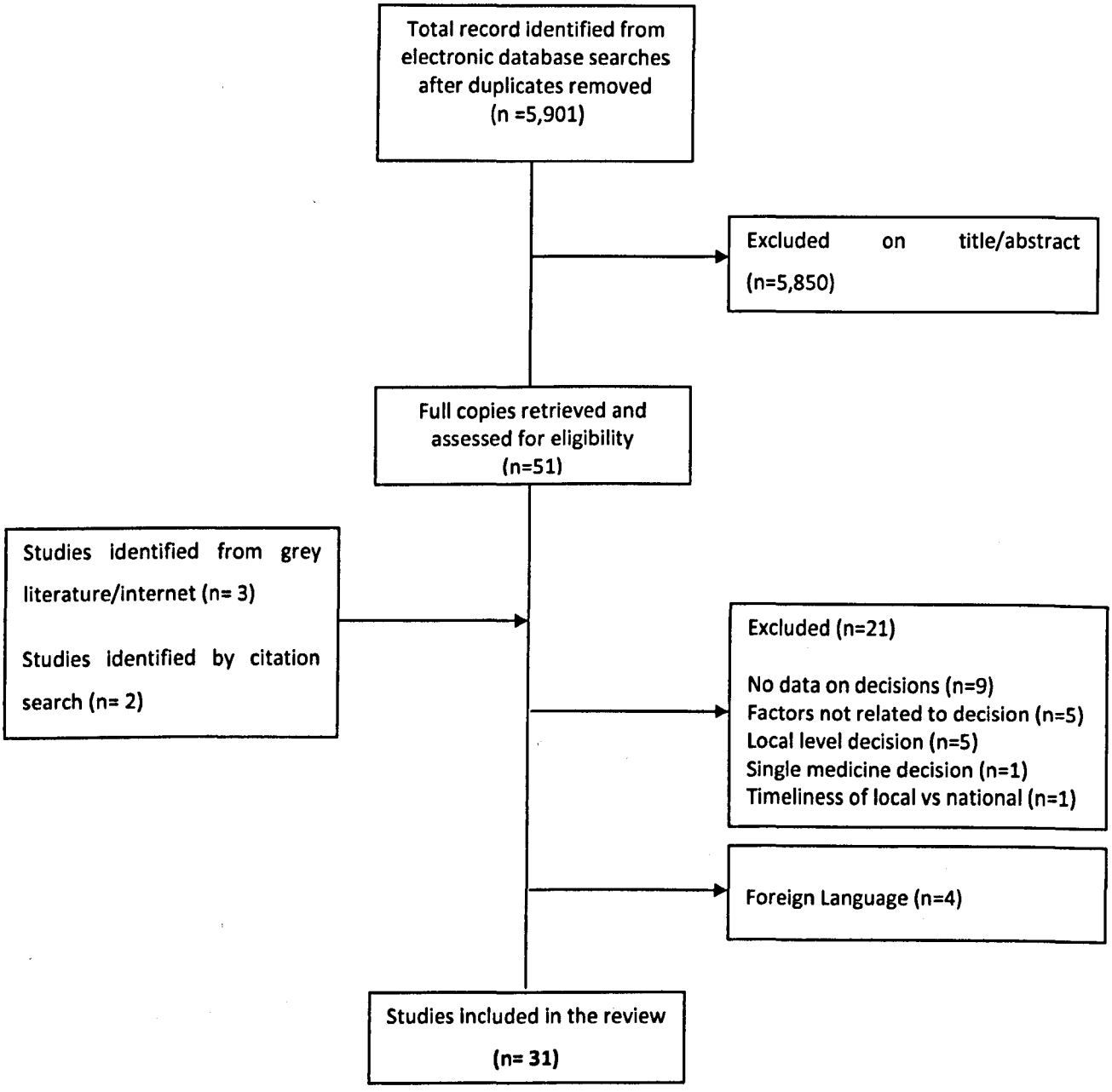


Figure 2.1 illustrates the flow chart of the study selection process. The database search identified a total of 8,369 hits and resulted in 5,901 individual studies after 2,468 duplicates were removed from across the databases. The title and abstract were initially screened against the study

inclusion criteria and 5,850 studies were excluded. This stage identified 51 studies that were potentially relevant. In addition 3 studies were obtained through grey literature searching and 2 studies through citation searching. After review of the full text 25 studies were excluded and a detailed description of the exclusion reasons can be found in Table A2.2 and Box A2.2. There were 31 studies included in the final review. The data extracted from the quantitative and qualitative studies can be found in Tables A2.3 and A2.4.

Table 2.9: Studies included by type and country

Category	Quantitative	Qualitative	Total
Cross-country comparisons	1	5*	5*
Reimbursement factors in Australia	4	1	5
Reimbursement factors in Belgium	1	0	1
Reimbursement factors in Canada	0	1	1
Reimbursement factors in England	5	7	12
Reimbursement factors in Finland	0	1	1
Reimbursement factors in the Netherlands	1	2	3
Reimbursement factors in Sweden	0	2	2
Reimbursement factors in USA	1	0	1
Total number of studies included	**13***	**19***	**31**

*One study uses both a Quantitative and Qualitative approach and appears in both the quantitative and qualitative columns (Total sums to 32 examples of quantitative and qualitative methods because of one mixed method study).

Table 2.9 show the studies by country and type of methodology. The search identified a total of 13 quantitative studies and 19 qualitative studies that included 5 cross country comparisons studies and 26 country specific studies. The empirical studies included analysis for elements of ten OECD countries reimbursement systems. A number of studies that used both qualitative and quantitative methodology were excluded for Canada because they either related directly to decision-making at the provincial level or they were concerned with the linkage of the national decision-making body (CADTH CDR) with the provincial reimbursement decision-making:

- Australia (Pharmaceutical Benefits Advisory Committee);
- Belgium (Committee for Reimbursement of Medicines);
- Canada (CADTH CDR);
- England and Wales (National Institute for Health and Clinical Excellence);
- Finland (Ministry of Health and Social Affairs);
- Netherlands (Dutch Health Boards, CVZ);
- New Zealand (Pharmaceutical Management Agency, PHARMAC);
- Sweden (Dental and Pharmaceutical Board, TLV);
- Scotland (Scottish Medicines Consortium, SMC);
- USA (Medicare).

Comparisons of reimbursement systems were provided for Australia, Canada, England, New Zealand and Scotland. Table 2.10 shows the country comparisons conducted across countries. Two studies compared the NICE in England with the SMC in Scotland, one study compared PBAC in Australia with CADTH CDR in Canada and NICE in England, one compared PBAC in Australia with CADTH CDR in Canada and SMC in Scotland and another compared PBAC in Australia with NICE in England and PHARMAC in New Zealand.

Table 2.10: Cross country comparisons of reimbursement decisions and factors

	Australia (PBAC)	Canada (CADTH CDR)	England (NICE)	New Zealand (PHARMAC)	Scotland (SMC)
(Barbieri et al., 2009)					
(Cairns, 2006)					
(Clement et al., 2009)					
(Lexchin & Mintzes 2008)					
(Raftery, 2008)					

The quantitative and qualitative studies were analysed with respect to the factors considered influential within countries. The evidence is classified into quantitative evidence, for which quantities and relationships between attributes have been estimated following a set of statistical methods, and qualitative evidence, for which data has been collected in a narrative and non-numeric form.

The quantitative studies identified are described in the following sections:

- Overview of quantitative methodology studies;
- Characteristics and definition of influence by countries considered;
- Influence of factors on decision outcomes in studies identified.

2.3.1 Overview of quantitative methodology studies identified

The search identified thirteen studies that used a quantitative methodology to consider the association between factors and decisions in reimbursement systems in six countries (institutions, agency or entity):

- Australia (PBAC);
- Belgium (CRM);
- Canada (CADTH CDR);
- England (NICE);
- Netherlands (CVZ);

- US (Medicare).

A summary of the quantitative studies is provided with respect to the country (institutions), number of observations, methodology, decision outcomes, study observation period and factors considered to influence decisions in Table A2.5. The quantitative studies identified can be grouped into two frameworks of study, those that are revealed preference studies and those that are stated preference studies. The revealed preference studies are those in which previous decisions made by the reimbursement system reveal the factors influencing decisions. The stated preference studies are where committee members are asked to state the impact of factors on the decision outcome in the respective system. Eleven of the studies used a revealed preference framework and two of the studies used a stated preference framework.

2.3.1.1 Revealed preference framework

The revealed preference framework was used in thirteen studies considering one reimbursement system and one of these studies compared three reimbursement systems. These studies focused on a retrospective analysis using past decisions made by the national agency responsible and the factors that can be identified to explain these decisions. The sample of decisions considered in the analyses varied from 33 to 824, and the studies covered different periods between 1991 and 2009.

The studies used a range of statistical methods from simple Chi squared tests, logistic regression, probit regression and multiple logistic regression models (MNLM) to consider the association of factors on the decision outcome. The studies used univariate analysis in six of the studies and multivariate analyses were used in five of the studies. Multiple factors were included in seven of the studies. Multinomial decision outcomes – at least one more category than recommend and not recommend - were used in two studies.

The factors have been grouped into the general categories of factors considered. Evidence factors were considered across all eleven of the studies with respect to the clinical evidence and economic evidence. Non evidential factors were considered in six of the studies (Characteristics of the disease, burden, medicine type such as cancer medicine, other alternative). Process factors were considered in six of the studies (resubmission, application type, history of drug submission, stakeholder involvement and STA process).

2.3.1.2 Stated preference framework

There were two studies using a stated preference framework, one with a sample of NICE committee members in England and one with a sample of health policy makers in the Netherlands (including members of CVZ). The studies used a discrete choice experiment methodology to overcome some of the disadvantages of revealed preference studies such as the reliance on the reporting documented for each decision and the difficulty in accounting for wider factors because of the lack of reporting of some qualitative aspects of decision-making. These studies have more of an emphasis on the influence of non-evidence factors on the decisions such as disease severity, age of patient and availability of other treatments. These are factors that may be either applied to the evidence or considered separately from the evidence in the appraisal and resulting reimbursement decision.

2.3.2 Reimbursement factors investigated in quantitative country comparisons

Table 2.11: Cross country comparison (Clement et al., 2009)

	(Clement et al., 2009)
Institutions (Year)	Australia (PBAC:2005-2008), Canada (CADTH CDR:2004-2008) England (NICE:2001-2008)
Decision outcome (Number)	Binary: List/Do not list (PBAC: 153, CDR: 121, NICE: 199)
Influence (Methods)	Individual Factor Correlate Association with listing (Univariate analysis)
Sample of medicines	All medicines appraised by each agency
Clinical evidence definition	
Clinical uncertainty	None, some, considerable
Weight of clinical evidence	RCT with appropriate comparator
Study endpoints	Clinical endpoint, clinical scale, surrogate
Economic evidence definition	
Cost-effectiveness estimate	Incremental cost per QALY
Type of economic analysis	Cost utility, cost-effectiveness, cost-minimisation, cost consequence
Economic uncertainty	None, some, considerable
Non-evidence factors definition	
Life threatening	Mean 5 year survival<50%
Process factors definition	
Resubmission	Binary: Previously; Not previously considered

Table 2.11 describes the characteristics of the study and the definitions of each factor included in (Clement et al., 2009). There was one study that used a mixed methodology of qualitative and quantitative methods for reimbursement decisions in Australia (PBAC), Canada (CADTH CDR) and England (NICE), (Clement et al., 2009). The study aimed to describe the influence of effectiveness and cost-effectiveness evidence and other factors on decisions between 2001 and 2008. However, the study does not explicitly describe the meaning of the term influence. The authors stated:

> Using a retrospective analysis of past decisions, we describe how these committees use evidence on effectiveness and cost-effectiveness (including any barriers to such use), and what additional factors have influenced decisions, and explore how these issues maybe associated with listing decisions. (p.1438)

The study used Chi squared tests to identify how key factors were associated with the likelihood of listing (The authors report that Chi square tests are used to consider differences across factors and countries but the tests were not reported for the association with the listing. Contact with the authors confirmed that Chi square tests were used but not reported in the study). The agencies were selected because they consider both effectiveness and cost-effectiveness, provide documents in English and are reported to be similar in their underlying populations and public insurance coverage. The study analysed the composition of all medicine decisions produced by the agencies within and across countries with respect to a binary decision outcome (list/do not list) and each factor in a univariate analysis: the clinical evidence (clinical uncertainty, weight of clinical evidence, study endpoints), economic evidence (cost-effectiveness estimates, type of economic analysis, economic uncertainty), one non-evidence factor (life threatening disease) and one process factor (resubmission).

2.3.3 Reimbursement factors investigated in quantitative single country studies

2.3.3.1 Studies investigating reimbursement factors in Australia:

There were four quantitative studies that considered the influence of factors for the national reimbursement recommendations for PBAC in Australia (Table A2.6). They shared similarities in the decision outcomes and definition of influence by correlation between the factor and the decision outcomes. Two studies adopted a regression approach whereas the other two studies considered the impact of one factor upon the decision outcome. The studies shared differences in the sample of the medicines appraised and factors included and definitions of these factors when the same factor was used across the studies.

Two studies considered the influence of single factors on decision outcomes for those medicines that were submitted to PBAC with a cost-utility analysis (George et al., 2001, Scuffham et al., 2008). The aim of one study was to generate a league table of 355 medicines considered by PBAC between 1991 and 1996, (George et al., 2001). This study compared 26 estimates of cost per life year gained and 9 estimates of cost per QALY separately for those that were recommended for listing and those that were not by using a Mann-Whitney test to consider whether any difference was statistically significant. A ranking of the estimates of cost effectiveness was provided to elicit

a threshold value for PBAC. The second study compared the listing rates observed for different types of methods for obtaining QALY weights for 49 submissions provided to PBAC between 2002 and 2004. There were three categories of QALY weights namely, multi-attribute utility instruments, health state valuation and non-preference based (Scuffham et al., 2008).

One study considered whether cancer medicines were less likely to be recommended by PBAC by controlling for the influence of other factors for 243 binary decisions made between 2005 and 2008, (Chim et al., 2010). Chim *et al.* conducted both a univariate and multivariate analysis of the factors influencing PBAC decisions. The study analysed the univariate association between clinical evidence, economic evidence, non evidence and process factors and performs a multivariate logistic regression analysis using the statistically significant associations found in the univariate analysis. The multivariate analysis includes the medicine type (cancer/non-cancer), application type, estimated cost to the PBS and cost-effectiveness estimate. The study used a unique set of variables to characterise the clinical evidence, including whether the PBAC accepted the manufacturers claim for the effectiveness of the comparator and the clinical claim. The authors included a variable for whether the PBAC accepted the claims in the economic analysis and similar to some of the other studies considering PBAC included the type of economic analysis, cost-effectiveness estimate and budget impact estimate. The study also uniquely included two non-evidence factors that were the number of patients per year the medicine treats and whether the medicine was used to treat cancer or another disease.

One study considers the role of value for money amongst other factors through a retrospective analysis of 103 PBAC binary decisions produced between 1994 and 2004, (Harris et al., 2008). The correlative influence and relative weight of factors is considered using a probit regression model that produces a "marginal effect". The marginal effect estimates the change in the probability of listing for a unit change in each of the variables, holding the other variables constant at their mean. The study includes variables for clinical evidence, economic evidence, non-evidence factors and process factors. The study uniquely defines aspects of the clinical evidence by focusing on the quality of the clinical evidence through a categorical variable for clinical significance, precision of clinical evidence, type of clinical evidence, quality of studies and the relevance of the evidence. Similar to other studies for PBAC, a variable was included to consider the influence of the medicines cost-effectiveness estimate and a continuous variable for the budget impact. A single process factor is included that controls for whether the submission was a resubmission.

2.3.3.2 Reimbursement factors investigated in Belgium

Table 2.12: Characteristics of quantitative study(s) in Belgium

	(Van Wilder and Dupont, 2008)
Institutions (Year)	Committee for Reimbursement of Medicines (2002 – 2004)
Decision outcome (Number)	Binary: Positive/Negative (n=824)
Influence (Methods)	Individual Factor Correlate Association with listing (Univariate analysis)
Sample of medicines	All medicines appraised in the period
Clinical evidence definition	
Extent of the clinical evidence	Categorisation of those medicines in the "limited evidence" group (class 1, class 2 new medical entities and new indications in comparison to line extensions.
Indication of added therapeutic value	The approval of added therapeutic value in class 1 submissions only by a positive active control superiority trial.

Table 2.12 describes the characteristics of the study and the definitions of each factor included in (Van Wilder and Dupont, 2008). The study considered decisions made by the Belgium reimbursement decision-making body called the National Insurance Agency and aimed to assess whether evidence of therapeutic value were associated with reimbursement decision-making in Belgium (Van Wilder and Dupont, 2008). The study considered the difference in recommendations for those medicines categorised as new indications and those categorised as line extensions using a Pearson Chi squared test in 824 reimbursement decisions between 2002 and 2004. The influence of the clinical evidence was defined in terms of the impact of the evidence on the reimbursement decision by the correlation between the decision and the extent of the available evidence on the effectiveness for all medicines. The influence was also investigated by the Pearson chi-square for correlation between the decision and the medicine having added therapeutic value in those medicines categorised as Class 1.

2.3.3.3 Reimbursement factors investigated in England

There were four quantitative empirical studies that considered retrospective NICE decisions in England covering different periods of time, with different samples of recommendations using different factors (Table A2.7). There was greater consistency in the factor definitions for some aspects of the clinical evidence (number of RCTs), economic evidence (cost-effectiveness estimates), and process factors (date of decision and stakeholder involvement) in some of the retrospective studies of reimbursement decisions. Three of the studies used discrete choice regression modelling and the other used a Fisher exact statistical significance test for two categorical groups. The samples of decisions included all technologies following the technology appraisal process by NICE rather than specifically pharmaceuticals in three of the studies. A fourth

retrospective study considered cancer medicines only and uniquely considered the influence on decisions of a change in the NICE process.

One study used a logistic regression analysis for the first 33 NICE decisions between 1999 and 2002 to understand the influence of cost-effectiveness analysis and other factors (Devlin and Parkin, 2004). The study aimed to explore NICEs cost-effectiveness threshold and the tradeoffs and weight between cost-effectiveness and other factors influencing decisions. The factors relevant to NICE decision-making were identified by a description of the cost-effectiveness threshold in the context of NICE and considered with respect to all technologies (medicines and other technologies). The binary regression model included six explanatory variables; continuous variables for the ICER value, uncertainty surrounding the cost-effectiveness evidence, burden of disease, impact on the NHS budget and categorical variables for other available therapy and other factors. The meaning of the term influence is not defined explicitly within the study but a statement was made with respect to the aim of the study that:

> The aim of this paper is to consider the factors that operate to influence NICE decisions, to explore systematically the influence of each and to establish the characteristics of the cost-effectiveness threshold, if it exists. (p.438)

The author's use of the term alongside the methodology used implies that influence in this study is the correlate association between the factor and decision, controlling for other factors without explicit consideration of the counterfactual.

A multinomial decision outcome (recommend, restrict, not recommend) was used for the first time in one study to provide a more realistic description of 94 NICE decisions for technologies considered between 1999 and 2003 (Dakin et al., 2006). A model of NICE decision-making was developed to identify the determinants of decisions through the identification of two broad sets of factors, the inputs into decision-making and the factors pertaining to the decision process used by NICE. A multinomial regression technique was used to evaluate the impact of evidence factors, quantity and quality of the clinical evidence, cost-effectiveness estimates and budget impact. Non evidence factors were included in relation to existence of alternatives and the technology type. Two process factors were included with respect to the decision date and patient group submissions. The terms "impact" and "influence" are used interchangeably in the study but are not directly defined with respect to the methodology used. The definition of influence is implied by the analysis to be the observation of an association between the factor and decision controlling for the other factors included.

A further study was identified as a conference abstract that considers the influence of cost-effectiveness and other factors on a large sample of NICE decisions between the period 1999 and 2009 (Devlin et al., 2010). The study considers 184 NICE technology appraisals and innovatively approaches the analysis by breaking down into a number of binary decisions for each indication or defined patient group resulting in more than 600 binary decisions. The study reports use of regression analysis to identify the threshold and influence of other factors in NICE decisions. Influence or impact on decisions is not defined within the conference abstract. The study includes explanatory variables for the clinical evidence and cost-effectiveness evidence and includes non-evidence factors such as characteristics of the patients, disease or treatment and contextual factors affecting the conduct of the technology appraisal such as patient group involvement. The factors affecting the conduct of the technology appraisal are referred to as process factors in other studies. The results are not reported in the abstract because this is reported as work in progress.

A fourth study uniquely considers the impact of a change in process on the 56 decisions made between 2000 and 2006 for cancer medicines by NICE (Mason and Drummond, 2009). A structural break analysis is presented for the period before NICE introduced the STA process (2000-2006) to the period between which the STA process was introduced and in operation (2006-2008). The STA process was introduced to speed up the time that technology appraisals were completed in to six months and removed the requirement for an independent analysis by an academic assessment group. The analysis compares the multinomial recommendations (recommended, restricted, not recommended) for the first period with the second period by using the generalised Fisher exact test to determine whether the differences were statistically significant. This explores the extent of the change in the process in explaining differences in the decisions over the time period.

Table 2.13: England and Wales stated preference study

	(Tappenden et al., 2007)
Institutions (Year)	NICE (2005)
Decision outcome (Number of decisions/responders)	Recommended/Not Recommended (37 NICE committee member participants)
Influence (Methods)	Influence preference of committee members to recommend a technology (Stated preference binary choice experiment)
Sample of medicines/responders	Medical technologies
Economic evidence definition	
Incremental cost-effectiveness	Central estimate of cost-effectiveness for the intervention in comparison with the current standard treatment (categorical: £15,000 per QALY gained, 25,000 per QALY gained, £35,000 per QALY gained)
Uncertainty	The degree of uncertainty surrounding the incremental costs and effects (Categorical: Low degree of uncertainty and high degree of uncertainty)
Non-evidence factors definition	
Age	The mean age of the population who will benefit from the intervention (Categorical: Children (less than 18 years, working 18 to 64 years, Retired more than 64 years)
Baseline HR-QOL	An index utility score of patients prior to receiving the intervention 1 representing perfect health and zero representing dead. (Categorical, 0.25, 0.50, 0.75)
Availability of other therapies	An alternative effective therapies are available to manage the condition (Categorical, Yes or No)

A fifth study performed a discrete choice experiment of stated decision-maker preferences with a binary outcome for the decision rather than considering retrospective decisions (Tappenden et al., 2007). The study used a logistic regression to understand 37 committee members preferences for a number of factors including the incremental cost-effectiveness estimate, the degree of uncertainty surrounding the cost-effectiveness and health outcomes, the age of the beneficiaries, baseline health related quality of life and the availability of alternative therapies when considering the decisions for technologies considered by NICE (Table 2.13).

2.3.3.4 Reimbursement factors investigated in Netherlands

Table 2.14: Characteristics of study(s) conducted for the Netherlands

	(Koopmanschap et al., 2010)
Institutions (Year)	Dutch Reimbursement decision-making (2007-2008)
Decision outcome (Number of decisions/responders)	Recommended/Not Recommended (37 Dutch healthcare professionals including the Dutch Health Board)
Influence (Methods)	What criteria are important for participants in health care priority setting and what are the tradeoffs made with these criteria? (Stated preference binary choice experiment)
Sample of medicines/responders	Medical Interventions
Economic evidence definition	
Incremental cost-effectiveness	Categorical: €15,000 per QALY gained, €45,000 per QALY gained, €90,000 per QALY gained
ICER uncertainty	The probability the cost per QALY will be at least double compared to the average cost-effectiveness ratio (Categorical: 10%, 20%, 30%)
Budget impact	National additional medical cost per year (Categorical: €10m, €20m, €50m)
Productivity saving	National saving in cost of absence from employment per year (Categorical: €0m, €2m, €4m)
Non-evidence factors definition	
Disease severity	Disease severity before treatment (Categorical: Low, moderate, high)
QALYs gained	The number of QALYs gained per patient. (Categorical: 0.5, 2, 4 QALYS)
Composition of health gain	The composition of health gain (Categorical: 100% longer life, 100% improved quality of life, 50% of each)

The search identified one study (Table 2.14) that conducted a discrete choice experiment between 2007 and 2008 that specifically considered the factors in decision-making by 62 Dutch health care professionals (including members from the Dutch Health Board, CVZ). The study included a number of factors relating to the decision outcome of a choice preference between two treatments including clinical considerations such as the QALY gains and composition of health gain, economic considerations such as ICER value, uncertainty around ICER and budget impact, productivity savings and disease severity (Koopmanschap et al., 2010).

2.3.3.5 Reimbursement factors investigated in the USA for the Centre for Medicare and Medicaid Services (CMS):

There was one study that identified the influence of clinical evidence and the quality of the evidence for Medicare coverage decisions in 69 technologies (5 of which were for medicines) for between 1999 and 2003, (Neumann et al., 2005). The study focuses on the level of evidence as described as good if it included consistent results from well designed, well conducted studies in representative populations, fair if evidence was sufficient to determine the effect of health outcomes but strength was limited by the number, quality or consistency of individual studies and poor studies were identified if the evidence was insufficient to assess the effects on health outcomes because of the limited number of power studies, flaws in design or lack of information

on important health outcomes. A statistical test comparison between poor and good quality evidence was conducted in this study (Table 2.15).

Table 2.15: Characteristics of study conducted for the USA

	(Neumann et al., 2005)
Institutions (Year)	Medicare (1999-2003)
Decision outcome (Number of decisions/responders)	Completely covered, covered with conditions, local contractor discretion, not covered (69 Medicare national coverage decisions)
Influence (Methods)	To determine how evidence and other factors influence coverage decisions and review times at the Centres for Medicare and Medicaid Services (Descriptive statistics)
Sample of medicines/responders	Medical Technologies
Clinical evidence definition	
Quality of Clinical evidence	Categorical: Good, Fair, poor
Net benefit	Authors analysis of the net benefit based on review of data collected for Medicare Coverage Database Categorical: Substantial, moderate, small, zero/negative, insufficient
Process evidence factors	
Time to Medicare decision	Categorical: 0-3 months, 3-6 months, 6-9 months, 9-12 months and more than 12 months

2.3.4 Influence of factors within and across countries

The comparison of influence of a factor across studies for a country's reimbursement system and across studies conducted in different countries can only be examined in relation to the direction of the association with the decision and whether this was found to be statistically significant. This is because even where the same factor is constructed, methodological differences in the statistical analysis performed and decision outcomes used do not allow a comparison of the relative magnitude of each factor across countries systems. The association and statistical significance of factors considered in each country can be found in Table A2.8. Tables 2.16, 2.17 and 2.18 detail a summary of the direction of effect of each study for each of the factors based on the statistical significance in the quantitative studies. The influence of each factor is considered in the influence of a factor on a recommended decision or decision to list a medicine. The factors are considered within the follow groups:

- Evidence Factors (clinical and economic evidence);
- Non-evidence factors (age of patient, disease);
- Process Factors (resubmission, time period of decision).

The following section details those factors where a statistical association was found with the factor and decision in all studies and countries for which the factor was considered. The second group of factors concerns where there is mixed evidence of the association of the factors and reimbursement decisions within studies for a single reimbursement system and across countries reimbursement systems.

2.3.4.1 Consistency of the influence of factor across quantitative studies and countries

- **Clinical evidence considerations – Size of Clinical Effect**

There were two studies for national reimbursement decision's in Australia (PBAC), (Harris et al., 2008) and Belgium (CRM) where the size of the clinical effect was statistically significantly associated with the decision (Van Wilder and Dupont, 2008). The study conducted in Australia considered the clinical effect in a multivariate analysis whereas the Belgium study specifically considered the univariate difference in the proportion of positive and negative decisions. A further study considering PBAC in Australia provided a univariate analysis of the influence of the manufacturers' clinical claim on the decision and found this to be statistically associated with recommending the medicine (Chim et al., 2010).

- **Economic evidence considerations – Incremental Cost-effectiveness Ratio (ICER)**

In all eight studies that considered the impact of the ICER value on the reimbursement decision in Australia (PBAC), England (NICE), Canada (CDR) and the Netherlands (CVZ), a higher ICER value was found to be statistically significantly negatively associated with the decision to list (Chim et al., 2010, Clement et al., 2009, Dakin et al., 2006, Devlin and Parkin, 2004, George et al., 2001, Harris et al., 2008, Koopmanschap et al., 2010, Tappenden et al., 2007). These studies used different decision outcomes and a variety of methods, univariate statistical tests, multivariate probit regression models, multivariate logistic regression models, multinomial logistic regression models and discrete choice experiments using multinomial regression models. Two of the studies consider a cost per QALY threshold for decision-making. One study reports a threshold range for decisions of between £34,000 per QALY and £47,000 for NICE for past NICE decisions in 1999 and 2002, (Devlin and Parkin, 2004). A study conducted in the Netherlands reports a threshold of EURO93,000 per QALY for high severity and EURO10-15,000 threshold for low severity disease for stated preferences of decision-makers between 2007 to 2008, (Koopmanschap et al., 2010).

2.3.4.2 Mixed evidence of association with reimbursement decisions across studies and countries

- **Clinical evidence considerations – Quality and quantity of clinical evidence**

There were six studies that analyse attributes relating to the quality and quantity of clinical evidence and there were multiple measures used within each study. The studies used composite scores to assess the overall quality of studies and the association with reimbursement decisions and specific characteristics of the quality and quantity of clinical evidence. There are difficulties in making comparisons within and across studies in this review of the association of the impact of quality and quantity of clinical evidence because these measures have different constructs and each construct has been considered exclusively in each study for the countries of interest.

Four of the studies consider composite measures of the quality of evidence, one using a measure of clinical uncertainty that includes the type of trial, comparator and endpoint for studies assessed by NICE, PBAC and CDR (Clement et al., 2009), one using the mean Jadad score for trials assessed by NICE, (Dakin et al., 2006), one using a 12 item checklist for the quality of studies for PBAC decision-making, (Harris et al., 2008) and the consideration of well designed and conducted RCTs for Medicare decision-making in US (Neumann et al., 2005). The two studies that considered NICE decision-making used two different measures found no association. The US study of Medicare found that technologies (including pharmaceuticals) with good evidence were statistically significantly more likely to be listed than those with fair or poor evidence, although this study only included 5 medicines in the sample for Medicare decisions. The study considering

clinical uncertainty found that the presence of high levels led to a lower probability of listing in Australia and Canada. In a study that specifically considered PBAC decision-making in Australia, the use of 12 item quality checklist was not found to be associated with the decision outcome.

Three of the studies considered eight specific characteristics of the quantity and quality of evidence and number of RCTs and number of systematic reviews were found to be statistically significant in NICE decision-making, (Dakin et al., 2006), whereas a relevant clinical endpoint was found to be associated with a higher probability of listing in PBAC decisions in Australia and CDR decisions in Canada (Clement et al., 2009). There was no association found for RCT significance and RCT size for NICE decision-making, appropriate comparator and population and type of evidence (randomised, observational) for NICE and PBAC decisions and precision of treatment effect in PBAC decisions.

- **Economic evidence considerations – General requirements for economic analysis**

There were seven studies that considered the influence of different requirements for economic analysis for PBAC decision-making in Australia, CDR decision-making in Canada, NICE decision-making in England and reimbursement decision-making in the Netherlands. The measures broadly relate to composite measures of the quality or robustness of the economic evaluation, uncertainty surrounding the ICER estimates and other specific characteristics of the economic evaluations.

Two studies considered a composite measure of the robustness of the economic analysis. One labels this as 'economic uncertainty' on three levels of considerable, some and no uncertainty and finds that considerable economic uncertainty is associated with a lower probability of listing for PBAC decision-making and CDR decision-making but finds no association for NICE decision-making (Clement et al., 2009).

Four studies considered measures of uncertainty around the ICER and consistently found an association with the decision outcome. Two studies using discrete choice regression models found that higher levels of uncertainty (The NICE study considered the ratio of the range of cost-effectiveness divided by the average cost-effectiveness and the PBAC study considered the upper limit of the sensitivity analysis) were statistically significantly less likely to be listed for NICE and PBAC decision-making (Devlin and Parkin, 2004, Harris et al., 2008). The two discrete choice experiments performed in England (degree of uncertainty concerning costs and effects), (Tappenden et al., 2007) and in the Netherlands (probability that the cost per QALY will be at least doubled as compared to the average cost-effectiveness), (Koopmanschap et al., 2010) found that

higher levels of each attribute were statistically associated with a lower probability of choice of the intervention.

Three studies considered other characteristics relating to the economic evaluations. A study of NICE decision-making found that the type of economic evaluation (cost-utility analysis) was statistically significantly more likely to be not recommended in comparison to recommended (Dakin et al., 2006). A study for PBAC in Australia also found a similar relationship between cost-minimisation and no economic evaluation statistically associated with a recommendation in comparison to cost-effectiveness analysis and cost-utility analysis in a univariate analysis (Chim et al., 2010). This was an unexpected finding and possible explanations were suggested with regards to decision-makers using the same threshold for cost-effectiveness and cost-utility analysis, it may imply a 'rule of rescue' where decision-makers place more value on increased quantity of life rather than quality, the use of quality weights may increase the uncertainty around the CQG. A study of PBAC decision-making considered appropriate model structure, robust translation of clinical outcomes with quality of life, modelled cost outcomes and did not find any of these factors to be statistically associated with decisions (Harris et al., 2008). The researchers of one study judged whether the PBAC judged the economic claim to be acceptable and found that this was statistically associated with the decision in a univariate analysis but found this to be statistically insignificant in a multivariate analysis (Chim et al., 2010). A further study found evidence of a statistically significant lower probability of listing for those submissions that used non-preference based utility weights (Scuffham et al., 2008).

- **Economic evidence considerations – Budget Impact**

Budget impact was included as a factor in the decision-making in studies for PBAC in Australia, NICE in England, and reimbursement decision-making in the Netherlands. There was a negative association between increases in the size of the budget impact and a listing decision in two studies considering decision-making in Australia and one study in the Netherlands (Chim et al., 2010, Harris et al., 2008, Koopmanschap et al., 2010). One study performed for NICE England found no statistically significant association between budget impact and the listing decision (Dakin et al., 2006), which would be the result expected given that budget impact is not directly taken into account by the NICE committee.

2.3.4.3 Mixed evidence of non-evidence factors across studies and countries

- **Lack of alternative therapy**

There were four studies that considered this factor, one for PBAC decision-making in Australia and three for NICE decision-making in England. There was no association found between lack of alternative therapies in PBAC decision-making (Harris et al., 2008). There was mixed evidence of an association for NICE decision-making, two studies using different methods, found a positive association with the decision to list, one of which considered past NICE decisions (Devlin and Parkin, 2004) and one a stated preference of NICE decision-makers (Tappenden et al., 2007). A third study found no association between lack of alternative therapies for NICE decision-making and this may be because this study focused on a larger number of explanatory factors than the other two studies for NICE decision-making (Dakin et al., 2006).

- **Severity of disease and life threatening conditions**

There were two studies that considered the association between whether the disease was classified as life threatening and the decision outcomes for PBAC decisions in Australia, NICE decisions in England, CDR decisions in Canada and one study that considered severity of disease in the Netherlands. One of the studies found no association between disease severity and listing decision for PBAC in Australia, NICE in England and CDR decisions in Canada for decisions between 2001 and 2008, (Clement et al., 2009). In contrast, a probit regression model of past PBAC decision-making in Australia that featured a subset of the decisions in the first study for the period 1994 to 2004 found there to be a positive association between disease severity and listing (Harris et al., 2008). The stated preference study conducted in the Netherlands found severity to be positively linked to choice of intervention (Koopmanschap et al., 2010).

- **Other non-evidence factors**

One study conducted with decision-makers in the Netherlands considered other factors such as the number of QALYs gained per patient, the composition of the health gain and the cost of absence per year (Koopmanschap et al., 2010). The study found a statistically significant positive association between the number of QALYs gained and the choice of the intervention. There was a preference for those interventions that had quality of life improvements over extension of life with improved quality. The study found no association between productivity savings and the preference to list an intervention.

A second study aimed to consider the hypothesis that cancer medicines were less likely to be recommended other things remaining equal (*ceteris paribus*) (Chim et al., 2010). The study found that after adjusting for other factors there was no difference between the recommendation rates for cancer medicines and non-cancer medicines in the multivariate analysis.

2.3.4.4 Mixed evidence of the influence of process factors across studies

- **Patient group impact**

There was one study that considered whether the presence of a patient group submission was associated with NICE decision-making in England (Dakin et al., 2006). This was identified as whether a patient organisation was listed at the end of the guidance document and categorised for each decision as a categorical submission/no submission variable. The presence of a patient group had a large statistical effect on the odds of being the medicine being recommended in comparison to restricted. The study notes that this result may have been due to only three appraisals reporting an ICER value but lacking a patient group submission and were not recommended for use. The very small sample of decisions not reporting a patient group submission may undermine the reliability of this finding.

- **Resubmission**

One study found that a medicine that had been previously considered for the same indication by PBAC in Australia was statistically significantly more likely to be listed than one that had not been previously considered (Harris et al., 2008). In contrast a second study on PBAC found there to be no association between resubmission and the listing outcome in both the univariate and multivariate analysis (Chim et al., 2010). The results of the association between resubmission and the listing decisions were not reported in any of the other quantitative studies for other countries, although considered in one study for Australia, Canada and England (Clement et al., 2009).

- **Reimbursement time period**

There were two studies considering the effect of time on NICE decision-making in England and Wales over two different time periods. The first study considers NICE decision-making between 1999 and 2005 and finds that the later appraisals were more likely to be not recommended (Dakin et al., 2006). A second study found that the introduction of the Single Technology Appraisal process in 2006 partly explained the increase in negative decisions after 2006 but the differences were not found to be statistically significant. Mason and Drummond concluded that the higher rejection rates may be explained by an absence of evidence on cost-effectiveness where the manufacturer decides to terminate the NICE STA (Mason and Drummond, 2009).

Table 2.16: Clinical evidence factors by influence on recommendation

	Clinical Evidence Factors (Statistical association with recommended/listing decision)	Treatment effect and precision				Quantity of clinical evidence					Quality of evidence			Clinical uncertainty and judgements					
		1. Size of clinical effect	2. Number of QALYs gained	3. Improvement in QoI	4. Precision of clinical effect	5. No. of RCTs	6. No. of observational studies	7. RCT significance	8. RCT size	9. No. of systematic reviews	10. RCT quality (Jadad)	11. Quality of studies 12 point	12. Higher quality evidence	13. Comparator claim accepted	14. Clinical claim accepted	15. Weight of clinical evidence	16. Relevant clinical endpoint	17. Comparator appropriate	18. Clinical uncertainty (higher)
AU	(Clement et al., 2009)															NR	+		-
	(Chim et al., 2010)													+	+				
	(George et al., 2001)																		
	(Harris et al., 2008)	+			~							~						~	
	(Scuffham et al., 2008)																		
BE	(Van Wilder and Dupont, 2008)	+																	
CA	(Clement et al., 2009)															NR	+		-
ENG	(Clement et al., 2009)															NR	+		~
	(Dakin et al., 2006)					-	~	~	~	+	~							~	
	(Devlin and Parkin, 2004)																		
	(Devlin et al., 2010)																		
	(Mason and Drummond, 2009)																		
	(Tappenden et al., 2007)																		
NL	(Koopmanschap et al., 2010)		+	+															
USA	(Neumann et al., 2005)												+						

(Note: Statistically significant relationship and direction of association reported + = positive association with reimbursement decision, - = negative association with reimbursement decision, ~ = no association, NR=not reported)

Table 2.17: Economic evidence factors and Influence on recommendations

	Economic Evidence Factors (Statistical association with recommended/listing decision)	Economic analysis type and results					Appropriate economic analysis				Economic evidence uncertainty					Other	
		1. Type of economic analysis (CUA)	2. ICER (increases in cost per QALY)	3. ICER (inc. cost per QALY & LYG)	4. ICER (inc. cost per LYG)	5. Economic claim accepted	6. Modelled cost issues	7. Translation of clinical to QoL	8. Model Structure approp.	9. Non preference QoL weights	10. Economic uncertainty	11. High degree of uncertainty	12. Prob. CUA double average.	13. Range of CE divided by basecase	14. Upper Limit in model sensitivity	15. Budget Impact	16. Savings in costs of absence/year
AU	(Clement et al., 2009)	NR	-								-						
	(Chim et al., 2010)	-	-			+										-	
	(George et al., 2001)				-												
	(Harris et al., 2008)		-				~	~	~						+	-	
	(Scuffham et al., 2008)									-							
BE	(Van Wilder and Dupont, 2008)																
CA	(Clement et al., 2009)	NR	-								-						
ENG	(Clement et al., 2009)	NR	-								~						
	(Dakin et al., 2006)	-		-													
	(Devlin and Parkin, 2004)			-										-			
	(Devlin et al., 2010)																
	(Mason and Drummond, 2009)																
	(Tappenden et al., 2007)		-									-					
NL	(Koopmanschap et al., 2010)		-										-			-	~
USA	(Neumann et al., 2005)																

(Note: Statistically significant relationship and direction of association reported + = positive association with reimbursement decision, - = negative association with reimbursement decision, ~ = no association, NR=not reported)

Table 2.18: Non evidence and process factors influence on recommendations

	Other factors (Statistical association with recommended/listing decision)	Non evidence factors									Process factors				
		1. Severity/Life threatening	2. Burden of disease (higher)	3. No alternative therapy	4. Type of intervention	5. Medicine type (cancer/other)	6. Number of patients/year	7. Mean age of pop. benefiting	8. New medicine versus line ext.	9. High baseline HrQoL	1. Patient group submission	2. Resubmission	3. STA process	4. Date of decision	5. Appeal
AU	(Clement et al., 2009)	~										NR			
	(Chim et al., 2010)					~	~					~			
	(George et al., 2001)														
	(Harris et al., 2008)	+		~								+			
	(Scuffham et al., 2008)														
BE	(Van Wilder and Dupont, 2008)								~						
CA	(Clement et al., 2009)	~										NR			
ENG	(Clement et al., 2009)	~										NR			
	(Dakin et al., 2006)			~	-						+r			+	~
	(Devlin and Parkin, 2004)		+	-											
	(Devlin et al., 2010)														
	(Mason and Drummond, 2009)												~		
	(Tappenden et al., 2007)			~				~		~					
NL	(Koopmanschap et al., 2010)	+													
USA	(Neumann et al., 2005)														

(Note: Statistically significant relationship and direction of association reported + = positive association with reimbursement decision, - = negative association with reimbursement decision, ~ = no association, NR=not reported)

2.3.5 Qualitative studies results

2.3.5.1 Cross country comparisons

The search identified five cross country comparisons of national reimbursement decision-making bodies covering the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia, Canadian Agency for Drug and Technologies in Health (CADTH) in Canada, National Institute for Health and Clinical Excellence (NICE) in England, Pharmaceutical Management Agency (PHARMAC) in New Zealand and Scottish Medicines Consortium (SMC) in Scotland (Barbieri et al., 2009, Cairns, 2006, Clement et al., 2009, Lexchin and Mintzes, 2008, Raftery, 2008).

Two studies conduct a narrative retrospective comparison of decisions between SMC and NICE decision-making, the earlier study considers the process similarities and differences and provides a comparison of medicines licensed for the same indications and the respective reimbursement decisions (Cairns, 2006). The second study is an extension of the first that considers the influence third party assessment on decisions (Barbieri et al., 2009). The studies both argue that there are some similarities between the two agencies which allow comparison such as both agencies being part of the NHS in England reflecting the system objectives and few differences between the agencies guidance on economic evaluation. The earlier study concluded that there were broadly similar decisions made with a few noted differences, whereas the extension study considered there to be a trend towards more restrictive NICE decisions in comparison to the SMC. The studies attributed these differences to the extent of the assessment and timing of the decisions. Both studies identify the difficulties with making comparisons such as the limited number of comparative decisions, time differences and potential to collect evidence, process differences and the potential interdependency between the two agencies. The two studies both consider the trends in decision-making and identify the complexities with considering the impact or influence of different processes or criteria but do not consider whether other factors contribute to the decisions made by the two agencies. These studies suggest that independent third party assessment impacts upon the reimbursement decision.

Process factors:

- The use of third party assessment in the process of assessment of medicines results in differences in the restrictions applied by the SMC in Scotland and NICE in England (Barbieri et al., 2009). NICE was more restrictive on some occasions and SMC on other occasions.

- The fundamental differences in the process are reported to be the timing of production of the guidance and extent of the evaluation performed between NICE and the SMC. A study finds general agreement in decisions but differences in any restrictions on use (Cairns, 2006).

There were three studies that made cross country narrative comparisons of reimbursement decisions made between countries which were perceived to have similarities with regards their health care systems and processes and criteria in considering evidence. One study considered 19 common medicines for the same indication for NICE, PBAC and CDR (Clement et al., 2009), another considered 29 common medicines across CDR, PBAC and SMC (Lexchin and Mintzes, 2008), and a further study considered 10 common medicines across PBAC, NICE and PHARMAC in New Zealand (Raftery, 2008). The other two studies included New Zealand and Scotland in their comparison of decisions. The three studies attributed differences in the decisions, three with respect to process and three with respect to the characteristics of the medicines considered:

Process factors:

- Differences in the decision outcomes across countries (Lexchin and Mintzes, 2008);
- Different processes for identifying subgroups by cost-effectiveness in NICE decision-making and price negotiation by PBAC to ensure cost-effectiveness (Clement et al., 2009).

Evidence based factors:

- Pharmacoeconomics used in the evaluation in PBAC (Australia), CDR (Canada) and SMC (Scotland), (Lexchin and Mintzes, 2008).

Non-evidence based factors:

- The composition of the decision panel (Lexchin and Mintzes, 2008);
- Nature of disease treated and severity of disease (Lexchin and Mintzes, 2008, Raftery, 2008);
- Number of drugs in a therapeutic class (Clement et al., 2009);
- Prevalence of disease that the drug is designed to treat (Lexchin and Mintzes, 2008).

2.3.5.2 Qualitative studies for Australia

One study provided a narrative comparison of decisions made by PBAC for twelve cases studies of medicines that met the cost-effectiveness requirements and were listed, decisions not to list based on evaluation of effectiveness, listing of some products despite limited cost-effectiveness, listing on the basis of limited evidence conditional on further monitoring (Hailey, 1997). This study was conducted in a period where economic analysis provided in the submission was voluntary in 1991 and then requested as a compulsory requirement in 1993. The study found that clinical effectiveness and cost-effectiveness are important but other considerations may become important for those with limited evidence of cost-effectiveness such as the nature of the condition (life threatening), the public profile that it generates and budget impact.

- Clinical-effectiveness;
- Cost-effectiveness;
- Budget impact;
- Life threatening disease;
- Patient group lobbying.

2.3.5.3 Qualitative studies for Canada

One study performed a narrative analysis of the first 62 recommendations of the Common Drug Review (CDR) for the period of between 2003 and 2007 and a focus group of decision-makers on the use of economic analysis in decision-making (Rocchi et al., 2008). The most frequently cited factors for the reasons for recommendation found in the documentation with respect to the clinical evidence were:

- Type of outcome (surrogate, intermediate, final);
- Magnitude of the benefit versus comparator;
- Choice of comparator;
- Trial duration;
- Generalisability of the trial population;
- Trial size;
- Comparative safety for the clinical evidence.

The factors described for reason in relation to the economic evidence

- Price;
- Quality of model;

- Clinical benefit used in model;
- ICER.

The following factors were not cited as important across the recommendations:

- Type of disease;
- Prevalence of the disease;
- Equity;
- Rule of rescue;
- Lack of alternatives;
- Budget impact;
- Appropriateness of utilisation;
- Innovative drug.

There were some reimbursement recommendations that were seen to be inconsistent with respect to clinical evidence, economic evidence and this was attributed to lack of transparency or context-sensitive interpretations. The focus group discussion suggested that economic evidence does not dictate or predict the reimbursement decision, but instead can be one of several pieces of information that contribute to a decision. The discussions also repeatedly acknowledged the decision-making tasks as complex and it is sometimes difficult to reconcile competing interests. This may mean that every decision is unique and must be considered in the specific context. The discussion suggested a hierarchy for health gain or diseases of which merit additional funding over others. There were often problems found with the submitted economic evidence, but when this was deemed to be helpful, it was described whether this was considered an attractive level of cost-effectiveness. The inconsistencies in the cost-effectiveness maybe where there are other factors that are considered in the analysis. The study concluded that decision-makers in Canada struggle with assigning a consistent weight to evidence and non-evidentiary factors.

The literature search identified a number of studies that considered reimbursement decision-making at a provincial level but these were deemed to fall outside of the inclusion criteria for this review because they were considered regional decision-making. These studies can be identified in Table A2.2 that describes the reasons for exclusion and the full references of excluded studies can be found in Box A2.2.

2.3.5.4 Qualitative studies for England and Wales

There were seven studies identified with regards the influence of factors upon decision-making (Andronis et al., 2009, Bryan et al., 2007, Raftery, 2006, Raftery, 2009, Williams et al., 2007,

Williams et al., 2008, Williams and Bryan, 2007, Wirtz et al., 2005). The studies referred to NICE national decision-making with the exception of one study that referred to local formulary decision-making that included pharmaceuticals. These were categorised into the following two groups of studies:

- Evaluation of NICE process changes;
- The use of cost-effectiveness analysis in NICE decision-making;
- Other decision-making factors.

Evaluation of NICE process changes and additional appraisal factor

One study considered the impact of end of life guidance by applying the guidance to past decisions to not recommend a drug because the drug was not deemed to be cost-effective (Raftery, 2009). The introduction of supplementary end of life guidance can be viewed as an additional appraisal factor (non-evidence) and a change to the NICE process for considering such medicines that meet the criteria. The study found that very few of the drugs would have met the criteria imposed and therefore the process change is thought to be unlikely to impact decisions. The imposition of such a special consideration under the end of life guidance sets a precedent for other groups to seek changes in process when this is politically deemed acceptable. Both of these studies considered the process change in a relatively small group of decisions and there may be doubt regarding the generalisability of such findings.

The use of cost-effectiveness analysis in NICE decision-making

There were four studies that qualitatively considered the impact of NICE decision-making using a qualitative approach through interview or focus groups of the impact of economic evaluation (Bryan et al., 2007, Williams et al., 2007, Williams et al., 2008). The studies considered the impact of economics on decision-making by considering the ways in which economic analysis was used in decision-making, the value of economic analysis and the types of stakeholders' influential on the decision-making committee. At a national level the studies concluded that economic analysis was highly integrated into the decision process with an ordinal approach to considering clinical and cost-effectiveness information. The decision-makers reported that cost-effectiveness analysis allows them to structure and provide a framework to the considerations within the decision problem.

There was one study that considered the first 86 guidance produced by NICE that examined the clinical and cost-effectiveness of technologies (Raftery, 2006). The study found that of the

negative recommendations, nearly two thirds were due to insufficient evidence and the rest were categorised as due to unacceptable cost-effectiveness. The highest cost per QALY accepted in this period was £39,000 for riluzole to treat motor neurone disease. The study found some evidence of prioritising life saving therapies through the 'rule of rescue', (Raftery, 2006). Following this study, political sensitivity and discomfort resulted because of the rejection by NICE of a number of cancer medicines. NICE introduced new supplementary guidance for end of life medicines in January 2009. Raftery reviewed the criteria for medicines undergoing NICE supplementary guidance following the guidance for 11 medicines (final and provisional guidance) for which the results are discussed in the previous section (Raftery, 2009).

There was a further that employed a mix of stated and revealed preference methods for identifying the impact of sensitivity analysis, by consideration of 15 MTA NICE documented guidance and by a sample of 28 NICE committee members (Andronis et al., 2009). The study observed that uncertainty was explicitly noted as a justification to not recommend two technologies in the sample. The interviews reinforced this as an influence as it was suggested that the width of the confidence intervals around the ICER should impact the coverage decision (when uncertainty is greater decisions should tend towards being negative. Uncertainty is therefore a factor considered by NICE when arriving at a coverage decision.

Other decision-making factors

There was one study which used 20 interviews to consider the other aspects of decision-making which have not been captured in previous studies (Wirtz et al., 2005). The interviews were conducted with a number of decision-makers and stakeholders in the NHS and included three drug therapies, rivastigmine, statins and sildenafil. The stakeholders included regional policy makers, pharmaceutical advisors, drug advisors, lay members, patient interest groups, the pharmaceutical industry and academics in health policy. The interviews captured two aspects of decision-making which are not usually captured in the rationales usually cited. The first dimension was 'subjectivity' that includes personal factors that influence the kind of evidence and interpretations of the evidence, such as personal experiences related to the disease or the novelty of the benefit of the technology. The second relate to the overall social and political functions of decision-making which relate to the importance of maintaining relationships, the achieving of politically and legally defensible decisions and the reduction of organisational burden. The researchers did not imply by referring to these dimensions that they were inappropriate but rather the opposite conclusions were drawn. The authors believe that including these factors helps to articulate the other unexplained elements of decision-making. The study concludes that

the factors identified were often buried under the rationales given to legitimise the decisions made. The authors suggest that personal and political factors should be recognised as a dimension of decision-making when it is done within a discourse of reasonableness.

2.3.5.5 Qualitative studies of Finland reimbursement factors

A study conducted in Finland examined different stakeholders perspectives through 18 interviews on the reimbursement decisions made in Finland with a specific focus on the higher reimbursement category (Vuorenkoski et al., 2003). In Finland there is specific priority for some diseases and treatments that fall under a higher reimbursement category. In 2001, The Pharmaceutical Pricing Board of the Finish Ministry of Social Affairs and Health includes the drug in the reimbursement system if it considers the price of the drug to be reasonable. An expert opinion is provided from the Advisory Board for Social Medical Affairs (ABSMA) of the Social Insurance Institution of Finland (SIIF). If the proposal from SHIF is negative, it is unlikely that the pharmaceutical would be considered by the Ministry of Social Affairs and Health. The stakeholders discussed how the decision-makers tried to keep the decisions as evidence based and non-political but there appeared to be hidden non-technical rationales behind many decisions and this may be attributed to a lack of transparency. There has been indirect means by which some stakeholders have tried to influence decisions such as lobbying by media, parliament or other stakeholders. However, these stakeholder groups are seen to have restricted influence.

- Process categorises diseases by serious and less serious;
- Price;
- Budget impact on the system;
- The criteria taken into account in the decision-making process was unclear that led to stakeholder involvement in decision-making through lobbying and media attention.

2.3.5.6 Qualitative studies of reimbursement factors in the Netherlands

The search identified two qualitative studies conducted in relation to factors influencing Dutch reimbursement decision-making, one considering the revealed preferences of CVZ and ministry of health decision-makers for reimbursement of outpatient drugs during the period of 1999 and 2002 (Pronk and Bonsel, 2004). This study identified a number of factors across the decision to list unique and valuable drugs (DPRS-list 1b) and considered therapeutic value, budget impact and burden of disease as being considered important by considering trends in the submissions considered.

A second study focused on the role of budget impact in decision-making by conducting semi-structured interviews of eleven key stakeholders. The interviews confirmed that budget impact did play a role in certain cases and gave examples such as clopidogrel and sildenafil. It was considered to have more of a role when there was uncertainty around other criteria such as cost-effectiveness or severity of illness. The interviewees could not explain how this interacted with other criteria such as clinical effectiveness and cost-effectiveness and severity of illness. The study suggests rationales in favour of budget impact that include opportunity costs, loss aversion and endowment effects, uncertainty and equal opportunity (Niezen et al., 2009).

The following factors had evidence of importance across decision-making:

- Clinical effectiveness/added therapeutic value;
- Cost-effectiveness;
- Burden of disease;
- Budget impact;
- Severity of disease.

2.3.5.7 Qualitative studies of reimbursement factors in Sweden

There were two studies that identified the trends in factors used in decision-making for the national Swedish Pharmaceutical Benefits Board (LFN) during 2002 to 2005 (Anell and Persson, 2005, Jansson, 2007). The reimbursement decisions produced by the LFN are based on three main principles, the principle of human dignity where health care is provided equally for all individuals, the principle of need and solidarity where those with the greatest medical need are provided more health care resources than others, the cost-effectiveness principle that includes the marginal utility principle where the costs must be reasonable from the medical, humanitarian and socioeconomic points of view. The two studies both consider 107 decisions and find that cost-effectiveness supports decision-making and is used restrict by identify cost-effective subgroups in those areas with large patient groups and for rejected applications. The system produces unconditional, conditional, rejected and time limited decisions. The time limited reimbursement decision, is where the applicant is obliged in time to prove the cost-effectiveness shown in early modelling. The frequent use of economic analysis has been central to decision-making because the vaguer principles, such as need and solidarity and human dignity, do not discriminate well between individual products. The studies similarly found that the cost-effectiveness principle was less important for those drugs that were for an orphan indication. One of the studies also performed interviews with stakeholders to accompany the documented evidence and found that

cost-effectiveness is given a prominent role in decision-making and that a number of stakeholders have tried to exert direct influence on decision-makers. There have been a number of stakeholders that have been affected (patients, prescribers, pharmaceutical companies and patient associations) lobbied during the decision-making process sending official letters, contacting and visiting LFN. The influence of these processes may have had an effect through the appeal process but only one of these appeals revision of the decision occurred. The following themes were found to be important in LFN decision-making:

- Cost-effectiveness principle has been given a prominent role in decision-making;
- Proven marginal benefits of the treatment;
- Consideration of cost-effectiveness in subgroups with high potential budget impact;
- Disease type – orphan drug indication;
- Lack of alternative therapies;
- Stakeholder lobbying.

2.4 Critical appraisal of validity of results and risk of bias

2.4.1 Quantitative studies using a revealed preference methodology

The following domains were considered when appraising the quantitative regression analysis for the validity of the results and risk of bias:

- Reporting of the definition of influence and statistical methods
- Statistical Model Specification
    - Dependent variable and construct of independent factors;
    - Sample Size;
    - Sample Selection bias;
    - Omitted Relevant Variables;
    - Regression assumptions.
- External validity of results

2.4.1.1 Reporting of the definition of influence and statistical methods

The definition of influence or impact was not always explicitly stated in the studies design but all imply a linkage to association rather than causal influence of each of the factors. For example (Harris et al., 2008) does not explicitly define influence but states the aim:

> This article examines the factors that influenced drug coverage decisions in the Australian Pharmaceutical Benefits Scheme (PBS) that since 1993 has required detailed evidence of both clinical effectiveness and value for money prior to coverage and price setting—the first and still the only national prescription drug insurance scheme to do so. (p.714)

The influence of factors in reimbursement decisions has been studied by consideration of the statistical correlation of factors with the decision outcome using a number of different statistical approaches such as simple chi square tests, logistic regression, probit regression and multinomial logistic regression. These statistical techniques imply certain functional forms to the decision-making processes that may be considered more or less appropriate depending on the behaviour of decision-makers. The factors have been considered influential in these studies if they were found to be statistically significant at conventional levels, with occasional focus on the magnitude of effect for certain factors such as the ICER value. The use of statistical significance of a factor rather than magnitude of the effect of a factor was the norm across studies for describing whether a factor was influential. It is, clearly, very difficult to collect experimental evidence of the impact of different reimbursement factors on decisions. The consideration of each factor with respect to the counterfactual (the effect on the decision had the factor not been present) is a challenging task for this research area. In other areas of economics, natural experiments have been used to examine the causal influence of economic variables (Angrist and Pischke, 2010, Deaton, 2010). For example, researchers considering the economics of education have used natural experiments to identify the causal impact of years of schooling on earnings (returns to education) (Devereux and Hart, 2010, Harmon and Walker, 1995). However, establishing methods for identifying random policy changes that allow instruments to develop may be a step too far, until studies have identified potential factors considered important in larger observational datasets of decision-making that collect data on all factors potentially important.

The majority of quantitative studies consider multiple factors and control for the influence across decisions but some studies consider one factor without a control for other factors in decision-making (Clement et al., 2009, George et al., 2001, Mason and Drummond, 2009, Scuffham et al., 2008). There are a number of differences between the variables used in those studies that

consider multiple factors for the economic and clinical considerations. These present difficulties for making comparisons within countries and across the different country studies. The consideration of different factors in the regression analyses may legitimately reflect different considerations overtime within the countries and may reflect differences across countries with respect to the importance of such factors. However, they may also reflect the reporting of the considerations by the agency for the decision-making. This may explain why many of the studies are carried out for NICE, England and PBAC, Australia where there is sufficient reporting of the evidence to allow a more detailed understanding of the influential factors. There may therefore be potential for collection of data on the evaluation factors that are not directly reported in the documentation and which are influential factors such as stakeholder influence. The studies which only consider one or two factors in relation to decisions may be identifying the combined effect of all of the other factors and may not be very useful for considering the influence of such factors on decision-making.

2.4.1.2 Statistical model specification

Dependent Variable: Decision outcomes

The decision outcomes for studies that consider factors for one country's reimbursement agency are classified into a number of different decision groups. For example in England and Wales, NICE decisions, have been classified as binary (recommended, not recommended) in some studies and in one study recommended for routine use, restricted and not recommended. This is in contrast to the definitions of recommendations used by NICE: recommended, recommended only in research, optimised and not recommended. In Australia, PBAC studies have classified decision-making outcomes into classified as recommended and not recommended and grouped deferred decisions under not recommended decisions. The decision outcomes provided across countries are different for certain groups of drugs reflecting the process differences. The impact on the results of the different grouping of the variables is unknown and affects the interpretation and potential comparisons within and across country studies.

Construct of independent variables: Independent factors

The majority of quantitative studies consider factors that are directly documented and the documentation may not reflect all relevant factors. Further to this, some factors documented require subjective consideration of the guidance document to be able to construct the variables for the quantitative analysis. There were a number of different constructs of the variables to identify the clinical considerations and economic considerations for decision-making across

countries. For example, some studies considered evidence with regard to specific measures of the quantity and quality of the evidence such as the number of trials, RCT significance, type of evidence and appropriate comparator and population in combination with a composite indicator of quality. In contrast, some studies focused exclusively on a composite measure of the quality of evidence. The varieties of composite measures used to identify the quality of the clinical evidence were the Jadad score for RCTs, 12-item checklist and study specific measures such as clinical uncertainty (type of trial, comparator and endpoint) and quality of evidence (well designed and conducted RCTs). The application of each of these scales will introduce an element of subjectivity in the extraction of data from the documented evidence. These measures may not identify the relative weight that decision-makers considered trials to have in terms of the potential risk of bias. The potential differences observed across countries may be a true reflection of differences with regards to the importance of clinical considerations but may reflect the differences in the construct of the factors. Further to this, the Cochrane handbook distinguishes between bias and quality, recognising that a high quality study may have a high risk of bias and a low quality study may have a low risk of bias (Higgins and Green, 2011). The handbook advises against using rating summary scales (especially the Jadad scale) for consideration of the quality or risk of bias because such scales have been shown to provide an unreliable assessment of the validity. Instead the handbook proposes a tool across a number of domains where judgement is made of the risk of bias and the judgement is provided in a qualitative table (Higgins and Green, 2011).

The consideration of the specific cost-effectiveness estimate considered important for decision-making may be subjective when the documentation does not specifically state the value deemed appropriate for decision-making. The consideration of pooled cost-effectiveness and cost-utility may also ignore differences between the uses of such evidence by decision-makers. The ICER should ideally be constructed so that the value and units (cost per life year gained (CLY) and cost per QALY gained (CQG)) are specified and considered in relation to the decision.

Sample Size: Total number of reimbursement decisions

The studies that have performed regression analysis of the influence of factors on decision-making have included a relatively small sample of between 33 and 243 decisions and a focus on NICE and PBAC decision-making in England/Wales and Australia. This was of course an unavoidable limitation for these studies because of the number of guidance documents available. However, it does limit the number of variables that can be considered and whether the analyses are sufficiently powered to detect differences between the decision outcomes and the factors considered. There are some factors noted in the analysis that do not achieve statistical

significance, such as budget impact, that the authors suggest could be due to the small sample size of the study. One new study reported as a conference abstract described analysis which will consider 184 NICE technology appraisals covering 600 binary decisions which should provide more precise estimation of the influence of factors in England and Wales (Devlin et al., 2010).

Sample selection bias – missing data for the dependent variables:

The characteristics of the samples of medicines were different within countries and across the country studies. This was not due to the researcher selecting certain medicines for their analysis. The types of medicines that were included in some studies were limited because of the remit of the agency such as NICE in England and Wales which only considers medicines referred by the Department of Health. This was illustrated in the cross country comparison that found that across the period of 2001 and 2008 that those countries using similar evidence only had 19 medicines that were commonly appraised across the three agencies (Clement et al., 2009). The supply side incentives (patents, public funding of research and development, research environment) collectively present in each of the reimbursement systems are likely to impact upon the development of medicines for each disease area and partly determine alongside the pricing and reimbursement decisions the development of new medicines and the type of medicine appraised by each agency in each system.

Omitted relevant variables – Missing (un) measurable factors

The regression studies performed include a proportion of decision-making that is unexplained by the factors that are included. This could be related to the sample size of the studies but may also relate to the exclusion of other potential factors in the decision-making; some that could be measurable but others that are qualitative in nature and difficult to construct into a variable for analysis. Two studies consider stakeholder influence for NICE and this factor has had a more limited consideration in other studies and may be a potentially important consideration to analyse across other countries (Dakin et al., 2006, Devlin et al., 2010). There were fewer process factors and non-evidence factors controlled for across the studies and it is only possible to control for some process factors that are country specific within cross country comparison studies. There are also factors that cannot be measured from the documentation and would require observing each of the appraisal meetings to record details of the deliberations such as timing of evidence considerations and professional disciplines involved in decision-making.

Regression model assumptions

Endogenous Factors – relationships between reimbursement factors

The studies that included regression analyses were all retrospective observational analyses and some studies consider the potential relationships between the factors identified in the analyses. For example, the inclusion of both factors such as RCT size and RCT significance may be related (those trials with a larger number of patients are likely to be significantly powered to detect a significant treatment effect), the number of systematic reviews and number of RCTs (for example as more RCTs are available it likely that there will be more potential for systematic reviews of the effect of RCTs). Those studies that are found to have potentially weaker evidence of effect may also be found to be accompanied with lower quality economic evidence. The inclusion of both the effectiveness and cost-effectiveness in some of the included analyses may be inappropriate due to the potential relationship that exists between the price and effect (through the consideration of a value for money range) and the cost-effectiveness ratio. The cost-effectiveness ratio is a function of the effect and the price chosen by the manufacturer that will be to some extent a function of the threshold range. In these circumstances, an observed correlation between the cost-effectiveness and clinical effect would not be found because this is mediated by the price chosen by the manufacturer. The variable effect is a function of the CE ratio and would imply the problem of multi-collinearity and would not allow a meaningful separation of the influence of the two factors. The inclusion of endogenous factors across the studies may not allow identification of the actual influence of each of the factors in the regression analyses performed.

Model specification tests

Model specification tests were reported in four studies out of the seven multivariate factor regression studies (Chim et al., 2010, Dakin et al., 2006, Devlin and Parkin, 2004, Harris et al., 2008). These studies all included a goodness of fit test in the form of the pseudo R^2. Two of the studies considered regression model assumptions by either applying a formal test for multicollinearity called the VIF or by looking at the correlation between factors. One study looked at the impact of potential structural change through process overtime (see Table A2.9).

2.4.1.3 External validity of results

The generalisability of the influence of factors across studies for each countries reimbursement system will depend upon the consistency over time of the characteristics of the medicines that are assessed and appraised. The reforms to each reimbursement system over time may influence the extent by which factors are influential overtime. A number of the smaller sample quantitative studies viewed their results as generating a number of hypotheses that could be tested in future research using a larger sample of decisions.

2.4.2 Validity and reliability of qualitative studies

The majority of studies were narrative analyses of reasons for retrospective decisions for national reimbursement agencies. These studies generally allow us to understand the processes that led to the consideration of factors in decision-making and generate hypotheses for the relative influence of factors. The influence upon decisions is generally not defined across studies and many of the studies consider examples that illustrate specific reasons and their impact upon decision-making. The use of documented evidence may be a poor representation of the actual considerations in decision-making or there maybe circumstances where the evidence may be used to justify a decision, even though other factors may have been the true explanation for the decision observed. The interpretation of the reasons for reimbursement decisions in the narrative studies is subjective and will be dependent on the backgrounds of the researchers undertaking such narrative analysis.

The majority of studies identified that considered other forms of qualitative analysis were performed for NICE decision-making in England and used case studies, focus groups, semi-structured interviews and observation of the committee meetings. Many of these studies consider the influence of one factor within decision-making with reference to other factors but do not necessarily gain insight into the relative influence of each factor in the decision-making. There are difficulties in generalising whether the factors considered in England maybe important for other reimbursement decision-making because of the potential differences in processes for consideration of the evidence. There were a limited number of other studies that considered semi-structured interviews and focus groups for of decision-makers performed in Sweden, Finland and the Netherlands.

2.5 Discussion

The discussion will focus on the evidence for factors within countries to understand which are influential and then consider the factors commonly influential across countries. The discussion will then focus on the findings of studies that conduct cross-country comparisons and then any issues identified in the current literature. The discussion will be structured as follows:

- Summary of quantitative and qualitative studies;
- The influence of factors within countries;
- The influence of factors in cross country comparisons;
- Issues identified in the evidence and opportunities for further research.

2.5.1 Summary of quantitative and qualitative studies

Table A2.10 provides a summary of the quantitative factors and the validity of the results. The definition of influence in each study and the number of factors included depends upon the perspectives of the researchers. The table demonstrates that the majority of studies consider the statistical significance of the correlation/association of each factor with decisions and determine this to be the influence of a factor with occasional reference to the magnitude of effect of each factor. The search did not identify any experimental, quasi-experimental or natural experiment evidence for the influence of factors on reimbursement decisions and this possibly reflects the difficulties inherent in identifying the causal influence of factors on reimbursement decisions. If the meaning of influence is to obtain the causal influence then this review has not identified any evidence on influence of factors for each reimbursement system.

The majority of the quantitative studies identified focus on a retrospective analysis of the documented evidence (revealed preference) available for reimbursement agencies in Australia (PBAC), Belgium (National Insurance Agency), Canada (CADTH CDR), England (National Institute for Health and Clinical Excellence), Netherlands (CVZ) and USA (Medicare). Over half of the quantitative evidence was identified for Australia (PBAC) and England (NICE) decision-making. The majority of studies were based on one country and there was only one cross country comparison of national reimbursement agencies in Australia (PBAC), England (NICE) and Canada CDR (CADTH), perhaps reflecting the difficulties in collection of similar quantitative data and constructing similar variables across the countries reimbursement agencies.

The table shows the number of factors considered for each study and shows that nearly seventy percent of the factors considered were with respect to the clinical and economic evidence with more factors considered for the economic evidence across countries. The factors included by the researchers were all available or were separately constructed from the agency documentation of the assessment and appraisal of the medicine. Studies included multiple factors in their analysis for Australia, England, Canada and the Netherlands. A few studies included at least one factor across all the factor types (clinical evidence, economic evidence, non-evidence and process) for Australia and England which may indicate the lack of documentation of non-evidence and process factors in the other countries. Process factors were not frequently explored in the single country studies and none of these factors were included in the one cross country comparison.

The sophistication of statistical analysis ranged from individual univariate analysis to a multinomial logistic regression analysis of factors. The analysis sample sizes ranged from 33 decisions to 824 with many of the multivariate regression analyses including smaller sample sizes. There were four studies that included model specification tests with only two studies considering tests for multicollinearity and the relationships between included studies. Potential associations between the independent variables and potential endogeneity/confounding were rarely discussed in the studies included.

The qualitative studies identified in the review focus on a descriptive narrative of retrospective reimbursement decisions, interviews, focus groups for national reimbursement decision-making. Eleven of the qualitative studies included descriptive narratives of retrospective reimbursement decisions for Australia (PBAC), England (NICE), Canada (CADTH CDR), Netherlands (CVZ), New Zealand (PHARMAC), Scotland (SMC) and Sweden (TLV). Interviews, semi structured interviews and focus groups were methodologies used in eight studies to consider factors influential in national reimbursement decision-making in Canada (CADTH, CDR), England (NICE), Finland (PBB) and Netherlands (CVZ). Over half of the qualitative studies considered NICE decision-making in England and Wales.

The studies explore the influence or support of types of evaluation on decision-making and define this with regards to the context of the study. The studies explore some factors already captured in the quantitative studies such as cost-effectiveness, clinical effectiveness, and severity of disease and identify other factors within countries that are not considered in the quantitative evidence such as stakeholder involvement, composition of the committee that makes the decision, approaches to consideration of evidence, process considerations and non-evidence factors such as end of life criteria and disease severity.

2.5.2 The influence of factors within countries

There were a number of factors considered that were similar across some groups of countries and the influence of the factors considered in the quantitative analysis may be partly attributed to the design of study and other factors included. The majority of research to date has been conducted for established agencies with the majority of studies found in Australia (PBAC) and England (NICE). Table A2.11 includes the factors that were found to be influential within countries and categorisation of the factors considered influential by quantitative and qualitative studies. The quantitative factors include those that were studied and were statistically significantly associated with the reimbursement decision in **'bold text'** and those that were studied but there was no association between the factors in 'normal text'.

The quantitative and qualitative studies all concurred that the incremental cost-effectiveness estimates were statistically significant in the regression models and therefore considered influential within Australia (PBAC decision-making), England (NICE decision-making), Canada (CDR decision-making) and the Netherlands (CVZ decision-making), regardless of the time period considered and the statistical methods used. The studies used a range of quantitative statistical analysis and different measures of cost-effectiveness such as CLG and CQG but all concluded that this was statistically significant and therefore influential in decision-making. There were two studies that identified a cost-effectiveness threshold estimate, one for the NICE decision-making and one for decision-making in the Netherlands. The magnitude of effect of the ICER estimate was identified in some studies but these estimates are not comparable between studies because of the differences in study design.

The qualitative studies of NICE decision-making highlighted the importance of cost-effectiveness for not just providing a single result for decision-making but presenting an analytic framework for elements of the decision problem that should be considered in the committee's deliberations. There was also evidence that different approaches to consideration of clinical and economic evidence with some citing concerns with the cost-effectiveness threshold and some citing the influence of other factors.

The studies contained a mixture of variables to identify the other clinical considerations, economic considerations, non-evidence factors and effect of process in decision-making. The construct of variables used to describe factors and the different time periods of individual technology decisions across studies makes comparison of the similarities and differences in the

effects challenging. A discussion follows of the mix of evidence for factors within and across the countries considered in the review and potential explanations for these differences.

The studies contained aspects of the clinical evidence such as the quality and quantity of evidence and explored a number of different measures using either a combination of composite quality indicators with specific indicators of quality and quantity or with only specific measures of quality and quantity of the clinical evidence. There was evidence of aspects of the quality of evidence found to be important in PBAC decision-making, CDR decision-making and Medicare decision-making but no association for the studies that considered the quality of clinical evidence in NICE decision-making. The only attributes with respect to clinical evidence considered only in the context of NICE decision-making and found influential were the number of RCTs and the number of systematic reviews. A qualitative study of NICE decision-making that observed decision-making committees suggested that the 'clinical hurdle' was in some situations the most influential factor in the committee's deliberations and the perception of technology's clinical value and benefit could override the conclusions drawn from the reported evidence. In some reimbursement processes the economic analysts were found to be more important as they have the technical expertise to understand the evidence. One study suggested that it was controversial whether one such group should have disproportionate influence in such committees.

There were differences observed across countries in the consideration of the robustness of economic evaluation and consistent findings of the influence of sensitivity analysis in studies conducted for NICE decision-making, PBAC decision-making and CVZ decision-making through the use of retrospective data and stated preference data with different constructs for providing a proxy measure of uncertainty. The studies find that those with higher levels of uncertainty using measures from the sensitivity analysis were more likely to be not recommended. The findings for NICE decision-making were supported by qualitative evidence of the importance of uncertainty being considered explicitly in decision-making and high levels of uncertainty being accompanied with negative decisions. The study highlights that there is a high level of variation in the univariate sensitivity analysis used, methods and ranges employed. These differences may not be found in the construct of the variables used in the quantitative data to consider the uncertainty around the estimates of cost-effectiveness.

There is evidence of the influence of budget impact in studies for PBAC decision-making, CDR decision-making, NICE decision-making and CVZ decision-making. One study performed for NICE found no statistically significant influence of budget impact. However, Dakin *et al.* notes that even though there was no significant effect in the regression model, it was shown that those restricted

for use had a significantly higher budget impact than those for routine and this factor additionally improved the explanatory power of the regression. The study suggested that this may be considered alongside the cost-effectiveness and requires further investigation for NICE decision-making. One qualitative study performed in the Netherlands argue that budget impact is influential in decision-making and there are supporting rationales for this are opportunity costs, loss aversion, uncertainty and equal opportunity.

The evidence with regards to lack of alternative therapies is mixed for the quantitative and qualitative studies performed for NICE decision-making. There was no association found in PBAC decision-making and one qualitative study suggested that this is an influential factor in decision-making for New Zealand.

The severity of disease was found to be a significant influence of decisions in qualitative studies for NICE decision-making for cancer medicines, PBAC decision-making qualitatively, Finland, and CVZ decision-making in the Netherlands. There was one quantitative study that found an impact of severity of disease in one study for PBAC decision-making during 1994 and 2004 in contrast to another that did not find evidence of an impact in NICE decision-making, CDR decision-making and PBAC decision-making. This may be attributed to differences in the construct of the variables, Clement *et al.* defined disease severity as those interventions with a mean 5 year survival of less than 50% whereas Harris *et al.* defined this as a survival of less than 5 years, differences in statistical analyses (control of other factors) or the different time periods of study (Harris et al., 2008). A study of the stated preferences of decision-makers in the Netherlands found that disease severity was positively associated with the choice of the intervention (Koopmanschap et al., 2010).This factor could be a potential factor for consideration across studies quantitatively and qualitatively.

Patient group involvement was only considered quantitatively in one study of NICE decision-making and found to be influential in decision-making. This factor was found to be important in qualitative studies of decision-making in PBAC decisions, NICE decisions making and New Zealand decision-making, although all the other quantitative studies did not control for this factor. This factor could potentially be important for consideration across other contexts.

There were then factors that were considered specific to the nature of the process and how the agency considered pharmaceuticals for decision-making in PBAC decision-making such as the number of resubmissions, composition of the decision panel for PBAC, CDR, PHARMAC and NICE decision-making, the introduction of STA in the NICE decision-making process, impact of third

party independent assessment in NICE decision-making and fitness for purpose of manufacturer submission in SMC decision-making, categorisation of diseases by severity in Finland (PPB, Ministry of Health and Social Affairs) decision-making and other factors that relate to quality of life gains for decision-making in the Netherlands.

2.5.3 The influence of factors within cross country comparisons

There were limited number of studies that considered comparisons of factors across countries and these focused on those countries with established agencies, one quantitative study performed for agencies that consider both clinical effectiveness and cost-effectiveness evidence which were for NICE decision-making, PBAC decision-making and CDR decision-making that included statistical univariate comparisons of similarly constructed variables across the three countries.

There were differences observed across the countries with respect to the economic uncertainty and clinical uncertainty but regression analyses were not performed for each of the countries to identify the influence within countries. The study stated that statistical regression analyses were not possible due to the differences in processes but did not report such analyses, although univariate comparisons were made across the countries. The study also considered a qualitative investigation of common medicines similar to other studies that in addition considered SMC in Scotland and PHARMAC in New Zealand. The reasons suggested for differences between countries and suggested process differences such as differences in outcomes considered across the countries, different approaches to handling uncertainty in decision-making such as the consideration of subgroups in NICE decision-making rather than rejection, composition of the decision panel, number of drugs in the therapeutic class and the prevalence of the disease the drug is designed to treat. The generalisability of these findings across other pharmaceuticals may be limited but provide useful hypotheses for further quantitative empirical studies of the influence of factors within and across countries.

2.5.4 The limitations of previous studies and opportunities for further research

The review has identified a number of issues regarding the previous studies that could require further research to understand the factors influential within countries and across countries. The following main issues were identified and will be discussed:

- Lack of cross country comparisons of the influence of factors across countries

- Decision outcome categorisation
- Process and other factors in decision-making
- Construct of reimbursement factors and relationships between factors
- Quantitative studies past decision sample size

2.5.4.1 Lack of cross country comparisons of the influence of factors across countries

There are a limited number of comparisons (one quantitative study) across countries reimbursement agencies that consider the similarities and differences in the decision factors influencing decisions and the relative weight that these factors contribute. It is difficult to obtain comparisons across the current studies because of differences in the construct of the variables used, types of factors included and variation in the medicines considered. The results of the review demonstrate that a comparison may be limited by the details of the reporting of the factors that led to the final reimbursement decision but there is potential for some factors to be constructed across some of the developed countries. There would also need to be consideration of the different decision outcomes that were present across the countries and whether these can be categorised into certain similar outcomes given the process of the country. There are opportunities to explore the common factors that are important in those countries that share similarities in processes and methods of assessment with similar construct of factors across countries. However, this would first require categorisation of the reimbursement systems and consideration of those agencies that share sufficient similarities in methods and processes to make a comparison of common factors meaningful.

There are clear differences between some reimbursement agencies with respect to the methodologies used and processes followed. It would also be useful to explore how different processes and methods compare across countries with respect to the same medicine assessments and appraisals to consider whether differences in methods or process can explain these decisions. For example, the use of economic analysis in decision-making in comparison with a country that does not explicitly use economics in decision-making such as HAS in France.

2.5.4.2 Decision outcome categorisation

Decisions are commonly categorised as binary decision outcomes (recommend/not recommend) in the majority of the studies in this review. A more realistic approach to categorising decisions used in some studies identified in this review was to categorise the decision outcome as

recommended, not recommended and restricted. However, a very recent study on decision categorisation for a sample of decisions made by NICE in England and Wales recognises that 'restricted decisions' include an entire range of degrees of access to those medicines (O'Neill and Devlin, 2010). The definition and levels of decision outcome are therefore not only important within countries but can have implications for comparisons of decisions made across countries. A balance needs to be therefore made in cross-country comparisons between having sufficient data for each level of decision outcome to understand the influence of each factor and providing comparative categories of the decision outcome across countries.

2.5.4.3 Process and other factors in decision-making

There were controls included in a few of the studies for the agencies process of decision-making. The factor was included as a time variable to control for evolution in process over time or by considering specific aspects of the process such as stakeholder involvement, the fact that the appraisal was a resubmission, the type of process followed by the agency (i.e. STA for NICE) or whether the assessment and appraisal resulted in an appeal. There are a limited number of process factors that can be identified and quantified at the individual technology decision level within the documentation provided for each of the decisions by each reimbursement agency. There is still considerable to be learnt about the influence/impact of differences in processes that exist between reimbursement agencies and systems. This first requires a categorisation of the reimbursement process differences at the policy level and the individual technology decision level.

There is one element of decision-making that is unexplained by the model used to understand the influence of factors. The review has demonstrated across a number of the qualitative and quantitative studies that a number of stakeholders may have influence upon decision-making and these decisions take place within a political context. One quantitative study included a variable to identify whether a patient group submission was included in the submission and found to be influential on decision-making for NICE (Dakin et al., 2006). It has been suggested that there are dimensions of decision-making that relate to the role of 'subjectivity' and how personal experiences of a condition or excitement about the 'novelty' can affect the way decision-makers interpret the evidence in practice. The perception of the evidence will be influenced by the actual evidence, subjectivity and personal knowledge of the condition. The other reasons for decision-making maybe buried beneath rational factors that are reported by the agency. There may be a number of interpretations given by different stakeholders for the decision. The 'rational' decision-making is often mediated through other factors in decision-making such as personal and political

factors that may reasonably influence decisions. The 'rational' and 'reasonable' may diverge and this may be a reason for differences in the perception of the evidence, actual evidence and the decisions made. There is also evidence from interviews and observation that the excitement of a novel technology can influence the evaluation and interpretation of the evidence (Wirtz et al., 2005).

The influence of Patient Access Schemes (PAS) and risk sharing agreements has not been examined with respect to other factors on reimbursement decision-making in countries in the studies identified in this search. The review did not identify any studies because these are relatively new processes in each of the countries. Future datasets of decisions using PAS and risk sharing agreements in decisions in each country will be important when considering the influence of health economic analysis and other factors/criteria in decision-making.

There were no factors included in studies that were generated from external sources other than the reimbursement agency (such as public interest influence, patient and other stakeholder lobbying, year of election, health policy priorities and other non-evidence factors). There are certain external forces upon a reimbursement agency identified in the qualitative evidence (public interest) that may influence and partly explain decisions even in the presence of explicitly stated criteria for decision-making. A study that attempts to measure such influences may help to further explain decision-making, some form of variable that considers the political or public interest in the treatment area may additionally explain how decisions are made.

2.5.4.4 Quantitative studies past decision sample size

There were a limited number of studies addressing the relative weight of decision criteria that varied within and across countries. The most established reimbursement agencies have only been producing sufficient documented evidence of the decisions over the last 15 years and the number of drugs that have been assessed using cost-utility analyses has been limited. This has meant that the sample sizes of studies using such techniques have ranged from between 33 and 243 decisions. These studies include over 10 different factors in the analyses and some analyses are underpowered because of the lack of medicines falling into certain decision categories. Further to this, all analyses rely upon select samples; either because the reimbursement agency (NICE) has decided in the past which drugs to evaluate or the manufacturer has decided which of the drugs should be considered for reimbursement. This would require a first stage regression to understand why NICE chooses certain drugs to evaluate and why manufacturers choose certain drugs to submit to an agency. There is potential for insufficient variation in some factors if these

are selected to explain the differences in decision-making between agencies. Additionally, the small sample size suggest that some factors may be shown to be influential because of the existence of a number of outliers in the data and no studies have considered the potential for outliers in the data because there is no view of the characteristics of all drugs that could have potentially been evaluated by agencies. The regression analyses provided also summarise older decisions that were conducted pre-2006 and this could be updated in relation to a number of new decisions and the process changes that these agencies have imposed over this period. There is an opportunity to produce a study that includes a larger sample size that includes a number of countries reimbursement systems and decisions

2.5.4.5 Construct of reimbursement factors and relationships between factors

The construct of the variables used to identify dimensions of the clinical considerations and economic considerations will depend on the detail of the evidence reported in the documentation. Interestingly, the only factor with consistent construct was that of the ICER and the direction and influence of this was found across the studies that considered this factor in their analysis. Those documents that are transparent and provide details of the considerations in the decision-making will provide sufficient evidence to construct variables. There were a number of variables used in the analyses that required subjective judgement and were based on some documentation that was limited and involved assumptions to enable data across the sample of decisions.

The factors included in the studies assessing the clinical evidence considered bias in trials (composite scores such as the Jadad score), precision of clinical effect (statistical significance, RCT size and RCT significance) and type of evidence (type of study, appropriate comparator and number of RCTs) and one study introduced whether the drug was considered to have a clinically significant effect (Did the PBAC consider the size of the treatment effect to be clinically important?). The construct of these variables has relied on subjective assessment of the documents (clinical significant effect) and some assumptions where data is not reported for some decisions (Jadad score, RCT size, RCTs using a relevant comparator, RCTs showing a significant effect). For example where data was missing for RCT size across some trials the average number in the trial was extrapolated across those where this was not reported.

The studies have aimed to understand the relative importance of decision factors by focusing on different elements of the considerations and defining a number of specific measures to identify these. The problem with this pursuit is that it very difficult to obtain a reliable direct measure

across countries that summarises the complexities with consideration of clinical uncertainty and economic uncertainty. It may be difficult to capture in one or a number of quantitative measures the complexities and perceptions of decision-makers with regards these factors. For example, considering the influence between clinical and economic considerations may be captured through using qualitative methods for identifying the differences in decision-making environments and this influence on the perceptions of the evidence. This review has shown that study results may be sensitive to the subjective judgements made by construction of variables and it would be better to minimise the researcher judgement when constructing such variables in the quantitative analysis.

The difficulty in such analyses is to separate whether the clinical considerations obtain less/more weight than the overall economic considerations in decision-making. The studies have focused on measures of the quality of clinical evidence rather than the clinical effectiveness and its influence upon decisions. This maybe because the difficulties with separating the influence of clinical effectiveness from the influence of cost-effectiveness or the difficulties in the separation of other variables because whether a committee finds a medicine to have a clinically significant effect will be related to their judgements of the perceived type of evidence, quality and risks of bias within this evidence.

There is discordance across studies using similar statistical methods in determining whether a threshold value can be observed for cost-effectiveness. This is perhaps because of the perspectives by which the researcher approaches the study because of the policy of the countries reimbursement agency and country with respect to the use of thresholds. But there is potentially no reason why methods could not have been used to imply a certain threshold in these countries through the analysis of retrospective decisions.

2.6 Conclusions

The following main conclusions can be made from the review of the quantitative and qualitative evidence.

- The majority of evidence identified includes quantitative and qualitative studies for NICE decision-making in England, PBAC decision-making in Australia and CDR decision-making in Canada. There is limited evidence for the influence of factors for other OECD countries' reimbursement decision-making and a lack of cross country comparisons of decisions and factors.
- The quantitative regression analyses do not address causal influence only association of each factor based on relatively small sample sizes and further research should explore larger sample sizes and the relationships between factors included and the model specifications.
- The quantitative studies most commonly explored factors were with respect to the evidence considerations with fewer variables to capture non-evidence factors and process. There were a number of qualitative factors that were identified that had not been explored in the quantitative research which mainly related to the non-evidence factors and agencies' processes of decision-making.
- Cost-effectiveness was the most frequently explored factor across studies when this was included. This was the only factor to have a consistent construct and studies across and within countries found the same direction of effect but the magnitude of effect was not always comparable because of the different methodologies that were used. Some studies provided estimates of the cost-effectiveness threshold from the analysis of retrospective decisions but some authors did not produce an estimate.
- Mixed evidence of the influence within reimbursement systems and across systems was found with respect to other factors clinical evidence factors, non-evidence factors and process factors when these were included in the studies within countries and across countries (when included).

2.7 Further research opportunities

A number of gaps in the literature were identified with respect to the influence of health economic appraisal and other factors on reimbursement decision-making across the OECD countries:

- There was a lack of single country studies for many OECD countries' reimbursement systems and studies that compare the influence of factors on decisions across countries. There is an

opportunity to perform qualitative studies on systems that have not been studied and provide cross country comparisons of those systems not included using either a qualitative or quantitative methodology.

- Process has been identified from the review as a potential factor that is missing from comparisons across countries and where possible for single country studies. The effect of process may explain differences found across countries reimbursement decisions. This factor appears to have been given little attention in the current literature. This would first require categorisation of the reimbursement systems before any qualitative or quantitative studies can be performed to explore the differences between countries due to process considerations and the other factors identified in this review as potentially important in decision-making;

- It is no fault of the authors performing the studies that the samples are small because this is the number of decision that were available at the time of the study. There is potential to perform studies of larger sample size because the documented use of elements of HTA in reimbursement decision-making has grown over the last decade. Further studies could included new factors that have been highlighted in the qualitative evidence as potentially important in decision-making;

- Further exploration of the construct of factors across the quantitative studies may partly explain some of the differences in influence upon decision observed within countries. The relationships between factors could also be more thoroughly studied to identify whether it is possible to separate all factors into independent variables. The endogeneity problem has not been investigated in these types of regression modelling.

- The introduction of Value Based Pricing (VBP) schemes in countries reimbursement systems will require explicit definition of the criteria important for decision-making. This will require explicit documentation across the countries in the guidance for each reimbursement decision. This will allow more detailed examination of the factors and their weight in each of the countries and the desirability of the decisions and whether they are welfare improving.

Chapter 3: Categorisation of OECD Reimbursement Systems using Health Technology Assessment: Policy Implementation Level

Abstract

Objective: To apply a published analytical framework for describing and classifying pharmaceutical reimbursement decision-making systems using Health Technology Assessment (HTA) and to identify the similarities and differences between fourth hurdle systems at the policy implementation level.

Methods: OECD countries with universal health care and institutionalised HTA were included. Systems were classified in four categories: establishment of the system, objectives of the system, implementation of the decision and accountability of the reimbursement system. The reimbursement institution(s) responsible for decision-making was identified and their websites searched for data on each element of the framework. When data were unavailable from the institution's websites, published and grey literature were searched and contact was made with the institution to identify missing data.

Results: The sample included 24 OECD countries' reimbursement systems. Systems varied with respect to the institutions, their relationship with the Ministry of Health and the final reimbursement decision. The systems principle objective was categorised as affordability, access or cost-effective use of medicines and there was a degree of overlap and conflict between each objective, especially where multiple institutions were present. Systems implemented decisions through a sickness fund, Ministry of Health scheme, regional scheme or other schemes. Few detailed documents were identified with respect to the accountability of the reimbursement institutions. Where information was available this tended to be considered with respect to intermediate outcomes such as number of guidance rather than impact on final health outcomes. The ability of various stakeholders to appeal and processes of appeal varied widely across countries.

Conclusion: Reimbursement systems are diverse with respect to their objectives, purpose and remit. This may explain differences in reimbursement decisions across countries and the use and

influence of HTA on decision-making. Public information was sparse in some countries for elements of the policy implementation level and this limited comparison.

3.1 Introduction

Chapter 2 identified that many researchers have focused on the influence/impact of aspects of evidence such as the health economic analysis and clinical analysis upon reimbursement decision outcomes within a single country. The range of factors considered with respect to consideration of evidence displays some of the complexities involved in making comparisons between reimbursement systems that are complex and also contain other potentially important factors that affect the decisions made for new medicines in different countries. Few studies consider the characteristics of the entire reimbursement system in a more holistic approach that identifies the interdependencies between different elements of the system and the impact on how decision-makers judge the evidence and the final decision outcomes. The impact of the differences on the decision outcomes can be understood by comparisons between countries. The first step in understanding the differences between the systems and their impact on the decision outcomes requires a descriptive categorisation of the different elements of a system. Hutton *et al.* were the first to provide an analytical framework for classifying 'fourth hurdle' reimbursement systems that use HTA (Hutton et al., 2006). The study defines the term fourth hurdle as:

> 'The requirement to justify the reimbursement of pharmaceuticals by health systems has been labelled "the fourth hurdle", as it is perceived by manufacturers to be an additional barrier to market access, after demonstration of product quality, efficacy, and safety to obtain a product license.' (p.11)

The framework for classifying decision processes for the reimbursement of health technologies can be considered a positive framework that allows all systems to be described and classified. It does not provide a normative framework which considers how things ought to be within each of the systems, whether one system is better than another or what are good practices for each element of the reimbursement system. Although there is an element of subjectivity in what constitutes each element of the framework for all countries, the systematic collection of data across countries will enable further investigation of the key characteristics of the system and the potential impact of these characteristics on the process of making medicine reimbursement decisions. The aim of the framework is to help understand which elements of the reimbursement system are important when considering the impact on the final decision. The framework allows the systems to be described and classified, making an important distinction between the policy implementation level and the individual technology decision level.

The differences in reimbursement systems partly reflect their objectives. These are determined by the political institutions and health care sectors in which they operate. The policy implementation level aims to consider the establishment of the fourth hurdle system as a policy decision of the government that has particular objectives and involves institutions and stakeholders such as the public, patient groups and industry (Hutton et al., 2006). Hutton and colleagues define these as separate elements because they are likely to impact on the processes, methods and evidence requirements for the assessment and appraisal of individual medicines.

The individual technology decision level categorises specific decisions regarding particular technologies, the processes and organisations involved in the detailed assessment and appraisal of each technology. The framework distinguishes between the assessment phase, decision phase and the outputs and implementation of the decisions made by the reimbursement system.

The aim of this chapter is to describe the Fourth Hurdle framework and use it to classify the sample of OECD countries at the policy implementation level. The similarities and differences between countries can be identified within and across elements of the framework. This will provide a context within which the use and impact of health economic analysis, and other analytical methods, at the technology decision level, within each of the countries, can be examined.

3.2 Methods

Chapter 2 identified limited evidence on OECD countries reimbursement factors and found limited evidence of the process factors. The thesis aims to consider those reimbursement systems that use elements of HTA to inform reimbursement decisions for pharmaceuticals. This sample has been identified by those systems where a formal HTA programme operates and produces recommendations and elements of HTA are used for the reimbursement of medicines. The OECD reimbursement systems were included if they met the following conditions:

1. Countries with a reimbursement system for medicines that operates alongside an institutionalised HTA process. Formal HTA is defined as the institutionalisation of HTA provided either through a HTA agency or co-ordinated network of institutions undertaking HTA. The institutionalisation of HTA has been described as "promoting structures and processes that are suitable to produce technology assessments that will be powerful to guide policy and clinical practice towards the best possible health and cost outcomes", (WHO, 2000 - World Health Organisation. WHO Regional Office for Europe (2001). The institutionalisation of HTA will be identified by membership to the

International Network of Agencies for Health Technology Assessment (INAHTA). The membership criteria require that institutions; (i) are responsible on an ongoing basis for the coordination and/or development and operation of HTA programs, and the production of assessment reports; (ii) have an officially recognised role in relation to national or regional government; (iii) are non-profit making and at least 50% of their income is obtained from public sources and (iv) members provide free access amongst members of any publications (INAHTA, 2011a).

2. Countries with Universal Access to Health Care;

3. Those countries with sufficient public information sources to be able to categorise the system.

The sample includes 24 reimbursement systems including 25 countries (NICE covers medicine recommendations for England and Wales. Although Scotland is part of the UK its health service is separately organised and funded independently of UK government. Therefore it has been treated as a separate country):

1. Australia
2. Austria
3. Belgium
4. Canada
5. Denmark
6. Finland
7. France
8. Germany
9. Ireland
10. Israel
11. Italy
12. Hungary
13. Korea
14. Mexico
15. Netherlands
16. New Zealand
17. Norway

18. Poland
19. Portugal
20. Spain
21. Sweden
22. Switzerland
23. United Kingdom – England and Wales
24. United Kingdom – Scotland

The OECD countries excluded from the sample can be found in Table 3.1.

Table 3.1: Countries excluded from the sample

Countries without an institutionalised HTA process	Countries without universal access to health care	Countries with insufficient details across the system
Czech Republic	US	Chile
Estonia		
Greece		
Iceland		
Japan		
Luxembourg		
Slovak Republic		
Slovenia		
Turkey		

The 24 countries' reimbursement systems institutions and websites were identified. The official publically available documentation was downloaded and used to complete the qualitative framework. Where the information was unavailable from official documents, published literature was used to provide information on the missing elements and when neither source was available email contact (where possible) was made with the staff of the institution concerned.

The framework was originally developed to categorise reimbursement systems for all types of technologies but in this chapter will only be applied to the systems for the reimbursement of medicines. The framework is comprised of sixteen elements which aim to describe and provide categorisation of the reimbursement systems. The elements considered within the framework cannot be completed by a (yes/no) binary consideration of each element and require a qualitative description of each element in each of the countries. The first level of the framework concerned the policy implementation level and this comprised four different elements, establishment of the system, objectives, implementation and the accountability of the system. The Elements of the Policy Implementation Level are provided in Table 3.2.

Table 3.2: Policy Implementation Level elements (Source: (Hutton et al., 2006))

Establishment	Objectives	Implementation	Accountability
Relationship to health ministry; number of health system organisations involved	Broader political objectives: Social, industrial, health system objectives, cost control and health improvement	Directly by Health Ministry; dependent on other health system organisations or independent of government	Managerial, political, legal and obligations to consult.

3.2.1 Establishment of the reimbursement system

The establishment of the system is important to identify the institutions involved and their legal basis. The dates of establishment of the main reimbursement institutions are identified at a national level and a timeline provided for the development of these institutions. The establishment of the systems are categorised by the relationship to the Ministry of Health, number and type of institution and whether the institution provides the final reimbursement decision or makes recommendations to another decision body. The remit of the reimbursement institution is considered with respect to whether it is solely established for consideration of medicines, or whether it has other functions.

3.2.2 Objectives of the system

The objectives of the system may not always be publically stated and the long-term publically available objectives of the institutions may be inconsistent with the short term political objectives. This element aims to characterise the overall policy objective of the reimbursement system but it is acknowledged that this may be more difficult when there are multiple institutions contributing to the final reimbursement decision for medicines. The objectives of the entire system will be identified when possible and where this is not possible the individual objectives of each element will be taken as a proxy for the overall objectives of the reimbursement system.

3.2.3 Implementation

This element of the framework concerns the institutions responsible for the implementation of the reimbursement decision. The process and institutions responsible for the implementation of the decisions will be considered in each of the countries. This will be considered with respect to

the types of institutions and whether these operate at a centralised national level or regional level.

3.2.4 Accountability

The accountability of the reimbursement system relates to who monitors the performance of the system in meeting the stated objectives and who determines its budget. This may be an internal administrative process within the government or a more transparent democratic process with public involvement. Other considerations are the public availability of information on the assessment of performance and the opportunity for other stakeholders to hold the reimbursement institutions to account.

3.3 Results

The results are described for each of the four elements of the policy implementation level. A number of summary tables can be found for each element and a detailed summary of the data collected for each country can be found in the Table A3.2 and the references accompanying this data can be found in Box A3.1.

3.3.1 Establishment of the system, institutions and relationship to Ministry of Health

The reimbursement systems vary with respect to the relationship with the Ministry of Health and the institutes, organisations and committees involved in the reimbursement systems. The PBAC was the first reimbursement agency to be set up in 1954 under section 101 of the National Health Act 1953 which made recommendations to the Minister of Health on which medicines should be made available in the public system (Australian Government, 2011). The agency was also the first to require manufacturers to provide an economic analysis in the form of cost-effectiveness analysis (in 1993) to support reimbursement recommendations for medicines. Many OECD countries began to set up agencies or committees during the late 1990s and early 2000s, which covered different aspects of the reimbursement system, had varying remits, objectives and involved different stakeholders in the process of reimbursement decision-making. A timeline of the reimbursement institutes, agencies and committees establishment is provided in Table 3.3.

Table 3.3: Time line of establishment of reimbursement body/agency

Year	Reimbursement Body established
1953	Pharmaceutical Benefits Advisory Committee – Australia
1980	Transparency Committee - France
1989	Canadian Co-ordinating Office for Health Technology Assessment which is now known as the Canadian Agency for Drugs and Technologies in Health (CADTH)
1993	National Authority of Medicines and Health Products (INFARMED) – Portugal PBAC Economic Evaluation Committee – Australia
1995	Federal Drug Commission – Switzerland
1998	National Centre for Pharmacoeconomics (NCPE) – Ireland
1998	Public National Advisory Committee (PNAC) – Israel
1999	Health Insurance Board (CVZ) – The Netherlands National Institute for Health and Clinical Excellence (NICE) – England and Wales
2000	Health Insurance Review and Assessment (HIRA) – Korea
2001	Scottish Medicines Consortium – Scotland Committee for Reimbursement of Medicines (CRM) – Belgium The Norwegian Medicines Agency (NoMA) – Norway Pharmaceutical Management Agency of New Zealand (PHARMAC) – New Zealand
2002	Dental and Pharmaceutical Benefits Board (previously known as LFN) - Sweden
2003	Directorate General of Pharmacy and Health Products – Spain General Health Council – Pharmacoeconomic evaluation – Mexico CADTH Common Drugs Review (CADTH) – Canada Reimbursement Committee (MTN) – Denmark
2004	Haute Autorité de santé – France Institute for Quality and Efficiency in Health Care (IQWIG) – Germany Pharmaceutical Pricing Board (PPB) – Finland The Italian Medicines Agency (AFIA)- Italy
2005	Medicines Evaluation Committee (HEK) - Austria
2006	Agency for Health Technology Assessment in Poland (AHTAPol) - Poland

The reimbursement systems vary with respect to the number of institutions and the establishment and relationship to the Ministry of Health are discussed by considering the countries in the following groups according to the final reimbursement decision (Table A3.1 and Table A3.2):

1. Systems with a single institute or agency using HTA to provide the final reimbursement decision;
2. Systems with a national advisory agency providing recommendations to a regional final reimbursement decision-making body using HTA;
3. Systems where the social insurance institution provides the final reimbursement decision;
4. Systems where an national agency or committee provides advice to the final decision-maker in the Ministry of Health
5. Other systems.

1. Systems with a single institute or agency using HTA to provide the final reimbursement decision;

There are countries reimbursement systems where a single institute or government agency is established as the central body responsible for the national reimbursement process and decision that is either under the direction or accountable to the Ministry of Health. These include reimbursement agencies in countries where medicines are predominantly tax funded in Denmark through the establishment of the Danish Medicines Agency (DMA), the Italian Medicines Agency (AIFA) in Italy, Pharmaceutical Management Agency of New Zealand (PHARMAC), Dental and Pharmaceutical Board (TLV) in Sweden and the National Institute for Health and Clinical Excellence (NICE) in England and Wales. These are public bodies central to the reimbursement system and provide a mandatory decision for the use of the medicine which is made by a committee comprised of members that are independent of the Ministry of Health. The assessment of evidence for individual medicines is performed within each of these agencies and a separate committee convened by the agency provides judgement on the evidence and other factors that are specified as important in each of the systems. These agencies all consider only medicines with the exception of NICE and TLV. NICE also produces other guidance for diagnostics, interventional procedures, medical technologies for medical devices, public health guidance and clinical guidelines. TLV also provides guidance on the use of dental products.

2. Systems with a national advisory agency providing recommendations to a regional final reimbursement decision-making body using HTA;

In Scotland, Canada and Spain a national advisory body using HTA provides reimbursement advice to a regional decision-maker that uses HTA and other criteria to make the final reimbursement decision at the regional level. The Canadian reimbursement system involves multiple agencies with a remit to consider different types of medicines.

The SMC in Scotland was established in 2002 to avoid duplication by the Area Drug and Therapeutic Committees (ADTCs) and provide advice to the 14 local Boards and their ADTCs across Scotland with a remit for new medicines. The Scottish reimbursement system involves firstly advice from the SMC and then a final reimbursement decision by the local boards. The local boards are expected to follow the advice of the SMC but consider this with respect to other medicines available and individual patient requests for decisions (Health Policy and Strategy Directorate, 2010).

The Canadian reimbursement system has the complexity that oncology and other medicines are assessed under different schemes but these schemes provide advisory recommendations to the provincial drug plans that provide the final recommendation. The Canadian Agency for Drugs and Technologies in Health (CADTH) which assesses medicine and devices established the Common Drug Review (CDR) in 2003 to provide formulary listing advice to 16 publically funded drug plans (12 provinces and territories) in Canada with the exception of Quebec that follows a separate process. The recommendations are advisory and the drug plans take into account other factors such as the laws governing the drug plans, the priorities of the jurisdiction and the financial resources that are available (CADTH, 2011a). The CADTH Common Drug Review does not include Oncology medicines which are considered within a separate process called pan Canadian Oncology Drug Review established in 2011, (pCODR, 2011).

The Spanish health system is decentralised with 17 autonomous regions with health coverage financed from general taxation. The Ministry of Health makes the final reimbursement decision in Spain for inclusion on either the positive list or negative list of medicines. There is an association of Spanish HTA agencies called AUnETS that aims to co-ordinate ten agencies representing regions in the Spanish National Health system (AUnETS, 2011). The Spanish regions have responsibility for their own health budgets (Vogler et al., 2009) Some of these HTA agencies are responsible for creating prescribing guidelines for the regions but the Ministry of Health decides which medicines should be included in the national formulary.

The health care systems of Austria, Italy, Portugal, Switzerland, Sweden, are all similarly decentralised systems. Decisions for the reimbursement of medicines are made at a national level in Austria by the Social Insurance Institutions, the Ministry of Health in Spain, TLV in Sweden, INFARMED and Ministry of Health in Portugal, the Federal Office of Public Health in Switzerland and AIFA in Italy. The reimbursement decisions are then implemented at a regional level in these systems. These systems fall into the other categorisations for the national systems.

3. Systems where the social insurance institution provides the final reimbursement decision;

The body responsible for the final reimbursement decisions is provided by the social insurance institutions in Austria and Hungary. The Federation of Social Security Institutions (HBV) is a public self-governing body of social insurance institutions in Austria that consists of 22 social security institutions that fund medicines. In Hungary, the National Health Insurance Fund Administration (NHIFA) provides the funding for medicines and is a public social insurance body that provides the final reimbursement decision (PPRI, 2007b). There are other countries where the social insurance institutions are important in the process of decision-making but do not provide the final reimbursement decision such as the CVZ in the Netherlands and the Commission for Reimbursement that provide advice to the Ministry of Health (CVZ, 2009, Schäfer et al., 2010).

4. Systems where an national agency or committee provides advice to the final decision-maker in the Ministry of Health

The other OECD countries have established a reimbursement agency or committee that is advisory to the Ministry of Health. The Ministry of Health provides the final decision in these systems and generally one committee is involved in providing the reimbursement advice. The reimbursement committees are based within agencies that evaluate medicines and other technologies by the Haute Autorité de santé (HAS) in France, CVZ in the Netherlands, National Institute for Health and Disability Insurance (NIHDI) in Belgium, AHTAPol in Poland, HIRA in South Korea and solely medicines in Australia called the Pharmaceutical Benefits Advisory Committee, the Norwegian Medicines Agency (NoMA) in Norway, National Authority of Medicines and Health Products (INFARMED) in Portugal.

There are no separate agencies in Switzerland and Finland rather committees that advise the Ministry of Health. The Federal Office of Public Health (FOPH) is part of the Federal Department of Home Affairs in Switzerland and is the government department responsible for defining the benefit package made available in the social insurance system delivered by private insurers. The department is advised by the Federal Drugs Commission (FDC) that consists of scientific experts and wide range of stakeholders that include health insurers. In Finland, the Pharmaceutical Pricing Board is a committee that is based within the Pharmaceutical Services of the Ministry of Social Affairs and Health and makes the final reimbursement decision.

In Israel the reimbursement system is operated entirely by the Ministry of Health and the process is uniquely setup to only update medicines included in the National List of Health Services (NLHS) once a year. The Medical Technology Administration (MTA) of the Ministry of Health provides an

assessment of the technology and then a committee with representatives of the Ministry of Health called the Public National Advisory Committee (PNAC) provides recommendations and the final decisions are provided by the Ministry of Heath in an act of government (Shemer et al., 2009).

5. Other types of systems

There are other types of systems where the final reimbursement decision is held by a self governing body in Germany, the responsibility of multiple insurance agencies in Mexico and the Health Service Executive (HSE) responsible for running public health services in Ireland.

In Germany, the Federal Joint Committee is a self governing independent body delegated by law in 2004 to decide the benefits provided under social health insurance with advice from the advisory agency the Institute for Quality and Efficiency in Health Care (IQWIG), (Federal Joint Committee, 2010).The body includes representation from the sickness funds, physicians and patients.

A government decision-making body called the General Health Council (GHC) decides on the medicines that should be made available in accordance with the Presidential Agreement of 2002 that specifies that the NHS in Mexico should only use medicines from the basic formulary for primary care and the catalogue of inputs for secondary and tertiary care. The public institutions in Mexico such as the social insurance institutions, Mexican Social Security Institute (IMSS) and the Institute of Security and Social Services for Government Workers (ISSSTE) along with the voluntary insurance programme operated by the Ministry of Health must consider these when making the decision on which medicines should be included in each of their respective formularies (Moise and Docteur, 2007). The public institutions are represented on the GHC.

In Ireland, there is no legal agreement applicable to reimbursement. There is an agreement which came into force in September 2006 between the Health Service Executive (HSE) and Pharmaceutical industry called the Irish Pharmaceutical Healthcare Association agreement (IHPE). The HSE is a public organisation which is accountable to the Minister of Health and Children. There is a General Medical Services (GMS) scheme and a Drugs Payment Scheme (DPS) provide reimbursement for those eligible in Ireland. The HSE is responsible for the operation and management of the public health services in Ireland on behalf of the Department of Health and Children. The Corporate Pharmaceutical Unit of the HSE makes final recommendations on the reimbursement and pricing of medicines. The final decision is informed by recommendations from a separate institution called the National Centre for Pharmacoeconomics (NCPE) for those high

cost or high budget impact medicines that require an economic evaluation established in 1998, (Tilson et al., 2010).

3.3.1.1 Other functions of reimbursement institutions/agencies

These systems are developed alongside institutions that set the price through statutory price setting, price negotiations or other types of agreement. There are a number of separate institutions or bodies that may administer statutory pricing decision (prices are set on a legal basis) or perform price negotiations either before the reimbursement decision or in some cases after the decision. There is an entire literature on pricing of pharmaceuticals and this is not the topic of this thesis but the relationship with the reimbursement institutions and the use of HTA is important (Danzon and Furukawa, 2008, Danzon et al., 2005, Goldman et al., 2008, Vogler et al., 2009). Eight countries agencies have a dual role of considering both the price of pharmaceuticals and the reimbursement decision. These may be through the agreement of a statutory maximum price, negotiation of the price or both types of pricing policy (Table 3.4).

Table 3.4: Countries systems agencies of dual remit of price and reimbursement

Reimbursement System (agency)	Type of pricing policy	Reference
Germany (Federal Joint Committee)	FJC agrees maximum price and reimbursement (Price negotiation follows with sickness funds)	(Leverkus, 2011)
New Zealand (PHARMAC)	PHARMAC negotiates price and reimbursement	(PHARMAC, 2011a)
Italy (AIFA)	AIFA negotiates price and reimbursement	(AIFA, 2011)
Hungary (NHIFA)	NHIFA negotiates price and reimbursement	(PPRI, 2007b)
Ireland (CPU)	CPU agreement of price and reimbursement	(CPU, 2011)
Switzerland (FOPH)	FOPH agrees maximum price and reimbursement	(Paris and Docteur, 2007)
Finland (PPB)	PPB sets statutory maximum price and reimbursement	(Ministry of Social Affairs and Health, 2011)
Norway (NoMA)	NoMA agrees maximum price and reimbursement	(Norwegian Medicines Agency, 2011)
Sweden (TLV)	TLV is responsible for statutory pricing and reimbursement.	(TLV, 2010)

3.3.2 Objectives of the reimbursement system

The objectives of the systems vary overtime depending on the individual political priorities that exist at different points in time. A review was conducted of the stated objectives of the main schemes or institutions that are responsible for the reimbursement of medicines in each of the countries. The overall principle of all the health systems is to improve the health of the population

but with respect to other policy objectives. The review revealed that the stated objectives of the agencies and institutions across the reimbursement system focus around improving health, access to care, quality of care, cost-effectiveness or value for money, need, solidarity, equity of access, equal access, reduce regional variation in access and to ensure a timely reimbursement decisions (Table A3.2). Interpreting the systems documented objectives it is possible to determine the principle objectives of the reimbursement systems. The systems can be broadly grouped into those systems where the central objective is cost-effective use of medicines, access to medicines or affordability of medicines. These objectives are considered in most systems with respect to other objectives, some of which are conflicting and overlapping objectives (Table 3.5).

A central objective of some reimbursement systems is to obtain cost-effective use or value for money. These systems aim is to maximise health from a limited budget available that has been politically predetermined. This objective is stated alongside other objectives in 12 countries. A range of other objectives that accompany the cost-effective use of technologies are the need to produce consistent decisions across regions, affordability, stated objectives concerning equity, solidarity and need and objectives concerning process such as timely decisions.

In England and Wales, Scotland and Canada cost-effective use of medicines is an objective alongside the requirement for consistency of reimbursement across regions is a main objective. NICE was set up on 1 April 1999 to ensure everyone has equal access to medical treatments and high quality care from the NHS, regardless of where they live in England and Wales. NICE's technology appraisals programme makes recommendations about the use of medicines in the NHS, based on how well a medicine works, and whether it offers value for money compared to existing treatments (cost-effectiveness) (NICE, 2011a). Similarly, the SMC in Scotland SMC is to accept those newly licensed drugs which clearly represent good value for money and reduce postcode prescribing (SMC, 2011a). In Canada the objective of the CDR process are to reduce duplication, to maximize the use of limited resources and expertise, and to enhance the consistency and quality of Drug reviews (CADTH, 2010). This objective is delivered by the consideration of clinical effectiveness and cost-effectiveness evidence for all new medicines with the exception of cancer medicines. The drug plans then have their own individual objectives.

In the Netherlands and New Zealand, the cost-effective use of medicines is accompanied by the stated objective of affordability. That is the need to obtain medicines at low cost in order to contain costs within the system. The corporate brochure of the CVZ states that quality, accessibility and affordability are the three pillars of the Dutch Health Insurance system. The CVZ objective is to "safeguard and develop the public conditions for health care insurance system, so

that Dutch citizens can obtain their right to care." (CVZ, 2009). There are four stated package criteria of necessity, effectiveness, cost-effectiveness and feasibility that were developed from the funnel of Dunning. The first package principle called necessity is with reference to need and requires the committee to consider whether the illness or care given in the context of society justify a claim on solidarity. This criterion includes both the burden of disease and considerations relating to personal responsibility for the disease (CVZ, 2010a). The second criterion 'effectiveness' refers to whether the medicine or care does what is expected of it. The third criterion 'cost-effectiveness' requires a consideration of whether the costs and benefits are broadly acceptable. The last criterion 'feasibility' aims to consider whether inclusion of the medicine in the care package is feasible in both the short and long term (CVZ, 2009). In New Zealand, PHARMAC's statutory objective is to "secure, for eligible people in need of pharmaceuticals, the best health outcomes that are reasonably achievable from pharmaceutical treatment and from within the amount of funding provided." (PHARMAC, 2010b).

There are other principles with respect to equity of access that are stated objectives alongside cost-effective use in Sweden, Poland and Korea. The objective of the TLV is to examine which medicines, medical devices and dental care treatments will be subsidised by society in Sweden. This objective is achieved by consideration of three criteria, the human value principle, need and solidarity principle and the cost-effectiveness principle (LFN, 2007). The principles of human value which concerns the respect for equality of all human beings, need and solidarity which concerns agreement amongst the Swedish Society that those with more severe diseases are prioritised over less severe diseases must be taken into account alongside the cost-effective use of the medicine. The Polish Constitution requires all citizens of the Republic of Poland to be entitled to equal access to health services from public providers of health services and these should be free of charge and provided by public funds. The objective of the AHTAPol is to provide recommendations for the classification of health care services as guaranteed benefit (AHTAPol, 2011). In Korea, HIRA is dedicated to maintaining and improving national health by fulfilling its commitment to health care review and quality assessment. HIRA aims to be an organisation that is recognised and respected by all physicians, patients, parties and people in the country. It is established under the National Health Insurance Act for improving the national health care and developing social security though fair and efficient heath care review and evaluation. HIRA is directed to deliver this efficiently and to monitor and assure medical necessity, appropriateness and quality of health care (HIRA, 2011). This is delivered through a value based pricing scheme by considering the clinical usefulness and cost-effectiveness of medicines.

The Irish reimbursement system states that timely decisions are an important stated objective in addition to cost-effectiveness. The HSE in the Corporate Pharmaceutical Unit (CPU) in Ireland made an agreement with the pharmaceutical industry called the IPHA agreement in 2006. The objective was to ensure early access to and security of supply of new medicines for Irish patients and ensure that the medicine that best meets the patients' needs delivers best value for money (IPHA, 2006). The aim of the NCPE that provides recommendations to the HSE is to "promote expertise in Ireland for the advancement of the discipline of pharmacoeconomics through practice, research and education. Activities of the centre include economic evaluation of pharmaceutical products and the development of cost effective prescribing." (NCPE, 2011).

The second group of countries includes those countries where the main objective of the reimbursement system can be categorised as delivering access on the basis of those medicines that are demonstrated to be clinically efficacious and/or clinically effective. The systems of Belgium, Denmark, France, Germany, Italy, Mexico, Portugal and Switzerland can be broadly classified into this group. There are a number of European systems which rely on a single institution to provide a judgement of the clinical efficacy in Denmark, France, Italy, Norway and Portugal. These systems include other objectives alongside providing access to medicines. There are some systems that include the objective of high quality care alongside accessible care, for example, in Belgium aims to "provide reimbursement of medical costs in order to make high quality health care accessible to as many people as possible", (NIHDI, 2011: The NIHDI: a closer look). The French systems reimbursement body adds equity alongside access to medical care stating the objective of the HAS "a number of activities designed to improve the quality of patient care and to guarantee equity within the healthcare system" (HAS, 2011a).

The German reimbursement system aims to provide timely decisions in addition to cost-effectiveness. The objectives of the G-BA operate according to a legal basis through a code of procedure of the G-BA (Social Code (SGB V)). The services provided by the statutory health insurance must be "adequate, expedient and cost-effective" (Federal Joint Committee, 2011: How Innovations Enter Statutory). The German Health reforms called the Pharmaceutical Market Restructuring Act (AMNOG) mean that an early benefit assessment will take place followed by negotiation on the price to provide access to medicines in Germany (Leverkus, 2011). IQWIG is contracted by the G-BA to provide early benefits assessments and an economic analysis only where necessary for medicines where agreement cannot be made on the price. The agency's stated aims are to "examine objectively the advantage and disadvantages of medical services for patients" (IQWIG, 2011a).

The final group of countries can be broadly defined as those that consider affordability with respect to other stated objectives. In Australia, the primary objective of the Pharmaceutical Benefit Scheme is to improve health (PBAC, 2008). The scheme's stated objectives are to focus on timely, reliable and affordable access to medicines (Department of Health and Ageing, 2011). The scheme achieves this through the advisory reimbursement body called Pharmaceutical Benefits Advisory Committee and the pricing body called the Pharmaceutical Benefits Pricing Authority (PBPA). The main objective is one of providing medicines that are value for money or cost-effective by maximising health from a given budget (PBAC, 2008). The PBPA will then consider the price that should be recommended based on the PBAC analysis and expected budget impact. The Austrian reimbursement system aims to provide access but on the basis of affordability. The Austrian Health care system is built upon the principles of solidarity, affordability and universality (Federal Ministry of Health, 2010: The Austrian Health Care System). The system ensures high quality medical care for all citizens, independent of their social status or income. The Main Association of Austrian Social Insurance Institutions "provides customer-oriented and conscientious protection against the risks of diseases, old age and unemployment." (Main Association of Austrian Social Security Institutions, 2010). In Spain although accessibility is one objective, the introduction of two new laws in 2010 with respect to reducing expenditure through price reductions and reference price modification categorise place cost containment as the current principle objective of the system (Ferre, 2011). The Norwegian system has implemented a number of cost containment measures through price control after assessing the medicines clinical efficacy and effectiveness (Håkonsen et al., 2009).

Table 3.5: Principle objectives of the reimbursement systems

Affordability (cost containment)	Access (Principally based on providing reimbursement when clinically effective/clinical efficacy)	Cost-effective use of medicines (amongst other stated objectives)
Australia	Belgium	England and Wales
Austria	Denmark	Scotland
Israel	France	Canada
Spain	Germany	Finland
Norway	Italy	Ireland
	Mexico	Hungary
	Portugal	Netherlands
	Switzerland	New Zealand
		Poland
		Sweden
		Korea

3.3.3 Organisation of system and Implementation

The reimbursement systems implement the final reimbursement decision through a social insurance institution or sickness fund, a regional decision-making body, through a Ministry of Health scheme or through other processes, some of which are more complex.

3.3.3.1 Implementation by social insurance institutions or sickness funds

There are reimbursement systems where the implementation of the reimbursement decision is made by the social insurance institutions or sickness funds in systems where social health insurance is mandatory. The social insurance funds operate and implement decisions through a positive list for all eleven social insurance countries included. A positive list contains medicines for which the system will automatically fund the medicine.

The social insurance systems of Austria, Belgium, France, Germany, Mexico and Poland implement the decisions through a number of sickness or health insurance funds. In Austria, a list called the 'Reimbursement Code' operates using a traffic light system for three main levels (red, yellow and green) of reimbursement where physicians are provided with the medicines that can be provided by general reimbursement by the 22 sickness funds of the statutory social insurance system (General Social Insurance Act, ASVG). The traffic light system provides conditions on the reimbursement of medicines where the red box includes those new medicines or medicine applying for reimbursement, the yellow box includes medicines with restrictions (criteria upon reimbursement) and the green box automatically qualify for reimbursement (PPRI, 2007a). In Belgium, the National Institute for Health and Disability Insurance is responsible for the supervision and managements of the compulsory health care and benefits (HCB) insurance. The

health insurance funds are responsible for implementation of the reimbursement decisions made by the CRM in the NIHDI. In Germany, the Federal Joint Committee (including representatives of the National Association for Statutory Health Insurance Funds) provides the directives for those medicines that can be provided by the statutory health insurance fund (GKV) and reimbursed by the health insurance funds. The reimbursement decisions in France are published in the Official Journal by the Ministry of Health and funded by the social insurance institutions through the mandatory social health insurance system. The National Union of Health Insurance Funds (UNCAM) co-ordinates the three national sickness funds (general scheme, agricultural scheme and social system of independent) and decides the rate of reimbursement following a listing decision by the HAS and the Economics Committee on Health Care Products (CEPS). Mexico has two main schemes that implement the decisions through a mandatory social insurance system by the Mexican Social Security Institute (IMSS) and the Institute for Security and Social Services for Government Workers (ISSSTE).

In the Netherlands and Switzerland the positive lists for the mandatory social insurance system are delivered by regulated private health insurance organisations. The Swiss systems public reimbursement listings (SL medicines list) are implemented by the provision of these medicines by a number of private and public health insurers. In the Netherlands the institution appraising medicines, the CVZ is part responsible for implementation of decisions for the basic benefits package through providing the private health insurers with risk adjusted contributions according to the population served by the insurer.

A single National Social Insurance body provides the reimbursement and implementation of decisions in Hungary (National Health Insurance Fund Administration (NHIFA)) Norway (National Insurance Scheme) and Korea (National Health Insurance Corporation (NHIC)). The Norwegian system is unique in that decisions can only be made by the Norwegian Medicines Agency for medicines that do not have a very large budget impact for coverage by the National Insurance Scheme (NIS). The decisions for medicines with an annual cost increase of more than 5 million per year cannot be made by the NoMA because further advice must be sought from other institutions. The Ministry of Health Care Services (HOD) may seek advice from another body called the National Council for Health Care Priorities which assesses whether reimbursing the medicine would be money well spent. The HOD can then decide whether to reject or favour approval of these high budget impact medicines. The HOD must then pass a parliamentary bill for the approval of these medicines and these can then be funded under the National Insurance Scheme (PPRI, 2008).

3.3.3.2 Implementation of national decisions at a regional level

The reimbursement decisions for medicines by institutes/agencies in Denmark, Italy, New Zealand, Sweden, Denmark and those provided by the Ministry of Health in Portugal and Spain are implemented at the regional level. The institutions at a national level in Scotland and Canada provide advice to the respective regional decision-makers that are responsible for the final reimbursement decision and implementation. In Scotland, the fourteen Health Boards use the SMC advice and some NICE Multiple Technology Appraisal advice to determine the final decision in the form of a regional formulary and provide the funding for implementation of these decisions. Medicines accepted by the SMC are expected to be funded by the Health Boards but may receive a negative decision if there is already an equivalent treatment available on the Health Boards formulary (Health Policy and Strategy Directorate, 2010). In Canada the 16 publically funded health plans use CADTH CDR advice to provide their own decisions and implement these at a regional level.

3.3.3.3 Implementation through a Ministry of Health scheme

There are reimbursement systems where this is implemented directly by the Ministry of Health in Australia and Ireland. In Australia the Pharmaceutical Benefits Scheme (PBS) is part of the broader National Medicines Policy for which the government subsidises medicines and is administered through Medicare Australia. The scheme is eligible for those Australian residents who hold a Medicare card. The Irish system reimburses medicines through a voluntary agreement with the Pharmaceutical industry for which the Ministry of Health, Corporate Pharmaceutical Unit has decided are eligible either through the GMS, DPS, Long term illness scheme (LTI) or the Hi-Tech scheme.

3.3.3.4 Other systems of implementation

In Finland the Social Security Institution called KELA provides implementation of the final reimbursement decision provided by the Pharmaceutical Pricing Board. KELA is an independent statutory social insurance institution (sometimes referred to as a social insurance institution even though it is funded by tax) for which 12 Trustees are appointed by parliament. KELA is confirmed in the Finnish constitution and provides reimbursement to patients for medicines provided out of the tax funded National Health Insurance scheme (KELA, 2011).

The National Health Insurance Law (NLHS) specifies a list of medicines to be provided by publically tax funded Health Maintenance Organisations (HMOs) in Israel. The membership of one of the

four competing funds is mandatory and these provide the benefits approved by the Ministry of Health in the National List of Health Services (NLHS).

The NICE recommendations apply to England and Wales and are enforceable within three months of the publication of the appraisal. The NHS providers are required by direction of the Secretary of State to provide funding for medicines recommended under the Single Technology Appraisal (STA) and Multiple Technology Appraisal (MTA) processes. NICE is not directly responsible for the implementation of the recommendations and this is undertaken through the NHS providers and funders. The NHS bodies need to assess how much the medicine guidance will cost to implement and must plan for implementing these by identifying and releasing funding. Those medicines that are not recommended can still be funded in individual cases or general cases if the physician and local provider decide that this is appropriate (Department of Health, 2011).

3.3.4 Accountability

The public reimbursement systems are accountable through reporting directly to the Ministry of Health, directly to the country's parliament or through legislation delegating powers and providing rules for the reimbursement of medicines. The complexity of the accountability of the systems varies by the number of institutions and committees involved in decision-making and whether separate institutions operate at both the national and regional level. The accountability of the system relates to the funding and accountability lines of the national institutions and the assessment of performance of the institutions or committees to meet the objectives of the system. The main problem is that many of the reimbursement systems have conflicting objectives of balancing access, cost-effectiveness and affordability which are difficult to attribute to the operation of the system. The objectives of the institution are not always solely with respect to these objectives and may be more procedural such as delivering a number of decisions per year, transparency of process or consistency in decision-making. In addition, the overall long term objectives may be in conflict with the shorter term political objectives of the government in power. Perhaps the ultimate judgement of the performance of the institutions in a reimbursement system may be demonstrated by the long term survival of an institution over time.

An attempt was made to identify the budget of 20 reimbursement systems that included an institution which either provides an advisory decision or final decision (the other four countries' systems included a committee reporting to the Ministry of Health). The budgets of five countries' institutions could not be identified from the publically available information and contact by email

was made to each of these institutions to identify the budget but no response has been obtained. The details of the budget were identified from the institutions website or the annual report (where available for the institutions) and these were categorised as institutions paid for by the Ministry of Health through taxation, social insurance contributions or through mixed sources of funding. Seven of the institutions were directly funded through taxation and three were directly funded through social insurance contributions (Table 3.6).

Table 3.6: Institutions funded by fully through taxation and social insurance contributions

Ministry of Health through Taxation	Social Insurance Contributions
Australia (PBAC)	Austria (Federation of Social Insurance Institutions
Ireland (HSE)	Mexico (Social Insurance Institutions)
The Netherlands (CVZ)	Korea (HIRA)
New Zealand (PHARMAC)	
Poland (AHTAPol)	
Sweden (TLV)	
England and Wales (NICE)	

There are then systems where the funding is from a mixture of sources. In Denmark the DMA receives income from the Danish Finance Act, fees set by the Danish Minister for Interior and Health for assessments and income from the work conducted for the European Medicines Agency. The HAS in France receives funding from a number of sources with a large proportion of funding from the social health insurance agencies and government subsidies. The German Federal Joint Committee has a unique system of funding through a system of surcharges. These are composed of a surcharge for each billable hospital visit and from an additional increase in fees for outpatient's medical and dental care. The G-BA decides on a surcharge each year. In Canada the CDR is financed through central and regional sources from the federal, provincial and territorial governments. Similarly, the regional/local NHS Boards of Scotland are required to fund the SMC from the funds allocated to them.

The performance of the institution is reported in the annual reports of those that provide these on their websites (NICE, SMC, TLV, NoMA, PHARMAC, CVZ, HSE, HAS, DMA and CADTH). The focus of performance measures in the annual reports focus on procedural measures and intermediate outcomes or outputs such as the quantity or speed by which decisions are produced by each of the institutions. The focus on quantity and speed of decisions is linked to European Union Law that covers sixteen of the EU countries included in the OECD sample. The Transparency Directive of the EU lays down three major requirements for the individual pricing and reimbursement decisions that include that (i) decisions must be made within a specific timeframe (price within 90/180 days when additional information requested); (ii) decisions must be communicated to the

application and contain a statement of the reasons based on objective and verifiable criteria and (iii) the decisions must be open to judicial appeal at the national level (European Commission, 1989). The institutions do not tend to use quantitative measures of performance with respect to improving health outcomes for patients or to measure performance on all of the objectives that are set by the agencies.

The PHARMAC in New Zealand provides a section on the website devoted to accountability and the targets for the agency over the year period in relation to health outcome performance. The website provides a detailed section on accountability documents including a statement of intent (tabled at parliament) which summarises what the institutions plans to achieve over the year and then an annual report which describes what has been achieved with respect to the stated work plan. The system considers the intermediate outputs and the relation to the objectives of the system level final outcome of New Zealanders living longer, healthier and more independent lives (PHARMAC, 2010b). The outputs considered in 2011/2012 outputs and targets are as follows:

- Decision-making, Community pharmaceutical schedule decisions: All funding decisions are supported by evidence and made using PHARMACs nine decision criteria – This is assessed by more than 90% of decisions on medicines being made within 6 months;
- Influencing medicines use, Population health programmes: provide campaign materials on medicine use – This is assessed by 90% of the respondents rating their satisfaction as good (4 out of 5);
- Supply management, Contract management: Respond to low medicine stock reports – Ensure patients needs for medicines are met;
- Policy advice: Survey of policy requesters indicates satisfaction with timeliness and quality of PHARMACs policy advice;
- Rebates Distribution: All funds use is in accordance with PHARMAC policy (PHARMAC, 2011b).

The agency aims to measure the effectiveness of decision-making for the first time in 2010/2011 using the QALY on system level outcomes. PHARMAC decision lead to an overall increase in the number of new patients treated compared with the previous 12 months and an increase in extra life years gained. The agency aims to consider the average value of the funding options available on the entire prioritisation list (some of which are not included because of limited budget) and compare this with average value of the funding decisions actually made. The value will be expressed in terms of QALYs gained per dollar. The institution highlights that the effectiveness of their work depend on the work of other in the New Zealand Medicines System such as optimal

prescribing decisions and use by patients to achieve the best health outcomes (PHARMAC, 2010b).

A further consideration with accountability is the ability of stakeholders to challenge the reimbursement system's decisions. The involvement of different stakeholders and ability to appeal varies across the reimbursement systems. The public and patients are represented in some systems and do not play any role in the decision-making process in other OECD systems. For example in England patients can participate in the committee deliberation and the public in specific committees such as the Citizens Council at NICE that provides advice to the committee on social value judgements. In the Netherlands views of patients and societal aspects of decision-making are considered by a separate committee called the appraisal committee (ACP) at CVZ in the Netherlands. In contrast the French system provides no opportunities for patient participation in the reimbursement decision-making process. These differences will be discussed in further details at the technology decision level.

Chapter 4: Categorisation of OECD Reimbursement Systems using Health Technology Assessment: Individual Technology Decision Level

Abstract:

Objective: To apply a published framework for describing and classifying pharmaceutical reimbursement decision-making systems using Health Technology Assessment (HTA) and to identify the similarities and differences between fourth hurdle systems at the individual technology decision level.

Methods: OECD countries with universal health care and institutionalised HTA were included in the sample. Systems were categorised at the individual technology decision level: assessment of evidence, the decision and the output and implementation. The reimbursement institution(s) responsible for decision-making was identified and the websites searched for data on each element of the framework. When data were unavailable from the institution's website, published and grey literature were searched and contact was made with the institution to identify missing data.

Results: The sample included 24 OECD countries' reimbursement systems. Variation was present in the assessment and appraisal of clinical evidence. A health economic analysis was mandatory in 17 of the OECD countries for some types of medicines but there was variation in the guidelines for the conduct of the analysis and the requirement for third party review. The appraisals were conducted by committees of varying size and composition. Forty-one stated decision-making factors were identified across countries and categorised into clinical evidence, economic evidence and non-evidence factors. Variation across countries was identified in the implicit/explicit use of cost-effectiveness thresholds and the interpretation of the threshold with respect to other factors. Final decision outcomes varied across countries with respect to the types of restrictions and the status of the decision.

Conclusion: The influence of evidence on decision-making has been studied in some countries but less attention has been given to the impact of the reimbursement process upon the use of

evidence and the decision. Further comparative studies designed to control for process may help to address some of the unexplained variation in reimbursement decisions across countries.

4.1 Introduction

Chapter 3 categorised the reimbursement systems at a policy implementation level. This chapter categorises the process by which individual medicines are assessed and appraised to help understand how the objectives of the system influence the methods of assessment (use of health economic analysis) and the resulting reimbursement decisions by different systems. The 24 reimbursement systems are described and categorised for each element of the technology decision level and where appropriate grouped by similarities with respect to each element. The individual technology decision level characterises how medicines are assessed, the appraisal and reimbursement decision-making and the output and implementation of decisions in countries (Hutton et al., 2006). The aim of this chapter is to categorise the different reimbursement systems with respect to each of these elements to understand the stated use of health economic analysis within the context of the process and other stated factors.

4.2 Methods

Table A4.1 provides an overview of the elements of the technology decision level. This level distinguishes between the assessment of evidence, making the decision (which includes the appraisal of evidence and other factors) and the implementation of the decisions made by the system.

4.2.1 Assessment

The assessment of medicines is considered with respect to the consultation and involvement of stakeholders, methodological framework, source(s) of evidence for the assessment and presentation and communication of the results. The following elements and data are considered:

- Process, institutions and stakeholder involvement: This considers the institution(s) and stakeholders involved in the assessment (manufacturer, review group, independent third party assessment), the points in the process at which they might contribute and whether there are specific committees with responsibility for the scientific assessment of the evidence.
- Evidence and Methods of Synthesis: This considers the methods and elements of HTA used by the institution responsible for the assessment (source) of the medicines. The requirements and data sources are considered including:
    - The requirements for the manufacturer and the guidelines for the conduct of submissions by manufacturers;

  - The requirements for health economic analysis in each of the reimbursement systems;
  - Independent third party assessment of the evidence.
- Stakeholder consultation on evidence assessment: This describes the stages at which the manufacturer and other stakeholders can provide comments on the evidence assessment before this is considered within the decision-making process.
- Communication of assessment of evidence: This section describes how the results of the assessment are communicated either by publication of the manufacturer submission or through the provision of reports of the assessment considered for the decision-making stage. This also considers whether other evidence is provided by other stakeholders and whether this is made publically available.

4.2.2 Decision

The decision is interpreted as the process and institutions involved in producing the final decision on whether a medicine is publically funded by the reimbursement system. The categorisation thus separates the assessment of the evidence by the institutions or committees involved from the appraisal of evidence by the final decision-making body. The appraisal involves the application of decision criteria to the synthesised evidence and the consideration of other factors (either explicitly stated by the institution or not). The characteristics of the decision are separated in the framework into the consideration of who makes the decision, decision-making process, evidence base and additional influences on the decision and the content and documentation of the decision:

- Stakeholder involvement in deliberations: This considers the types of stakeholders involved on the committee(s) for the appraisal of medicines in relation to the final decision-maker in the reimbursement system.
- Decision process and institutions: This describes the institutions involved in the appraisal and number of stages of the process.
- Evidence base and additional Influences: This describes the evidence appraised and other stated factors considered by the institution responsible for the final reimbursement decision. This provides definitions of the stated factors and a consideration of how economic analysis is used in relation to the final decision.
- Content and documentation of the decision: This describes the information that is made publically available by the decision body and whether justifications are provided for the interpretation of evidence in the deliberations.

4.2.3 Output and Implementation

The outputs and implementation describes the opportunity for appeal and dissent, implementation and communication, monitoring and reappraisal and the evidence of the impact of the decision.

- Appeal and dissent: This describes whether the system has a formal appeal mechanism against a decision, the types of options that are available for appeal, the grounds for appeal and the types of stakeholders that can appeal in the process.
- Implementation and communication: This describes the types of decision outcomes produced, requirements or coverage with evidence development and the mechanisms and the status of the reimbursement decisions in practice.
- Monitoring and reappraisal: This describes the reimbursement system's ability to monitor changes in the evidence base and activate reappraisal where necessary. The systems will be assessed with respect to whether there is a formal process to monitor and reappraise technologies and the mechanism which triggers reappraisal.
- Evidence of impact of decisions: This refers to the systems accountability in assessing and documenting the impact of individual decisions. This concerns a review of the implementation and impact of decision by each of the reimbursement systems.

4.3 Results

The following section summarise the results and the detailed data extraction can be found in Tables A4.14, A4.15 and A4.16. The references for the data collection tables can be found in Box A4.2.

4.3.1 Assessment of medicines

4.3.1.1 Process, Institutions and stakeholder involvement

The process of assessing the evidence in countries reimbursement systems is distinguished from the appraisal of evidence in the description of the countries processes. The assessment of evidence can be undertaken by the manufacturer, an independent group commissioned by the institution responsible for appraising the assessment or an analytical team within the appraising body. The assessment performed may be a full Health Technology Assessment which, as defined by HTAi, is "The systematic evaluation of properties, effects, and/or impacts of health care technology. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care. HTA is conducted by interdisciplinary groups using explicit analytical frameworks drawing from a variety of methods." (HTAi, 2011). HTA can be broadly considered to cover five main areas; clinical-effectiveness, cost-effectiveness, social, ethical and legal aspects. The reimbursement systems may require elements of HTA in the assessment such as safety, clinical effectiveness and cost-effectiveness of evidence rather than a full HTA. The requirements and methods for the assessment of evidence may reflect the policy objectives of the system and particular value judgements of the countries reimbursement system.

The majority of the systems rely on the manufacturer to provide the assessment of the evidence regarding a medicine and to bear the majority of the cost. The manufacturers are required to provide a submission for new medicines to all of the reimbursement systems and the majority of these systems rely on the assessment of the evidence presented by the manufacturer (Table A4.2). There is an institution in each country which is responsible for reviewing the manufacturer submission. This review in different countries is either performed by the staff of the institution, a specific committee responsible for assessment within the institution or by multiple committees within the institution. The assessment institution is not necessarily the same body as the appraisal institution, but is responsible for delivering the final assessment to the appraisers.

There are single institutions responsible for processing the manufacturer submission and preparing an assessment for medicines in 17 of the countries (Table 4.1). The staff of the

institutions process the submissions made by the manufacturer in preparation for the appraisal by a separate committee within the same institution. Additionally an independent assessment of the clinical evidence is provided by a clinical review team at CADTH in Canada, independent assessment group in the NICE MTA process in England and by IQIWG in Germany. An independent economic analysis is provided by these groups in England (MTA only) and Germany.

Table 4.1: Single institution responsible for assessment and appraisal

Country	Institution/agency
Belgium	National Institute for Health and Disability Insurance (NIHDI)
Canada (excluding cancer medicines)	Canadian Agency for Drugs and Technologies in Health (CADTH)
Denmark	Danish Medicines Agency (DMA)
England and Wales	National Institute for Health and Clinical Excellence (NICE)
Frances	Haute Autorité de santé (HAS)
Germany	Institute for Quality and Efficiency in Health Care (IQWIG)
Hungary	Office for Health Technology Assessment (OHTA)
Ireland	National Centre for Pharmacoeconomics (NCPE)
Israel	Medical Technologies Administration (MTA)
Mexico	General Health Council (GHC)
Norway	Norwegian Medicines Agency (NoMA)
Poland	Agency for Health Technology Assessment in Poland (AHTAPol)
Portugal	National Authority of Medicines and Health Products (INFARMED)
South Korea	Health Insurance Review and Assessment (HIRA)
Spain	Ministry of Health, Directorate General for Pharmacy and Health Products
Sweden	Dental and Pharmaceutical Board (TLV)
Switzerland	Federal Office of Public Health (FOPH)

Some reimbursement systems contain a specific institution and committee that is responsible for the scientific assessment of the evidence for delivery of a report to a committee or institution responsible for appraisal. There are committees which focus on the scientific assessment of the clinical evidence in Italy and New Zealand. The Technical and Scientific Committee (TSC) in the Italian Medicines Agency provides a classification of the therapeutic innovative value of the medicine. In New Zealand, the Pharmaceutical and Therapeutics Advisory Committee (PTAC) advises on the clinical evidence provided and critically reviews the clinical evidence provided.

There are committees that focus on broader aspects of the assessment and provide a scientific assessment of the clinical and economic evidence in each institution. The committee's members include those with broad expertise including pharmacologists, medical physicians and health economists. These types of committees are established in the SMC called the New Drugs Committee (NDC), the Pharmaceutical Evaluation Board (HEK) in the Federation of Austrian Social Security Institutions (HVB) in Austria, the Pharmaceutical Assistance Commission (CFH) in CVZ in the Netherlands and the Expert Committee in the Pharmaceutical Benefits Board (PPB) in Finland.

The Australian reimbursement system is unique in that two committees advise the body responsible for providing the reimbursement recommendation called the Pharmaceutical Benefits Advisory Committee (PBAC). The PBAC is advised by the Economic Sub-Committee that was established in December 1993 to review and interpret the economic analysis submitted to PBAC, advises on technical aspects of economic evaluations and to provide advice with respect to the analysis submitted by the manufacturer. The Drug Utilisation Sub-Committee (DUSC) of PBAC collects and analyses data on medicine utilisation in Australia provide information on rational use and prescribing and to provide comparisons with other countries of use of medicines (Australian Government, 2011).

4.3.1.2 Evidence and methods of synthesis for assessment

All of the reimbursement systems recommend to the manufacturer the requirement for a description of the medicine's proposed use and pharmacological characteristics and details of the efficacy and safety from the regulatory marketing authorisation. All of the reimbursement agencies require clinical data on the safety and clinical efficacy of the medicine. The differences between the countries relate to the requirements for data on clinical benefit, either summary of the clinical efficacy, clinical effectiveness or a categorisation of the added therapeutic value of the medicine and other factors important In relation to the use of the medicine (Table A4.2). Actual effectiveness evidence is unlikely to be available at the initial reimbursement decision and systems have a variety of ways by which these uncertainties are considered either through economic modelling or the process by which medicines are appraised and reassessed/appraised.

The majority of reimbursement systems require the manufacturer to include a health economic analysis in the submission for the reimbursement of the medicine. A health economic analysis by the manufacturer is mandatory in 17 countries, is optional in Denmark, New Zealand and Switzerland and not required in the initial submission in France, Germany and Spain (Table 4.2).

Table 4.2: Requirement for health economic analysis

Mandatory for medicines	Mandatory for certain medicines	Optional	Not required
Australia	Austria	Denmark	France
Canada	Belgium	Italy	Germany
Finland	Ireland	New Zealand	Spain
Israel	Netherlands	Switzerland	
Hungary	Norway		
Korea			
Mexico			
Poland			
Portugal			
Sweden			
England and Wales			
Scotland			

All of the countries, with the exception of Switzerland, provide guidelines for the submission of economic analyses. There is variation in the types of economic analysis, perspective, comparator definition, costs, discount rates and requirement for sensitivity analysis recommended or required in guidelines for manufacturers submissions The economic analysis guidelines are provided to manufacturers specifically by the body responsible for assessment and/or appraisal of the medicine in most countries and published manuscripts are available in Austria, Denmark, Italy, Hungary and Spain (Table A4.3).

There are different recommendations with regards to type of economic analysis, such as the use of cost-benefit, cost-utility analysis, cost-effectiveness analysis, cost-value analysis and the efficiency frontier. A number of countries specify that cost-benefit analysis maybe presented but many have a preference for a different type of analysis. The majority of countries requesting manufacturers to provide formal health economic analysis recommend cost-effectiveness analysis and cost-utility analysis as the approach to economic analysis. The use of cost-utility analysis is preferred over other types of economic analysis in Australia, Canada, Ireland, Israel, Italy, Korea, New Zealand, Poland, Portugal, Sweden, England and Wales, and Scotland in the manufacturers submissions for new medicines. This may reflect the desirable characteristics of the measure for practical decision-making for the reimbursement of medicines. Exceptions are Germany which recommends the use of the efficiency frontier, Norway which prescribes the use of cost-value analysis and England and Wales which require cost-utility analysis.

In Norway the guidelines provided by the NoMA specify that cost-value analysis should supplement cost-utility analysis provided by the manufacturer (NoMA, 2005). Eric Nord and colleagues introduced the term 'cost-value analysis' to account for the degree of severity of the

disease and produces an equity adjusted cost-utility analysis (Nord et al., 1999). The approach follows two steps where the health gains are estimated using standard quality adjusted life years (QALYs) and step two involves producing weights. The weights are produced from a representative sample of the general population that are required to make person trade-offs between movements that are equal in terms of utility gains but different in terms of the starting utility. The weights are combined multiplicatively with the standard utility data for cost-utility analysis to provide cost-value analysis for what Nord calls 'societal value'. The technique adjusts estimates of cost-utility by considering how bad of the individual would be without the intervention (severity of disease).

The IQWIG convened a panel of experts in 2007 to develop the economic methods for the assessment of technologies in Germany in line with the legal requirement (§ 35b Social Code Book (SGB) V). The panel produced a document on the general methods for evaluating the relation between cost and benefits in 2009 recommending the use of an alternative approach called the 'Efficiency Frontier' in the evaluation of technologies (IQWIG, 2009). The method concerns finding a maximum price at which a medicine in a given therapeutic area should be recommended for reimbursement. The analysis aims to inform the decision-maker about the efficiency of a given medicine in the therapeutic area, but does not attempt to judge whether the condition deserves treatment or the willingness to pay for the medicine. The debate surrounding this methodology is provided in appendix Box A4.1.

The Reorganisation Act of the Medicinal Products Market *"Neuordnung des Arzneimittelmarktes"* (AMNOG) law was introduced on the 1st of January 2011 for the new procedures for reimbursement (Federal Ministry of Health, 2011). The manufacturer will be free to set the price for the new medicine for a maximum of the first year after launch. The manufacturer must submit a dossier of the added therapeutic value and IQWIG maybe commissioned to provide an assessment. The G-BA will provide an appraisal within 3 months and an agreement on price should be made within 6 months with the health insurance funds. If no agreement is reached arbitration committee will set the price for the medicine for the period after 12 months. The manufacturer or insurer can request an economic analysis following the arbitration decision. The IQWIG will produce an analysis using the efficiency frontier which will be complete in a maximum of three years. It would therefore appear that the recent introduction of the regulation has reduced the potential use of the efficiency frontier methodology because the benefits assessment will have been produced including a choice of appropriate comparator rather than all of the comparators for the efficiency frontier (page 16 of the General Methods Guide) and the analysis

will not necessarily be mandatory for setting the maximum price because of the new process (IQWIG, 2009). The practical use of this approach and extent of the use of this approach are yet to be observed.

4.3.1.3 Third party independent assessment of evidence

The processes used by some reimbursement systems do not rely solely on the manufacturer submission, in particular with respect to the review of clinical evidence. Few reimbursement systems' processes provide an independent health economic analysis for new medicines and these are normally provided in special circumstances or in the case of NICE in England and Wales, in the MTA process. There are independent assessments provided in Canada, Germany, New Zealand, Sweden, Netherlands and England/Wales to provide sufficient evidence for decision-making.

The CADTH CDR process for medicines (excluding oncology medicines) in Canada produces a separate independent clinical review of the evidence which draws on aspects of the manufacturer review which includes a systematic search. The review team develops a protocol for the review with inputs from the drug plans, CEDAC committee members and other members. It then designs and conducts an independent systematic review of the evidence from the protocol to supplement any data that has been provided by the manufacturer. The clinical review report is sent to the manufacturer for information. The CDR only provide a critical appraisal of the manufacturer's economic analysis and may provide revised estimates if the model is re-run but do not provide a separate economic analysis (CADTH, 2010).

In Germany the new proposals in the AMNOG law will mean that if requested following arbitration by the manufacturer or the health funds the IQWIG will produce an independent economic analysis called a cost-benefit analysis by IQWIG (although not a conventional cost benefit analysis from an economists perspective) by constructing an 'Efficiency Frontier'. The analysis is provided in a maximum of three years period by the IQWIG. The benefit assessment evaluation is used in the provision of the economic analysis in those medicines demonstrating added therapeutic value using the efficiency frontier and a model may be used to perform this. The assessments may be performed by research organisations that may be subcontracted by IQWIG. There have to date been no formal referrals using this process using the Efficiency Frontier approach but two assessments have commenced which are due to report later in 2011 (IQWIG, 2011b).

In New Zealand, PHARMAC expects to receive an economic analysis within the manufacturer's submission for reimbursement of new medicines and provision of analysis allows the submission to be prioritised earlier. The analysts may amend an economic analysis submitted and will report the manufacturers economic analysis and PHARMACs amended economic analysis with the differences explained between the two analyses. If this is not provided they will undertake an economic analysis and the stage at which this occurs will depend on the resources available and the priority of the new medicine. The process usually forms an iterative assessment process with more details added to the economic analysis as is required for decision-making. The extent of the analysis depends on the timeframes available for decision-making, the impact on the budget (high impact will require more detailed analysis), reliability of the results, extent of the information that is available, the extent of the expected impact of the economic analysis on the reimbursement decision and the availability of health economist resources. The economic analyses are normally published as "Technology Assessment Reports" that follow a template (PHARMAC, 2011d).

In the Netherlands, the CVZ prepares a pharmaco-therapeutic report from the claim of therapeutic value made in the manufacturer submission for outpatient medicines. The pharmaco-therapeutic report is written in consultation with experts and provides a systematic report of the literature for use by the CFH. The CFH make a decision on the added therapeutic value of the medicine using criteria for this assessment and the decision and pharmaco-therapeutic report are published on the CVZ website (CVZ, 2010b)

In England and Wales, NICE uniquely operates a process that provides both an independent clinical review and an economic analysis in the Multiple Technology Appraisal Process (MTA). The MTA process assesses several medicines used to treat the same condition. An independent evidence report is commissioned through the National Institute for Health Research (NHIR) at Southampton to one of nine independent academic centres, which has recently included two organisations that are not University institutions (BMJ Evidence Centre and Kleijnen Systematic Reviews Ltd) (NICE, 2011b). The Assessment group develops a protocol for the assessment after the scope has been prepared. The group will prepare an assessment report that is an analysis of the clinical-effectiveness and cost-effectiveness of the medicines based on a systematic review of the literature, the manufacturers' submissions and advice from clinical experts. The assessment may include a new cost-effectiveness model that is separate from that of the manufacturers and will follow the NIHR template for production of the report. These are normally published as a HTA monograph (NICE, 2009a).

4.3.1.4 Stakeholder consultation on the assessment of evidence

Consultation on the evidence assessment is defined as a stage or set of stages where stakeholders (such as manufacturers, organisations representing healthcare professionals, provincial funders, and national patient organisations) can comment or provide input to the assessment or comment on the draft reimbursement recommendations documentation. This does not include written or verbal appeals that follow after a reimbursement decision has been made. The consultation process was identified through the details and documents provided on each of the countries' websites.

Table 4.3: Consultation on assessment of evidence

Consultation with manufacturer and other stakeholders	Consultation with manufacturer	No documented details of consultation process
Netherlands (CVZ)	Australia (PBAC)*	Finland (PPB)
New Zealand (PHARMAC)	Austria (HEK)	France (HAS)
Norway (NoMA)	Belgium (CRM)	Israel (MTA)
Sweden (TLV)	Denmark (DMA)	Italy (AIFA)
England (NICE)*	Ireland (NCPE)	Hungary (TAC)
Scotland (SMC)	Korea (HIRA)	Spain (Ministry of Health)
Germany (G-BA)	Poland (AHTAPol)	Switzerland (FOPH)
Canada (CADTH CDR)*	Portugal (INFARMED)	Mexico (GHC)
*Multiple stages of consultation on the assessment of evidence.		

There is wide variation across countries with respect to consultation with stakeholders in the reimbursement process for new medicines. There were countries where the manufacturer and other stakeholders have the opportunity to comment on the assessment, countries where the manufacturer only has the opportunity to comment and those countries where there is no documentation of the consultation process (Table 4.3). There are some countries that only provide the manufacturer with the opportunity to consult with respect to providing comments and clarifications on the assessment report prepared for the decision-making (Austria, Belgium, Denmark, Ireland, Korea, Poland, Portugal). In Belgium and Denmark the manufacturer is only given the opportunity to comment if the draft recommendation is more restrictive than that requested in the original submission.

There are then those countries that include other stakeholders in addition to the manufacturer in the reimbursement process. The type of stakeholders that are consulted depends on the nature of the funding system and number of levels of decision-making. In New Zealand medical groups and other interested parties are able to comment on the assessment report prior to the appraisal and similarly interested parties can comment in Norway. The most sophisticated processes for

stakeholder consultation appear to be operating in Canada, England & Wales, Netherlands, Scotland and Sweden.

In Canada the CDR process enables the manufacturer to comment on the review report produced by the CDR team and also have the opportunity to comment on the CEDAC recommendations and request reconsideration. The CADTH added a patient group input to the CDR process in May 2010 (CADTH, 2011b). This integrates comments from patient groups in a formal process for organised patient groups to be consulted during the process. There is a template provided on the CADTH CDR website for patient input submissions. The patient input submission is included in the report prepared for recommendations performed by the CEDAC to consider the patient perspective on the drug's impact in comparison to other available therapies.

The reimbursement process operated by the NICE in England has many stages in which a wide variety of stakeholders are consulted. The documents consulted on differ between the Single Technology Appraisal (STA) process and Multiple Technology Appraisal (MTA) process. The process defines two different types of stakeholders; consultees and commentators. Consultees include national groups representing patients and carers, bodies representing health professionals, manufacturer (s) or sponsor (s) of the technology in development, the Department of Health, the Welsh Assembly Government, Specialised commissioning groups. Primary care trusts and local health boards. Commentator organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre, research groups working in the area and other groups (NHS confederation, BNF etc). A wide variety of consultees and commentators are identified at the start of the process and may provide comments on the draft scope for the guidance. The consultees (excluding the manufacturer) are invited to provide an evidence submission with information about the potential clinical and cost-effectiveness of a medicine using a template provide on the website. The Patient and Public Involvement Programme (PPIP) offer support (financial and non-financial) to patient organisations for their submissions to the process. NICE will release the manufacturer's submission (STA process only), statements from non-manufacturer consultees (STA process only), clarification letters (STA process only), Evidence Review Group Report and pre-meeting briefing (STA process only), assessment protocol (MTA process only), Evaluation report (MTA process only) to consultees and commentators with confidential information so long as they have signed a confidentiality agreement. The appraisal meeting includes nominated clinical specialists (usually two) and patient experts (usually two) and NHS commissioning experts (two) to attend and also prepare written statements. The manufacturer can have two representatives that attend to respond to any

questions from the committee. There is a session open to the general public and a closed session of the meeting in which commercial in confidence information is considered prior to formulating the recommendation. The consultees and commentators have four weeks to comment on the Appraisal Consultation Document (ACD) which is prepared as a draft decision when more restrictive than initially proposed by the manufacturer in the STA process and always prepared in the MTA process (NICE, 2009b, NICE, 2009a).

In the Netherlands the manufacturer, clinicians, patient associations and insurers are given the opportunity to comment on the draft reports produced by the Pharmaceutical Assistance Commission prior to this being provided to the CVZ board that produce the final reimbursement decision. There is a separate Appraisal Committee (ACP) that takes matters of social value judgements into account for medicines on an ad hoc basis (van Halteren, 2011).

Health boards are consulted in addition to external clinical experts who answer 5 questions on each assessment by the SMC in Scotland. The SMC encourages members of the public to be involved in the process and has a Patient and Public Involvement Group (PAPIG) that ensures the patient and carer perspective are always taken into account in the reimbursement process. Patient interest groups can provide a formal patient evidence submission in Scotland which describes the experience of those that suffer from the health problems that the medicine treats. These are presented in the SMC board meetings. There is a template provided on the SMC website for the patient group evidence submission (SMC, 2011c).

The TLV in Sweden consults with the manufacturer at various stages. The TLV will clarify the submission with the manufacturer and obtain any further information. The TLV may arrange a meeting with the manufacturer to do this if necessary (LFN, 2008). The documents that include the assessment and proposed decision are sent to the manufacturer for the opportunity to correct any factual errors and to comment on the justifications provided for the proposed decision. The Pharmaceutical Benefits Group for the County Councils are given the opportunity to provide comments and put forward any issues with the documentation and proposed decision. Patient groups are represented in the process by two members of the Executive Board that provide the decision having involvement with patient organisations in the past (LFN, 2007).

4.3.1.5 Communication of assessment of evidence

The communication to stakeholders involves two aspects that include the involvement in the assessment (ex ante) and the communication of the assessment and decision (ex ante). The first type of communication with stakeholders was dealt with in the previous section. This section

considers the communication of the assessment. The communication of the manufacturer's submission and assessment varies considerably across the reimbursement systems from no publication through to almost complete publication of all assessment documentation used to inform the reimbursement decision-making (Table A4.4). There are many reimbursement systems that do not provide any details of the assessment provided by the agency or body in Finland, Israel, Italy, Hungary, Mexico, Portugal, Spain and Switzerland. In Korea, the HIRA does not provide the HTA report on the website but this is made available to the manufacturer throughout the process. Austria only provides reasons for the decisions on the website when these deviate from the manufacturers proposed use but do not provide the assessment report or the manufacturer submission.

There are reimbursement bodies and institutions that do not provide the manufacturer submission but provide some details of the assessment and these are included in the appraisal and deliberation documentation that provides justification for the recommendation:

- In Australia these can be found in the PBAC Public Summary Documents by Product which includes details of the cost-effectiveness and clinical effectiveness considerations;
- In Belgium the CRM call this the Evaluation Report;
- In Canada CDR call this the Canadian Expert Drug Advisory Committee (CEDAC) Final Recommendation;
- In Denmark these are called the Minutes of the Reimbursement Committee;
- In France the HAS document is called the Summary of Opinion;
- In Ireland an NCPE Economic Evaluation is provided;
- In the Netherlands the CVZ report is called the Commission for Pharmaceutical Assistance (CFH) report;
- In Norway these are called the Minutes of the Blue Prescription Committee;
- In Poland these are called the Position of the Consultative Council;
- In Sweden this is called the Decision document; and
- In Scotland this is called the SMC advice document.

The PHARMAC agency in New Zealand provides some Technology Assessment Reports (TARs) for a few of the reimbursement decisions but does not publish all of these on the website because of the confidential nature of the submissions. The manufacturer submission is not provided alongside this information (PHARMAC, 2011d). The agency also provides the minutes of the Pharmacology and Therapeutics Advisory Committee that include some discussion around the assessment performed.

There are two systems that include elements of the manufacturer submission on the website which are the G-BA in Germany and NICE in England. The G-BA has a tracking system on the website for the status of early benefit assessments with the summary documentation, supporting reasons for the decision and the decision text. The details of the manufacturer submission are included but excluding any of the commercially in confidence information. The IQWIG also include the early benefits assessment on their website when they have been requested to conduct this on behalf of the Federal Joint Committee.

NICE in England provide a number of documents in relation to the assessment of the medicine. A full manufacturer submission is provided on the website for the STA process excluding any confidential information and appendices if these include information that is commercially sensitive. The executive summaries of the manufacturer(s) submission(s) are provided for the MTA process. Any clarifications made with the manufacturer(s) for both of the processes are published on the website. There are date stamps provided on the website for when each of the documents was uploaded. The Assessment group report and Evaluation Report (MTA) and Evidence Review Group report and Pre-meeting briefing (ERG) are provided for the appraisal committee meeting and consultation. Any other statements from stakeholders are also provided on the NICE website.

4.3.2 The Decision

4.3.2.1 Decision process and institutions

The appraisal stage involves value judgements about the evidence and its robustness and any other factors that are explicitly specified for consideration. The reimbursement systems vary in the number of institutions involved in the appraisal of medicines. The systems can be categorised by those that have established a separate institution that provides the final reimbursement decision or a separate institution that provides advice to the Ministry of Health. There are then reimbursement systems where a committee in the Ministry of Health is responsible for appraising medicines and either providing a final decision or advisory decision to the Minister of Health. There are other systems where multiple institutions are responsible for different stages of the appraisal and final decision. All of the OECD reimbursement systems in this study contain a committee that appraises the evidence using country specific criteria and that is either responsible for the final reimbursement decision or provides an advice to the final decision-maker (Minister of Health or other decision-making body).

A separate institution is responsible for the appraisal, using a committee to determine the final reimbursement decision in 11 of the countries. There are committees responsible for the appraisal of evidence and other factors in each of these countries' institutions and the names of these are described in Table 4.4.

Table 4.4: Country and reimbursement committee

Country (agency)	Committee
Austria (HVB)	The Medicines Evaluation Committee (HEK)
Denmark (DMA)	Reimbursement Committee
England & Wales (NICE)	Technology Appraisal Committee (TAC)
Germany (G-BA)	Federal Joint Committee
Hungary (NIHFA)	Technology Appraisal Committee (TAC)
Ireland (HSE)	Products Committee
Italy (AIFA)	Pricing and Reimbursement Committee and Executive Board
Mexico (GHC)	General Health Council
New Zealand (PHARMAC)	PHARMAC Board
Norway (NoMA)	Blue Prescription Board
Sweden (TLV)	Dental and Pharmaceutical Board

There is a separate institution which includes a committee which appraises the medicine and provides an advisory recommendation to the Minister of Health in 6 of the countries. These systems involve a two stage appraisal where the agency provides a first appraisal and the Ministry of Health provides the final appraisal and decision. The Ministry of Health may draw on other institutions such as the pricing authorities in Australia called the Pharmaceutical Benefits Pricing

Authority (PBPA) and the Economics Committee (CEPS) in France. The other reimbursement systems committees that provide the two stage approach to appraisal are the CVZ Board in the Dutch Health Insurance Board (CVZ), the Consultative Council in the Agency for Health Technology Assessment in Poland (AHTAPol), INFARMED Board in INFARMED and the Drug and Reimbursement Committee (DREC) in the Health Insurance and Review and Assessment Service (HIRA) in Korea.

A department or committee in the Ministry of Health is responsible for appraising medicines and providing the final reimbursement decisions in Belgium, Israel, Finland, Spain and Switzerland. A department called the Medical Technology Administration of the Ministry of Health and Finance has a committee called the Public National Advisory Committee (PNAC) which provides recommendations for which the government must approve in Israel. A Ministry of Health sub-section is responsible for the reimbursement appraisal and final decision called the Directorate General of Pharmacy and Health Products (DGHP) in Spain and the Federal Office of Public Health (FOPH) in Switzerland. Both departments are advised by a committee called the Inter Ministerial Price Commission in the DGHP and the Federal Drugs Commission in the FOPH. The Ministry of Social Affairs and Health appoints a committee called the Pharmaceutical Benefits Board that is responsible for appraising and providing the final reimbursement decision for medicines in Finland. Similarly in Belgium, the Ministry of Health and Social Affairs has a committee called the Committee for Reimbursement of Medicines (CRM).

The reimbursement systems in Canada and Scotland contain a two stage appraisal performed by two separate institutions. In Canada the CEDAC provides an appraisal and recommendation for the Drug plans. The Drug plans will then provide an appraisal given local priorities and provide a final decision for inclusion in the plans formulary. Similarly, in Scotland the SMC Board provide advisory recommendations for the Health Boards. The Health Boards provide an appraisal and take the final decision to include the medicine in the Board's formulary.

4.3.2.2 Stakeholder involvement in deliberations

The appraisal of the evidence was defined as the act of judging and valuing a medicine using stated criteria prior to the formal reimbursement decision for use or continued use in practice. The committees and types of stakeholders involved in deliberations were identified from the websites of the institutions conducting the appraisal of medicines for reimbursement. Table A4.5 reports the types of stakeholders that are members of each committee. Committees that

appraised the evidence were identified in all reimbursement systems with the exception of Spain where the appraisal and reimbursement decision are made by the Ministry of Health.

The size of reimbursement committees varied from between 5 members for the PHARMAC board in New Zealand to 38 members of the SMC in Scotland. There are variations in the types of stakeholder included in the reimbursement committees across the countries. All of the committees included medical practitioners which either included specialists or general practitioners with the exception of TLV in Sweden. Many of the committees included either a pharmacologist or a pharmacist with the exception of committees in Denmark, Germany, Israel, Mexico, Poland, Portugal and Spain.

Health economists are represented on the reimbursement committee in just over half of the 17 OECD countries reimbursement committees that require an economic analysis in the manufacturer submission. Health economists are members of the committees in Australia (PBAC committee), Finland (PPB committee), Ireland (NCPE committee), Israel (PNAC committee), Italy (CPR committee), on the scientific committee in Netherland's (CFH committee) but not in the appraisal committee, Korea (DREC committee), Sweden (LFN committee) and England and Wales (TAC). The health economic representation in Scotland is provided in a separate committee. The SMC committee has a sub-committee called the New Drugs Committee that includes health economists. The committee reviews the economic analysis presented from a purely scientific perspective and prepares advice to the SMC committee. In Germany a separate institution called IQWIG provides the Federal Joint Committee with an economic analysis on request following arbitration but health economists are not present in the reimbursement committee.

Patients are represented in committees in Australia (PBAC), Germany (G-BA), Korea (DREC), Sweden (TLV), Scotland (SMC) and England and Wales (NICE). In Scotland, patients and carers are represented in by a Patient and Public Involvement Group (PAPIG) which consists of 6 members. Public Involvement Officers are represented on the SMC committee that makes the final decision for inclusion. Similarly, NICE has a PPIP to involve patients and carers in developing the NICE guidance. The committees contain at least two lay members either patients or members of the public. Patient experts are also nominated to attend an appraisal meeting to provide their personal knowledge and experience of the condition. Members of the public are represented on the CDR committee in Canada, Public National Advisory Committee in Israel and the Federal Drugs Commission in Switzerland.

The Pharmaceutical industry is represented in the SMC committee in Scotland, the CRM committee in Belgium and NICE committee in England. Then industry representatives are consultative members in the CRM but do not have any rights to vote in the reimbursement decisions.

There are representatives of the insurers in many of those systems where the predominant funding system is that of social insurance. The other members represented across some of the committees included members of the Ministry of Health, other government department representatives, regional and health care planners and in a few representatives of the agency or institution.

4.3.2.3 Stated factors in the appraisal of evidence

The formal factors stated in the documentation provided by the reimbursement body or agency documentation provided on their website were considered in a table and grouped by types of factors. There were 41 factors identified across countries of which 17 were used within 2 or more countries and 24 were factors considered exclusively within one country. These factors were grouped into three categories clinical evidence factors, economic evidence factors and non-evidence factors (Table A4.6).

Appraisal of clinical factors

The reimbursement systems all consider the medicines with respect to the clinical value/benefit focusing on different criteria for formal consideration depending on the processes of pricing and reimbursement. The agencies all require an appraisal of clinical factors which may either be by considering clinical-effectiveness, added therapeutic value or benefit, clinical efficacy or country specific criteria such as clinical usefulness. There are a number of criteria some of which are similar across countries, some overlapping and used to appraise the available clinical evidence.

Clinical-effectiveness factor (some countries make the point of when this data is available)

Clinical effectiveness is a formal criterion for medicines in Australia, Canada, Ireland, Netherlands, Mexico, Norway, New Zealand, Poland, Sweden, England and Scotland. The International Network of Agencies for Health Technology Assessment (INAHTA) defines clinical effectiveness as follows (INAHTA, 2011b):

"The extent to which a specific intervention, procedure, regimen, or service does what it is intended to do under ordinary circumstances, rather than controlled conditions. Or more specifically, the evaluation of benefit to risk of an intervention, in a standard clinical setting, using outcomes measuring issues of importance to patients (e.g. ability to do daily activities, longer life, etc.)."

The definitions across these nine countries are similar but not identical. The definitions provided in these reimbursement systems generally relate to the benefit with respect to health gain of using the medicine in clinical practice within each specific country (Table A4.7). The clinical effectiveness evidence is used in all of these countries to inform the cost-effectiveness analysis. The cost-effectiveness analysis is required from manufacturers in the submissions to all these countries with the exception of New Zealand where it is optional but the agency will provide the analysis if this is not provided by the manufacturer.

Added therapeutic value/Benefit factor

The second most widely considered factor by the reimbursement systems is that of added therapeutic value or benefit. Eichler et al. highlights that payer bodies use the term "added therapeutic value" frequently but there is no widely accepted definition (Eichler et al., 2010). The authors use European Medicines Agency Working Group with Patient Organisations (EMWGPO) definition. "A new medicinal product can be said to have added therapeutic value if sound clinical data show that it offers patients better efficacy, and/or better safety and/or simpler administration, than existing alternatives."

The added therapeutic value or benefit factor is used in 10 of the countries Austria, Belgium, Denmark, Finland, France, Germany, Italy, Netherlands, Spain and Switzerland. The added therapeutic value is defined differently across these countries. The reimbursement bodies in Denmark, Finland, and Spain provide a broad statement on the meaning of Therapeutic Value which would appear to be consistent with the EMWGPO definition. Added therapeutic value is defined more widely in Belgium, France, Switzerland and Germany including other aspects of value (applicability, effectiveness and appropriateness). The CVZ in the Netherlands provides the widest definition including efficacy, effectiveness, side effects, applicability, convenience, experience and quality of life. Germany defines this as any benefit demonstrated by any patient related outcome. The definitions provided in Austria focus on the efficacy and perception of innovation and similarly in Italy, the therapeutic benefit is considered as part of a composite innovation assessment for the level of 'therapeutic innovation' defined as either important,

moderate or modest (Table A4.8). The therapeutic innovation level is decided by an algorithm that takes into account the availability of existing medicines and the extent of the therapeutic benefit provided by the medicine.

The factor is appraised descriptively in Denmark, Finland and Spain and in the other six countries is defined as a categorical scale. The scales have between 3 and 6 levels and depend on the committee's judgement of the extent of the therapeutic value of the medicine. In Belgium, Netherlands and Italy the medicines are categorised on three levels that are defined differently with respect to either type of medicine and the level of the benefit. The Swiss categorisation includes a 5 levels focusing on the level of therapeutic benefit and the economic savings by using the medicine, Level 1: therapeutic breakthrough, Level 2: Therapeutic progress, Level 3: Savings compared to other medicines, Level 4: No therapeutic progress and no savings, 5: Inappropriate for social insurance. The French, Swiss and German scales for categorisation of therapeutic value are similar with Germany having an additional sixth category of medicines with less therapeutic value than the appropriate comparator treatment. The categorisation used in Austria focuses on a 6 point scale with categories based on the level and extent (patient subgroups or wider population) of the therapeutic value.

Other clinical value factors

The deliberations in Hungary consider clinical efficacy, the extent to which an intervention does more good than harm under ideal circumstances, alongside the cost-effectiveness when appraising the medicine. Israel specifies two criteria to consider when deliberating on the clinical evidence; the degree of extension of quality and length of life. Korea specifies clinical usefulness as the criterion considered in the deliberations for reimbursement and this includes an assessment of the therapeutic benefit (superior or inferior to other relevant comparators), available alternatives and severity of disease. This is not measured on a categorisation scale.

Additional clinical factors

Australia has other formal stated criteria in addition to the clinical effectiveness which are likelihood of developing resistance to the medicine and the ability to target those patients that are most likely to benefit from the medicine. NICE in England and SMC in Scotland similarly consider those most likely to benefit and whether data on Health Related Quality of Life (HRQOL) sufficiently capture all of the benefits to patients. SMC has two further additional criteria to formally consider; the degree of extension of life and quality and whether the medicine provides a

bridging to another definitive therapy. Norway additionally considers whether the patients suffer from prolonged treatment or risk of prolonged treatment.

Appraisal of economic evidence factors:

Cost-effectiveness analysis in the form of cost-effectiveness, cost-utility or cost-minimisation is a stated decision-making criterion in 20 of the 24 OECD reimbursement systems. The other four countries' predominantly rely upon an initial assessment of the added therapeutic value provided by the new medicine amongst other factors. The German committee does not initially consider economic analysis but may request IQWIG to perform an alternative form of analysis – the efficiency frontier analysis on request of the manufacturer or the health funds. The French, Spanish and Swiss reimbursement systems do not use any formal economic analysis in the decision-making for new medicines. In France, the reimbursement agency does not perform economic analysis for new medicines but does have a department in HAS called the "Assessment of Health Economics and Public Health" (SEMESP) that performs economic evaluation. The department has produced 28 health economic assessment reports on a range of technologies, including a few medicines (HAS, 2011b).

4.3.2.4 Cost-effectiveness thresholds

The variation in the extent of the use of cost-effectiveness in decision-making across countries depends upon the acceptability of the assumptions and applicability of the values implied by the methodology. Cost-effectiveness analysis can be used to determine the most efficient allocation of resources after the budget has been allocated to the health sector (rather than describing the overall budget which is consistent with the efficient resource allocation across sectors). The efficiency criteria in this approach depend on the type of outcome used in the approach – the QALY approach is a commensurate measure of health benefit that can be applied across technologies and relates an individual's length of life and an individual's quality of life (McGuire and Drummond, 2001). The general objective assumed is one of maximising the level of health benefits given the exogenously determined budget. The simplest form of QALY calculation is to aggregate the unweighted QALY's and this assumes that a QALY is regarded as equal value to everybody (Williams, 1996). Of course this is not the only means of aggregating QALYs and these may be weighted in a more complex calculation to take into account of characteristics of the patients and distributional principles.

The central measure produced by cost-effectiveness analysis is the incremental cost-effectiveness ratio which represents the difference in costs between the two interventions divided by the

difference in effects. The measure of health effect can be expressed in a number of ways such as natural units, life years gained or quality adjusted life years (QALYs). The use of cost-effectiveness analysis does not describe which interventions should be funded and requires a decision on the cut-off point at which interventions are judged as cost-effective or not cost-effective. Weinstein and Zeckhauser introduced the first discussion of the critical cut-off point in a study on public economics (Weinstein and Zeckhauser, 1973). The authors discussed the computation of a "critical ratio" or λ cut-off in a constrained optimisation problem that became known as the "threshold" throughout the health economic literature. The determination of a threshold value relies on a number of assumptions such as a fixed budget, maximisation of health, perfect divisibility and constant returns to scale of all programs (Weinstein and Zeckhauser, 1973). The threshold has been further described by some authors as "hard and soft threshold" (Eichler et al., 2004). The "hard threshold" is where cost-effectiveness is the single criterion which leads to automatic acceptance or rejection of the medicine and a "soft threshold" where cost-effectiveness is taken into account alongside other societal preferences with a lower and upper boundary or in other words a threshold range.

Health Economists agree that the threshold value is an empirical question. There is disagreement between health economists by which the threshold value should be estimated. Welfare economists argue that social benefits should be maximised and willingness to pay would be the best means to estimate this value. Whereas extra-welfarist's argue that the marginal productivity measured by the benefit gained from extra expenditure (cost per QALY of least efficient treatment) is the correct approach in budget constrained systems (Hutton, 2011). This has practical implications for each of the systems judgement of the cost-effectiveness threshold and the nature of the assumptions to the context of decision-making.

A strict threshold cut-off point or "hard threshold" for below which a medicine is considered cost-effective and above which is not recommended for use is not used in practice in any of the OECD countries reimbursement systems (Table A4.9). An explicit threshold range – where the agency or institutions responsible for decision-making have stated the threshold in the documentation provided for decision-making, operates in Scotland, England and the Netherlands for informing decision-making (CVZ, 2011a, NICE, 2008, SMC, 2011b). The ranges are used with respect to other stated factors that are considered important in each of the respective decision-making processes.

There have been studies conducted in the medicine reimbursement systems of Australia, Canada, Ireland, Korea, Sweden that identify an implicit threshold through past decisions made in these countries. An implicit threshold is where a study that may be conducted independently from the

institution responsible for decision-making identifies a threshold value retrospectively. This may not be the actual threshold used formally by the committees responsible for decision-making but describes past decisions and the estimates of cost-effectiveness informing the reimbursement decision-making.

The other 12 countries using economic analysis either do not refer to an explicit threshold range, state that an explicit threshold range is not required because of other factors in decision-making (New Zealand) or studies have not been performed to find an implicit threshold because of a lack of information. The previous sections of this thesis on communication of the assessment and appraisal of evidence, show that eight of the twelve countries do not provide this information publically which explains why no studies have been conducted to estimate an implied threshold. The lack of a threshold range in these countries may be explained by the prominence of other factors in decision-making (clinical evidence, budget impact and price), the use of economic evaluation in determining the price rather than the reimbursement status and the early development of the use of economic analysis in the reimbursement systems.

Explicit Cost-effectiveness threshold ranges

England and Wales, NICE:

The use of a cost-effectiveness threshold range was not made explicit until five years after the setup of NICE where recommendations are mandatory for use in the NHS. In 2004, an Education and Debate article was written in the BMJ by Sir Michael Rawlins and Anthony Culyer that stated that NICE rejected the use of an absolute threshold for judging the level of acceptability of a technology in the NHS in England and Wales on the basis of four reasons which were: no empirical basis for deciding how this should be set, there may be exceptions where a threshold should be ignored, efficiency is not the primary priority over other objectives and price competition would be discouraged. The article stated: "The main considerations in making judgments about cost-effectiveness for ratios of £25,000-£35,000/QALY are: The degree of uncertainty surrounding the estimate; The particular features of the condition and population using the technology; The innovative nature of the technology; When appropriate the wider societal costs and benefits; When appropriate, reference to previous appraisals." (Rawlins and Culyer, 2004).

NICE has gained experience in using economic analysis as a central criterion in decision-making and evolved the use of methods in the process and transparency. The NICE methods guide published in 2004 stated that the threshold range to be £20,000 - £30,000 per QALY (NICE, 2004).

The range takes into account similar considerations as those made by Rawlins and Culyer for those technologies above a most plausible ICER of £20,000 but dropped with reference to previous appraisals. The methods guide in operation by NICE today includes a similar threshold range and there are differences in the stated other considerations (NICE, 2008).

"Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the technology as an effective use of NHS resources will specifically take account of the following factors:

1. The degree of certainty around the ICER. In particular, the Committee will be more cautious about recommending a technology when they are less certain about the ICERs presented.
2. Whether there are strong reasons to indicate that the assessment of the change in health related quality of life (HRQL) has been inadequately captured, and may therefore misrepresent the health utility gained.
3. The innovative nature of the technology, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the QALY measure."

The case must be explicit about the other factors when the ICER lies between the £20,000 to £30,000 range and must make a stronger case using these factors when the ICER is above a most plausible value of £30,000 per QALY gained. There has been an evolution in the guide to use of cost-effectiveness by NICE and the current 2008 guide appears to have tightened the criteria and definitions of each factor, possibly in an attempt to guard against the risk of benefit double counting. For example, the use of the cost-effectiveness criteria already rewards the manufacturer for the health benefit in the form of a premium price and to again consider the innovative nature of the technology would run the risk of double counting the benefit. This is unless the innovative nature of the technology provides benefits beyond the QALY measure. These have been proposed by some authors as larger dynamic benefits to society (Goldman et al., 2010), but examples are infrequently provided and these benefits are not clearly elucidated. Other benefits have been quoted as important such as severity of illness, unmet need and reduced care giver burden but the separate consideration of all of these remains controversial.

These issues have been explored by the NICE Citizens Council and a report commissioned by NICE, published in 2009 (Kennedy, 2009). NICE established a Citizens Council in 2002, which is made up

entirely of members of the public to provide an advisory function with respect to the social value judgements made in the guidance and guidelines produced by NICE. NICE defines social value judgements to "relate to society rather than to basic clinical data: they take account of the ethical principles, preferences, culture and aspirations that should underpin the nature and extent of the care provided by the NHS" (NICE, 2005). The Council has produced 14 reports as of the January 2011 and these include reports on innovation, rule of rescue, severity of illness, clinical need and departing from the threshold. The views of the council were taken in 2009 with respect to what makes an innovation valuable and the majority of citizens ranked increase in quality of life (26 out of 28) and other innovations may be developed from it in the future (11 out of 28) and a large number of people will benefit from it (10 out of 28), (NICE, 2009d).

The Council acknowledged that there were many different definitions of severity of illness – some members defined this as a threat to life, the extent to which they can no longer carry on living life as normal, extent of suffering and presence of intolerable symptoms, illness on top of an impaired state of health and illness of long duration. However, the Council concluded 24 to 2 that the NICE advisory bodies should take into account of severity of illness and this should be taken into account alongside the QALY estimate rather than incorporating this within weights in the QALY estimate.

In early 2009, supplementary guidance was published by NICE to take into account treatments at the end of life (NICE, 2009c). This was introduced to justify the use of medicines that are recommended when the estimate of cost-effectiveness was above a most plausible range. The supplementary guidance was produced with reference to the work of the Citizens council and previous appraisal committee decisions. The term end of life describes those technologies where the (i) the treatment is indicated for patients with a short life expectancy, normally less than 24 months and; (ii) there is sufficient evidence to indicate that the treatment offers extension to life, normally of at least an additional 3 months, compared to current NHS treatment, and (iii) the treatment is licensed or otherwise indicated, for small patient populations. NICE does not operate a separate threshold range for those technologies meeting this criteria but considers the weight that must be applied in order that the most plausible ICER falls within the current threshold range used by NICE.

The Kennedy report was commissioned to consider issues of innovation and other benefits of medical technologies later on in 2009 (Kennedy, 2009). The report recommended that NICE

should continue to use the explicit ICER approach but should consider relevant benefits. The report considered there may be some elements of other benefits such as severity of the illness and end of life that may not be taken into account in the current system and recommended that further research was undertaken to determine whether this was the case. The introduction of the new policy on value based pricing at the end of 2010 may result in criteria to weight a basic threshold depending on other considerations of benefit (Department of Health, 2010). The proposals include a basic threshold which would reflect the opportunity cost of the use of the new medicine and then three other criteria where a higher threshold would be given for; (i) Burden of illness – those disease with unmet need or that are severe would be given a higher threshold; (ii) Therapeutic innovation in comparison to other medicines would be provided with a higher threshold and (iii) Wider societal benefits. The final system will be introduced in 2014 and the final criteria are yet to be confirmed, including the value of the basic threshold.

Scotland, SMC:

The use of economic analysis is a central criterion in the SMC decision-making that provide advisory recommendations to the Health Boards in Scotland. The SMC does not operate a formal threshold and states that the cost per QALY is only part of a wider judgement of the value of a new medicine. The guide notes the importance of being transparent and explicit about the principles of decision-making but also must have flexibility to account for each individual particular case. The SMC makes note of the sections of the NICE guidance that state a plausible range for the threshold of between £20,000 to £30,000 which were reported in the previous section for England and Wales.

The guide to manufacturers explicitly refers to other factors that are referred to as 'modifiers' of the decision when the committee considers the estimate of cost-effectiveness to be robust (SMC, 2011b). The modifiers that are considered for approval of a high cost per QALY orphan medicines are:

1. Evidence of substantial improvement in life expectancy (with sufficient quality of life to make the extra survival desirable). Substantial improvement in life expectancy would normally be a median gain of 3 months;
2. Evidence of a substantial improvement in quality of life;
3. Evidence that a subgroup may derive specific extra benefit and the medicine can be targeted to that subgroup;
4. No available therapeutic options provided by the NHS for the disease;

5. Potential bridging to another alternative therapy in a defined group of patients;
6. Licensed alternative to an unlicensed therapy in Scotland for which the unlicensed therapy is the only option for the specific indication.

The SMC committee may consider other special issues highlighted by the manufacturer, clinical experts or patient interest groups that do not fall into the other decision modifiers that are identified above. The VBP consultation by the Department of Health in England covers the SMC so it will be affected by the changes to the pricing and reimbursement system.

The Netherlands, Dutch Health Insurance Board (CVZ):

The principle of cost-effectiveness in the form of cost-utility analysis is one of four criteria used in the appraisal of medicines by the CVZ Board. The decision-making process separates the process for inpatient and outpatient medicines and the functions of appraisal and assessment. The assessment is provided by the CFH committee and the appraisal is provided by the CVZ Board and Appraisal Committee (ACP). The appraisal of economic analysis is only performed for those medicines that demonstrate an added therapeutic value and these are called class 1B medicines. The Board provides advice to the Minister of Health, Welfare and Sport on the basic package of care to be included in the social health insurance. The Board can request consideration of the social impact by the Appraisal Committee (ACP) which was setup in 2008. The cost-effectiveness criterion must be weighted up in relation to the three other criteria which are necessity – whether the form of care delivers what is expected of it, effectiveness – whether the form of care delivers what is expected of it and feasibility – is inclusion in the package feasible, now and in the long term (CVZ, 2010b).

The threshold has been made explicit by the Council for Public Health and Health Care (RVZ) that provides independent advice to the government on public health and care. The RVZ suggested that the cost-effectiveness should be weighted according to necessity in terms of burden of disease through a range or 'bandwidth'. The range varies from €10,000 for a limited burden of disease up to €80,000 for an extremely severe burden of disease (RVZ, 2006). These judgements were made on a number of observations including information from past decisions published for NICE in England and Wales (Devlin and Parkin, 2004). However, this has not been explicitly endorsed by the Ministry of Health, Welfare and Sport.

A recent background study published by the CVZ provides guidance to the ACP on the meaning of cost-effectiveness in the appraisal in relation to the other three principles (CVZ, 2011a). The report was commissioned because of the lack of clarity with respect to the cost-effectiveness

criterion in decision-making. The report describes a list of factors that may be considered when weighting the role of cost-effectiveness in decision-making. Although the background study is not binding on the appraisal committee, it should be viewed as guidance for the criteria that are used. The table has been reproduced from the report (Table 4.5).

Table 4.5: CVZ criteria that affect the interpretation of cost-effectiveness

Criteria that affect the interpretation of cost-effectiveness	Increase the leniency with respect to the cost-effectiveness requirement	Make the cost-effectiveness requirement stricter	Should not be included
High burden of disease			
Rareness			
Informal care (positive effect)			
Public health risk			
Little overlap with health care domain			
High budget impact			
Future medical costs not included			
Unsuited to insurance because of high prevalence			
Unsuited to insurance because of excessive patient influence on the dose			
Uncertainty about the appropriateness of the intervention			
Lifestyle/high risk behaviour			
Age, gender, ethnicity, sexual preference and social economic status			

Source: (CVZ, 2011a): Table. Criteria that play a role in assessing cost-effectiveness)

The report stated that there is no threshold ceiling/cut-off point because there are other arguments in addition to cost-per QALY, to prevent manufacturer's strategic behaviour and a lack of consensus on how the price per QALY ought to be determined (a normative framework). However, it is suggested that many interventions lie within a range with a median value of €40,000 per QALY. The report states: 'CVZ has set up a committee, the ACP, to examine per intervention, whether the value of the package principle 'cost-effectiveness' counterbalances the three other package principles (necessity, effectiveness and feasibility) and other possible arguments. In other words the committee does not determine cost-effectiveness, but assesses it with respect to all relevant arguments'.

The criteria used in decision-making may relax the strictness of the cost-effectiveness criteria in the case of high burden of disease, rareness of condition, positive effect on informal care and when the condition is a public health risk. Burden of disease was not defined specifically under necessity because CVZ are yet to define this but the report refers back to the definition produced by the RVZ called 'proportional shortfall'. This makes a trade-off between the goals regarding equality in total and future health. It takes aspects of the fair innings argument that the size of the health gap is important but also considers the no treatment (severity) QALY expectation (Stolk et al., 2005). There are then criteria that are considered to make the cost-effectiveness stricter when there is uncertainty about the appropriateness of the medicine. High risk behaviour and

certain patient characteristics should not be included in the interpretation of cost-effectiveness. The CVZ report suggests that there is a lack of clarity by which the budget is limited but suggests that there are a number of measures that restrict budget growth. The assumption of a limited budget will be at the discretion of the committee and states 'Cost-effectiveness could play a more prominent role if the committee feels that the budget growth is limited, than if the committee feels that budget growth is still possible. In the latter case, other arguments than cost-effectiveness will gain the upper hand.'

The appraisals of inpatient medicines follow a different process with respect to the appraisal of the economic analysis. The process was amended on the 1st of December 2010 and there is no initial analysis or appraisal of the cost-effectiveness at launch of the medicines included for hospital inpatient use (van Halteren, 2011). Those medicines that are either orphan medicines or expensive hospital medicines (at least €2.5 million to budget after 3 years) have provisional coverage (conditional coverage) for a period of four years and are initially appraised with respect to therapeutic value and budget impact. A proposal for outcomes research is produced. In this period data is collected in practice for the effectiveness of the medicine and is cost-effectiveness in usual practice. The economic model for real cost-effectiveness should be completed by the four year reassessment process. This is then appraised with consideration for the four principles referred to previously. The results of the first real cost-effectiveness assessments are due to be published at the end of 2011.

Implied Cost-effectiveness threshold ranges:

The documentation and search of the literature identified those reimbursement systems that do not explicitly provide a cost-effectiveness threshold but evidence has been provided of a cost-effectiveness threshold.

Australia, Pharmaceutical Benefits Advisory Committee (PBAC):

There is no stated cost-effectiveness threshold or explicit range in Australia for use when appraising medicines. There are many factors taken into account and the guidance for submission categorises these as qualitative and quantitative factors (PBAC, 2008). The factors are not weighed equally and different factors may be more or less important depending on the situation.

The quantitative factors include comparative cost-effectiveness, comparative health gain, patient affordability in the absence of the PBS and budget impact for the Pharmaceutical Benefits Schedule. Comparative cost-effectiveness includes both cost-minimisation analysis, incremental cost-effectiveness ratios including cost per natural outcome and cost-utility analysis. Comparative

health gain maybe included as both the effectiveness and toxicity and the magnitude of the effect and clinical importance.

The qualitative factors include the uncertainty surrounding the evidence (types of studies, indirect comparisons, plausibility of assumptions), equity considerations such the equity implications of using cost per QALY analysis on a case by case basis, presence of effective alternatives, severity of the medical condition treated with respect to the nature and extent of the disease currently treated, ability to target the therapy in the proposed group of patients and the development of resistance.

Henry et al. stated that although the Pharmaceutical Benefits Scheme does not operate a threshold value there is a correlative relationship between cost-effectiveness and the probability of rejection (Henry et al., 2005). The authors state that between 1994 and 2003 the highest cost per QALY at which a medicine was recommended was $52,400. However, PBAC does not solely consider QALYs as the only outcome measure and no comment is made about a threshold or range for other types of outcome.

A report provided for the Commonwealth Fund states that the PBAC chair is on record as saying "That PBAC considers that an incremental cost-effectiveness ratio greater than AUS$50,000 per QALY a year would be on the high side." However, there have been a number of medicines with lower cost-effectiveness ratios that have not been approved because of the other factors that are taken into consideration in decision-making by PBAC (Lopert, 2009).

Canada, Canadian Agency for Drugs and Technologies in Health Care (CADTH) Common Drug Review:

The Canadian Expert Drug Advisory Committee (CEDAC) appraises both the clinical effectiveness evidence and the cost-effectiveness evidence for a new medicine to provide advisory recommendations. There is no explicit formal cost-effectiveness threshold for the Common Drug Review or details of how the appraisal of medicines is performed by the committee. The terms of reference for the CEDAC committee state that they are required to provide reasons for the recommendations in accordance with the procedure that has been established by CADTH (CADTH, 2008). A common threshold figure that is cited is US $50,000 per QALY (Menon et al. 2009). Rocchi et al. considered whether an explicit or implicit threshold had been identified in the CEDAC deliberations of Canada's CDR process. However, ICERs were frequently not reported in the

recommendation guidance or the manufacturers estimate was not considered robust. There were 25 recommendations included for which 12 were negative with a range of cost-effectiveness of between $32,000 to $137,000 per QALY and 13 were positive decisions with a range of ICERs of between $31,000 to $80,000 per QALY (Rocchi et al., 2008).

Sweden, Pharmaceutical Benefits Board (TLV):

There are three criteria that must be fulfilled if a medicine should be reimbursed (Health and Medical Services Act 15) which are the human value principle, need and solidarity principle and the cost-effectiveness principle. The Human Value principle considers the respect for equality of all human beings and the integrity of every individual. The TLV may not discriminate against people because of sex, race, age etc. when making a decision for reimbursement. The need and solidarity principle states that those in greatest need take precedence when considering reimbursement of pharmaceuticals. Individuals with more severe diseases are prioritised over people with less severe conditions. The cost-effectiveness principle states that the cost of using a medicine should be reasonable from a medical, humanitarian and social-economic perspective.

The TLV Board must ensure that none of the three criteria are contravened. The Board primarily weighs up the need and solidarity principle with the cost-effectiveness principle. They must be weighed equally against each other as none of them have an absolute priority over each other. The cost-effectiveness criterion must be therefore weighed against the severity of disease (categorised on relevant, initial condition, risk of permanent injury or death without treatment with the medicine). The guidance states that the cost of the achieved relevant health benefit should be reasonable in proportion to the additional cost of the treatment (LFN, 2008). There is no formal explicit cost-effectiveness range. Persson et al. report that the principle of cost-effectiveness requires determination of the willingness to pay for the health benefits (Persson et al., 2010). The study reports that two different methods have been used to identify this, one using individual responses from a willingness to pay survey that resulted in a maximums of €40,000 per QALY, (Hjalte et al., 2005) and one from a value of preventing fatality that resulted in a maximum of €70,000 per QALY (Persson and Hjelmgren, 2003).

Ireland, National Centre for Pharmacoeconomics (NCPE):

There is no explicit cost-effectiveness threshold in practice in Ireland (Tilson et al., 2010). The primary decision criterion considered is that of cost-effectiveness. Although no threshold range is

stated, the experience of past decisions has demonstrated that medicines with an ICER of below €45,000 per QALY have tended to be reimbursed by the Health Service Executive (HSE). Those medicines that have significantly higher cost-effectiveness estimates may have other factors that are taken into account. The other factors taken into account are the level of uncertainty associated with the clinical and cost-effectiveness evidence, the budget impact of the medicine, the innovative nature of the medicine and lack of available alternatives.

Korea, Health Insurance Review and Assessment Service (HIRA):

The DREC considers cost-effectiveness with respect to a number of other criteria which include clinical usefulness or value, international countries reimbursement status and guidelines and the budget impact of the medicine. There is no explicit threshold reported in the HIRA documentation for the inclusion of medicines. The HIRA Reimbursement Committee has been reported to have drawn a discussion on the threshold and provided an implicit range of between 0.8 to 1.2 times that of GDP per capita (GDP per capita 2010 = 21.3million) which equates to a threshold of between 17 million to 26 million per QALY (Yang, 2009). Shiroiwa et al. reported the results of an international survey of willingness to pay for one additional QALY which included Korea. The WTP values for the Republic of Korea were estimated to be KWN 68 million (Shiroiwa et al., 2010).

New Zealand, Pharmaceutical Management Agency of New Zealand (PHARMAC):

PHARMAC has no threshold below which a medicine will be considered cost-effective (Metcalfe and Grocott, 2010). This is because cost-effectiveness is only one of nine criteria (PHARMAC, 2010a). The threshold is also likely to vary year on year with changes to the fixed budget. PHARMAC uses the following decision criteria:

1. The health needs of all eligible people within New Zealand.
2. The particular needs of Māori and Pacific peoples.
3. The availability and suitability of existing medicines and related products
4. The clinical benefits and risks of pharmaceuticals.
5. The cost-effectiveness of meeting health needs by funding pharmaceuticals, rather than by using other publicly funded health and 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 Pharmaceutical 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, in PHARMAC's Funding Agreement, or elsewhere.

9. Any other criteria that PHARMAC thinks are relevant. The PHARMAC will conduct a consultation whenever taking into account other criteria.

The past decisions have shown that the cost-effectiveness for those approved medicines has ranged between -NZ$40,000 to NZ$200,000 per QALY. The authors state that this would imply a threshold based on the estimates of NZ$200,000 that they state is clearly not the case because of the other factors that are taken into account in decision-making (Metcalfe and Grocott, 2010, Simoens, 2009).

No stated or observed threshold identified for countries using cost-effectiveness:

There were 11 agencies or institutions websites that did not report an explicit threshold. A search of the literature was conducted to identify any studies conducted with implied a threshold for the reimbursement of medicines, where literature could not be identified the agency was contacted to identify whether an explicit or implicit threshold is in operation.

The literature identified stated that threshold ranges were not in operation in:

- Austria (KCE, 2010);
- Belgium (KCE, 2008);
- Denmark (Sorenson, 2009b);
- Israel (Greenberg et al., 2009);
- Italy (Ettelt et al., 2007);
- Hungary (Sorenson, 2009a);
- Poland (Sorenson, 2009a).

There were responses from three of the countries emailed that confirmed that no explicit threshold range is in operation in Finland (Personal Communication: Blom, 2011), Norway (Personal Communication: Svanqvist, 2011), Portugal (Personal Communication: Leite, 2011). No indication of either at threshold range could be identified from the literature and to date there has been no was obtained from the institutions in Mexico.

4.3.2.5 Explicit and Implicit threshold ranges in relation to other factors

There are differences between countries with respect to the stated threshold ranges, the methods of elicitation of implicit ranges and the time period and medicines from which these

were elicited (Table A4.10). England, Scotland and Ireland consider other factors when the threshold is in the upper end of the threshold ranges, whereas the Netherlands, Australia and Sweden weight cost-effectiveness evidence in relation to other factors regardless of the estimate of cost-effectiveness. The countries all recognise the fixed budget assumption but the Netherlands states that the committee may judge whether the budget is constrained for each individual decision. The uncertainty surrounding the evidence was a stated factor in Australia, Scotland, England, Ireland and Korea.

A number of countries consider factors that relate to equity. Equity is an ethical concept and has no precise definition (Stolk et al., 2005). These factors were grouped under equity concerns and concepts that include severity of medical conditions, need, human value principle of equality, end of life and general statements of the consideration of equity. Of those countries with evidence of a threshold range, these concepts were stated decision factors in England and Wales, the Netherlands, Australia, New Zealand, Korea and Sweden.

There were other economic considerations such as budget impact and patient affordability. The other considerations were more country specific and included innovative nature of the medicine, alternative medicine present, international reimbursement status, feasibility, governments set priorities for health spending, patient perspective and other special criteria.

4.3.2.6 Content and documentation of decision

The appraisal documents are communicated on the website of the committee that is responsible for deliberations in many of the countries. There is no evidence of the details of the deliberations being publically available in Finland, Israel, Italy, Hungary, Mexico, Portugal, Spain, Korea and Switzerland. (See Table A4.4).

4.3.3 Output and implementation of the decision

4.3.3.1 Reimbursement systems decision outcomes

The systems decision outcomes are either mandatory decisions or advisory recommendations for prescription and reimbursement. These are considered with respect to the institution or committee that appraises the evidence and other factors and produces a decision for use in the system or recommendation to the Ministry of Health or other institution that decide the final decision. The reimbursement decision outcomes may be characterised with respect to a number of different dimensions, the type of list produced (negative/positive), the decision outcome and the level of copayments.

Positive lists operate in 22 of the 24 OECD countries where medicines included in the positive list are only available for prescription and reimbursement by the public system. There are also individual reimbursement schemes that operate in Austria, Denmark and Norway. The individual reimbursement schemes allow the clinician to apply on behalf of the patient for reimbursement of a medicine that is not included within the positive list of medicines (Table A4.11).

Negative lists operate in Germany and England and Wales and in addition to the positive list a negative list operates in Austria, Hungary, Scotland and Spain. Negative lists are lists of medicines that may not be prescribed by the clinician for funding by the public reimbursement system. In Scotland, England and Wales, the negative list can be described as more of a 'partial' negative list. This is because in Scotland the list is provided by the recommendations made by the SMC that should not *routinely* be made available by the NHS Boards. There may be exceptions where the Health Boards have a written policy for exceptions where individuals can receive reimbursement for the medicine (Health Policy and Strategy Directorate, 2010). Similarly, in England and Wales, NICE 'not recommended' medicines should not be routinely prescribed and reimbursed by the NHS and the ultimate decision lies with the clinician responsible for the patient. This means that a clinician can prescribe any licensed medicine if the local funder (currently the PCT) is willing to pay for the medicine (Department of Health, 2011).

The restrictions may generally be classified according to a decision to list or recommend the medicine, restrictions as defined by the agency and either not listed or not recommended. However there are differences between the systems with respect to the numbers of types of restriction, definition of the restrictions and requirements for outcomes based conditional reimbursement. There are a number of countries that include restrictions on the reimbursement decisions either with respect to the indication or characteristics of patients prescribed with

respect to the marketing authorisation or by prescription or authority of a specialist. The restrictions may sometimes be referred to as 'conditional reimbursement' or 'limited reimbursement' but to avoid confusion with other concepts (conditional outcome based coverage) these will be described as restricted decisions or recommendations in each reimbursement system. The recommendations for listing may be restricted by indication or the characteristics of the patient in reference to the marketing authorisation in nineteen countries and the use of restrictions was not identified in five of the countries national reimbursement systems (Table 4.6).

Table 4.6: Systems decision outcomes

Decision outcome may include restrictions	No restriction on decision outcome
Australia	France
Austria	Hungary
Belgium	Israel
Canada	Korea
Denmark	Mexico
Finland	Spain
Germany	
Ireland	
Italy	
Netherlands	
New Zealand	
Norway	
Poland	
Portugal	
Sweden	
Switzerland	
England and Wales	
Scotland	

NICE in England and Wales did not provide a system for officially categorising the recommendations until 2010. The NICE decision outcomes have a type of restricted decision called 'optimised decisions' which were introduced in 2010 and are technically different to restricted decisions in other systems. The 'optimised decision' represents the case where the recommendation has a material effect on the use of the medicine and it is recommended in a smaller subset of patients than the marketing authorisation. The definition of materiality provided is "test of materiality takes into account advice from clinical experts on the anticipated use of the technology in routine practice" (NICE, 2011e). This means that a decision that there may be situations where a medicine categorised as a restricted listing decision in one of the other reimbursement systems would be categorised as a 'recommended' decision by NICE in England and Wales.

There are further restrictions that may apply for use or approval for reimbursement. The decision outcomes provided in Scotland and the Netherlands can require that only a specialist prescribes the medicine. There are further approval processes for some decisions in Australia, the Netherlands and New Zealand. In Australia the scheme is called 'authority required' where the medicine can only be prescribed once approval has been gained from either Medicare Australia or the Australian Government Department of Veterans' Affairs (PBAC, 2008). In New Zealand a similar process operates for some decision outcomes where 'special authority' may be required where an application is made for an individual for the listed medicine. The criteria for special authority are included alongside the listing of the medicine (PHARMAC, 2011c).

There are a number of systems where performance-based schemes are agreed between the reimbursement body and the manufacturer. These can be categorised as either non outcomes based schemes and health outcomes-based schemes (Carlson et al., 2010). The health outcome-based schemes can be further categorised into conditional coverage and performance linked schemes. Since the focus of the framework is to categorise the reimbursement decision outcomes the focus will be on the conditional coverage schemes rather than the performance-linked schemes which focus on the price of the medicine. There are a number of systems that have formal coverage with evidence development processes either by condition the decision on require further evidence to be collected or by only allowing prescription for those patients who are participating in research.

Coverage with evidence development schemes operate where the decision allows the medicine to be prescribed on the condition that further evidence is provided in Belgium, Sweden, France, Netherlands and Poland. The use of coverage with evidence development is central to the process of reimbursement for inpatient medicines in the Netherland. Those medicines on the Expensive inpatient Medicines are assessed with evidence collected four years after launch for the real life cost-effectiveness. HAS in France requests post-listing studies as a condition for the reimbursement of medicines and reassesses the medical benefit (SMR) 5 years after their initial decision. In Sweden the recommendation can be conditioned with the requirement for the manufacturer to provide within a specific period a study to show how the medicine is used in real clinical practice with supplementary information on the clinical effect and the cost-effectiveness. Similarly, those recommendations provided in Belgium for Class 1 medicines that are claimed to demonstrate added therapeutic value may be required additional evidence to demonstrate the clinical effect and real life cost-effectiveness between 18 and 36 months.

The coverage with evidence development scheme in England and Wales is called 'Only in Research' and is the fourth category of NICE decisions in addition to recommended, optimised and not recommended. This is where insufficient evidence has been collected at the appraisal but the committee has judged the medicine to be promising but further research is required. The medicine may only be used in the context of a research study such as a clinical trial which is designed to reduce the evidence uncertainties (NICE, 2011e). PBAC[1] in Australia and CADTH in Canada can also request that the decision is deferred while further information or clarification of the data on the medicine is provided.

The level of copayment is important in determining the budget impact of the medicine on the public health system, implications for the equitable use of medicines depends on the payment and to prevent moral hazard in insurance based systems. There are no copayments required in Scotland (prescription fee recently abolished) and for medicines with added therapeutic value in the Netherlands (CVZ, 2011b). In other systems there are a number of types of copayments across systems where either a fixed prescription charge is paid, percentage of the price of the medicine or more complex systems where a percentage of the price of the medicine is paid up to a maximum ceiling level (Table A4.11).

4.3.3.2 Status of the national reimbursement decision or recommendation outcome

The decisions provided by the national institutions are final decisions with a legal basis for inclusion in the positive lists in Austria, Belgium, Denmark, Germany, Italy, Hungary, New Zealand, Norway, Sweden, Israel, Finland, Spain and Switzerland.

The reimbursement recommendations are of an advisory nature by PBAC in Australia, HAS in France, CVZ in the Netherlands, AHTAPol in Poland, INFARMED in Portugal and HIRA in Korea. The final reimbursement decisions are made by the Ministry of Health taking into account the reimbursement bodies recommendations. These are then included within the positive list schemes in operation in each of these countries.

In England and Wales the final decision for reimbursement depends on the NICE guidance and the clinician. The NHS in England and Wales is legally required to provide funding for medicines that are recommended for reimbursement normally within 3 months of the decision by NICE where the medicine is deemed appropriate by a clinician for a patient (NICE, 2011d). As discussed earlier the not recommended decisions should not normally be prescribed in routine practice but

[1] The Government has recently started to defer listing of medicines that have been judged to be recommended by the PBAC for listing because of the forthcoming budget cuts that are required. April 2011: http://parliamentflagpost.blogspot.com/2011/04/making-savings-from-pbs-is-deferring.html

exceptions can be made when funding is available and it is considered appropriate by the clinician. NICE does not provide recommendations for all medicines and the decision for these medicines will depend on the clinical and local funder. The Scotland process of reimbursement partially overlaps with the recommendations provided by NICE for some MTAs. The NHS Quality Improvement in Scotland is involved in the NICE MTA process and reviews the guidance using experts for applicability in Scotland. The NHS QIS will validate whether the recommendations are appropriate for Scotland and Health Boards are required to normally provide these routinely (a SMC recommendation is therefore not required). The recommendations for other new medicines made by the SMC are considered by the NHS ADTC Boards in Scotland and will either provide the medicine in the formulary or not recommend if an existing equivalent treatment option is already available in the formulary (Health Policy and Strategy Directorate, 2010).

The decisions made for the Basic Formulary and Catalogue of Inputs produced at the national level in Mexico must inform the basis of the social insurance institutions formularies and are only part of the final decision for inclusion in each of the positive lists. The Common Drug Review in Canada provides advisory recommendations to the drug plans and these can decide the formulary listings on the basis of their local priorities.

4.3.3.3 Appeal and dissent

The majority of countries have some form of mechanism of appeal or dissent for the reimbursement decisions but these differ in the number of stages, the stakeholders that are entitled to appeal and the grounds for appeal (Table A4.12).

The manufacturer is the only stakeholder entitled to appeal the decisions made by many of the reimbursement bodies. The CDR process allows both the manufacturer and the drug plans for which the recommendations to request reconsideration by the CEDAC committee. The CVZ has a "participation procedure" where the manufacturer and those of that the chairman regards as stakeholders can respond to the draft advice before the final recommendation. The final decision made by the Ministry of Health maybe appealed on procedural grounds. There are three different types of stakeholders that can appeal in the NICE process in England and Wales which are referred to as consultees (National body representing patients, bodies representing health professionals and the manufacturer).

There are independent appeal committees that operate in separately providing the reimbursement decision in Austria (Independent Drug Commission UHK), Ireland (Expert Committee), Hungary (Appeal Committee) and Switzerland (Appeal Commission). The appeal

committee operates within the responsible agency in England and Wales, NICE (Appeal Panel) on procedural grounds and within the SMC (Independent Review Panel) to review the existing data and analyses.

The NICE website contains the most detailed information on the appeals process for technology appraisals (NICE, 2011c). An appeals panel is appointed by the appeals committee. The consultees can make an appeal within 15 days of the release of the provisional guidance on any of the following three grounds; 1. The Institute has failed to act fairly where the appellant believes that they the process has not been followed as set out in the NICE technology appraisal process guide. This does not consider unfairness in the sense that it is unfair that the treatment is not provided to patients, 2. The Institute formulated guidance which cannot reasonably be justified in the light of the evidence submitted. This means that the recommendations produced are "unarguably wrong, illogical, or so absurd that a reasonable Appraisal Committee could not have reached such conclusions." 3. The Institute has exceeded its powers in relation to the directions and guidance issued by the Secretary of State for Health in England and Wales. There are three options for the outcome of the appeal; 1. Appeal upheld and Final Appraisal Documentation (FAD) returned to the Appraisal Committee, 2. Appeal Panel request alteration to the FAD but no further consideration by the Appraisal Committee or 3. The appeal is dismissed. There is no possibility for further appeal and the final guidance may be challenged by applying to the High Court in England and Wales for a judicial review.

The manufacturers can provide a resubmission or request the formation of an Independent Review Panel (IRP) to appeal advice produced by the SMC (SMC, 2011d). The IRP route can be used when there is no significant new data or analyses but the manufacturer would like the SMC to look at the existing data and analyses. The IRP comprises 3 members not previously involved in the advice from the SMC and 4 members form the Scottish Area Drug and Therapeutic Committees). The IRP provides a review of the clinical and health economics assessment and will report back to the SMC Board that makes the final decision on these cases.

In cases where the reimbursement body provided advisory recommendations in Australia (PBAC) and Canada (CDR on procedural grounds) the procedure allows the manufacturer to provide a resubmission or reconsideration rather than a formal appeal procedure. The HAS reimbursement agency is also advisory in France and provides manufacturers with hearings following a recommendation. They can then appeal a final decision by the Ministry of Health to the Administrative Courts. The manufacturer is able to resubmit to the GHC in Mexico, although there does not appear to be any other appeal process. In New Zealand and Korea, the manufacturer

may reapply and/or make an appeal to the countries respective Courts. The appeal procedure in Belgium (procedural grounds), Finland, Netherlands, Portugal and Sweden was by the countries Administrative Courts. The Ministry of Health is responsible for the appeal decision and process in Denmark (procedural grounds) and Norway. The German system is unique in that following the lack of a price being agreed in arbitration, the manufacturer and the sickness funds can request a cost-benefit analysis following a lack of agreement on price. There does not appear to be any formal mechanism for appeal in Germany.

There were no mechanisms identified from the published process guides for reimbursement systems in Israel, Italy, Poland and Spain.

4.3.3.4 Requirements for re-appraisal and monitoring of medicines

The requirements for reappraisal are considered with respect to the agency or body that previously provided the reimbursement appraisal of the evidence amongst criteria for providing either reimbursement recommendations or decisions for the medicine. There are a variety of processes for the reappraisal of medicines and these countries have been grouped into three broad categories; process allows the manufacturer to provide a resubmission but the reimbursement body does not have a procedure for reappraisal, the body responsible for reimbursement appraisal decides reimbursement overtime and does not specify a process time period for reappraisal and finally those countries that specify a time period for the reappraisal of medicines (Table A4.13).

There are processes where the manufacturer may resubmit to the body responsible for reimbursement but the body does not specify a reappraisal procedure for medicines. This process operates mainly in reimbursement systems where the agency appraising the evidence provides advisory recommendations to the respective authorities, Ministry of Health in Australia (PBAC), Hungary (TAC) and Israel (Medical Technologies Administration), HSE in Ireland (NCPE) and local health boards or drug plans in Canada (CDR) and Scotland (SMC). The majority of these systems require the manufacturer to provide new evidence with the exception of the CDR process where in addition to new evidence the manufacturer may submit a new price during the embargo period (CADTH, 2010).

There are systems where the body responsible for reimbursement appraisal does not specify a time period for the reappraisal but reviews the medicine over time. Those medicines that are perceived to no longer meet set criteria such as the medico therapeutic and health economic criteria are reappraised in Austria (HEK), are no longer prescribed or another product has been

included with greater efficacy or lower toxicity in Mexico (GHC), no longer meet criteria in New Zealand (PHARMAC) and Norway (NoMA). There are then countries that provide criteria for those medicines that should be prioritised for reappraisal. In Denmark, the DMA prioritises the medicines according to the significance of the medicine to the primary sector, public health considerations, new evidence and the medicine is found to have high costs or high consumption. In Korea, HIRA re-appraises medicines by therapeutic class and uses fewer prioritisation criteria that include growth in the use of the medicine and the budget impact of the medicine. The G-BA in Germany may reappraise medicines when significant new evidence becomes available. Additionally, PHARMAC in New Zealand, G-BA in Germany 12 months after the decision and HIRA in Korea also allow the manufacturer to resubmit when new evidence becomes available.

In Sweden (TLV) medicines following conditional reimbursement are reappraised and a review of 2,000 medicines was undertaken, reviewing one therapeutic area at a time to decide eligibility when the reimbursement system was reformed in 2002 (LFN, 2007). There is an ad-hoc review of medicines in the new system and the manufacturer is contacted with regards each case.

In England and Wales (NICE) a proposed review date is provided on the guidance document. NICE decide the review date based upon the available evidence in the medicines guidance publication and any knowledge about when ongoing research will be reported (NICE, 2008). NICE may review the guidance earlier than the proposed date if significant new evidence becomes available. If a large amount of evidence is available the guidance will be reviewed by a guidance document or within a clinical guideline and if there is little evidence may be assigned as static guidance, deferred to a future date, or incorporated into a guideline.

There is a time specific reappraisal process for which medicines are reviewed which ranges from between 1 year and 5 years in Belgium, Finland, France, Netherlands, Poland, Portugal, Spain and Switzerland. Some of these reimbursement systems operate processes of coverage with evidence development (CED) for those medicines where there was judged to be uncertainty. Coverage with Evidence Development represents a specific approach to coverage for promising technologies, for which the evidence remains uncertain (Hutton et al., 2007). The technologies are provided under conditions of generation of further evidence for a defined period after which these are reviewed.

Chapter 5: A retrospective analysis of factors commonly associated with reimbursement decisions in those agencies using clinical and cost-effectiveness evidence for the appraisal of cancer and cardiovascular medicines

Abstract

Objectives: Clinical-effectiveness and cost-effectiveness evidence explicitly informs alongside other factors, the decision to recommend a medicine by committees in many established public national reimbursement agencies. National agencies stated factors and the details of past decisions, increasingly allow manufacturers to make more efficient investment decisions and develop new medicines that are determined to be of sufficient value to society. The objective of this study is to explore whether there are common factors used to consider the value of a medicine and determine reimbursement across countries with similarities in evidence requirements and objectives.

Methods: A pooled sample of 189 appraisals for cardiovascular and cancer medicines for four HTA agencies were considered. This was analysed using multi-response models for all appraisals and a sub-sample that provided cost-utility estimates.

Results: The results demonstrated that different factors were important for different types of decision. The number of RCTs, publication date and sensitivity analysis were found only to be important in a not recommended decision, whereas budget impact was only important for restricted decisions. The public interest and type of medicines were important for both restricted and not recommended decisions. The type of economic analysis and cost-utility estimate were not found to be statistically significant.

Conclusions: The factors in this study explain some of the variation in reimbursement decisions across countries. Further variation may be explained by differences in the countries values, processes and institutions within which decisions are made. The type of quantitative analysis may not adequately be able to control for non-evidence factors and process which could potentially explain variability in decisions within and across these countries.

5.1 Introduction

Over the last 20 years, national reimbursement agencies have been established in many developed countries with the complex task of assessing the value of a medicine and deciding whether this is sufficient to be recommended for use. Reimbursement agencies state factors for establishing the value of a medicine but differ in the transparency in the reporting of the considerations and the factors. The Pharmaceutical Benefits Advisory Committee (PBAC) in Australia, Common Drug Review (CDR) in Canada, National Institute for Health and Clinical Excellence (NICE) in England and Scottish Medicines Consortium (SMC) in Scotland provide the criteria informing decisions and are considered established agencies with respect to economic evaluation methods (Barbieri et al., 2010). These established reimbursement agencies all consider whether a medicine can be considered value for money and in some circumstances will judge the medicine with respect to other criteria such as the innovativeness of the medicine, disease severity or high level of unmet need. The stated criteria of these agencies and an understanding of the factors that influence past actual decisions, increasingly allow manufacturers to make more efficient investment decisions and develop new medicines that are determined to be of sufficient value to society. The past decisions can be used to understand and establish the demand curve in those countries using health economic analysis.

There is limited quantitative evidence of the factors influencing past decisions for the national reimbursement agencies in Australia, Canada, England and Scotland. Three quantitative studies have been conducted for the relative influence controlling for factors, two for NICE decision-making (Dakin et al., 2006, Devlin and Parkin, 2004), and one for PBAC decision-making (Harris et al., 2008). One further mixed method study considers a comparison of CDR, PBAC and NICE decision-making, identifying some factors that were important across countries and some factors within countries but this was a univariate analysis without any analysis to control for the effect of each factor (Clement et al., 2009).

The studies have considered different aspects of the clinical considerations with respect to the characteristics of the clinical evidence finding these to be important (number of RCT's, clinical endpoint) (Dakin et al., 2006, Harris et al., 2008). One study demonstrates differences in the impact of uncertainty surrounding decision-making being important for CDR and PBAC but unimportant for NICE decision-making (Clement et al., 2009).

All of the studies reported that the cost-effectiveness estimate was important for decision-making (Clement et al., 2009, Dakin et al., 2006, Devlin and Parkin, 2004, Harris et al., 2008). In addition,

the studies reported evidence of a cost-effectiveness threshold range for NICE, PBAC, CDR, with the exception of Harris et al. where the authors described the threshold range as mediated by other factors in decision-making. For NICE decision-making, a pooled sample of cost per QALY gained (CQG) and cost per life year gained (CLG) demonstrated that the threshold based on previous decisions was between £35,000 and £57,000 per QALY; higher than the currently declared threshold range of between £20,000 to £30,000 for NICE in England. The uncertainty in decision-making has been captured through a different variables relating to the outcomes of the sensitivity analysis (Devlin and Parkin, 2004, Harris et al., 2008) or through a subjective assessment of whether the economic analysis was uncertain (no uncertainty, some uncertainty, considerable) (Clement et al., 2009).

There has been a focus on some common factors within each of these single country studies. These studies provide evidence that some factors are influential in decision-making, irrespective of whether the decision was made in Australia, Canada or England. However, the factors considered conceptually important for these countries national reimbursement agencies have low explanatory power. The low explanatory power maybe because of the studies small sample size or construct of quantitative variables that do not measure the decision-makers criteria applied or may legitimately indicate the actual relevance of each factor in the decision process for each country.

5.2 Objectives

The aim of this study is to examine the common factors influencing the past decisions for cardiovascular and cancer medicines used by fourth hurdle agencies that use cost-effectiveness and clinical effectiveness evidence. As described in chapter 3, Hutton *et al.* (2006) explained the term 'fourth hurdle' as the manufacturers' perception of the value for money criterion as an additional market access barrier, after demonstrating the quality, efficacy and safety of a technology to obtain a marketing license.

This study considers elements of the clinical and cost-effectiveness considerations and other factors that can be consistently obtained across a number of countries using broadly similar decision-making criteria. The rationale for the pooled analysis is to firstly explore whether there are factors in decision-making that are important for determining the value of a new medicine regardless of the country for which the decision was made when the agencies have broadly similar evidence and requirements. Secondly the pooled analysis will allow a larger sample size to

assess additional factors that have not been previously explored. Influence will be defined as the correlation or association between the factors and the decision outcomes.

The technology appraisals included were undertaken to inform decisions taken by the National Institute for Health and Clinical Excellence (NICE) in England, the Common Drugs Review (CDR) and Joint Oncology Drug Review (JODR) in Canada (for non-supportive care cancer medicines) informed by the CDR, the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia and the Scottish Medicines Consortium (SMC) in Scotland. Those published prior to February 2008 were included.

The countries share the following similar characteristics:

The agencies are established within similar economic environments with GDP per capita ranging from $32,961 in the UK to $36,814 per capita in Canada. Each country's health system is funded largely through a publicly-funded tax-based system with broadly similar objectives of making decisions on the basis of value for money;

1. The agencies are established with processes and guides to their submission process with documentation of the decisions available, Australia (PBAC, 2008), Canada (CADTH, 2010), NICE (NICE, 2008), SMC (SMC, 2011b);

2. The manufacturer makes an initial submission to the agency that includes an economic analysis. This is the primary source of the economic evidence. NICE is an exception where an independent assessment group or evidence review group produces an additional economic appraisal and/or a critical review of the manufacturer's model;

3. The type of economic appraisal is broadly similar across the agencies. CADTH CDR, JODR (cancer medicines for which CDR contributes to reviews), PBAC and the SMC specify in their guides to submitting evidence that CUA is the generally preferred form of economic analysis but they will consider other forms such as cost-effectiveness analysis using other measures of health benefit. Current NICE technology appraisal guidance stipulates that in their reference case the QALY should be the only measure of health effect (NICE, 2008). This agency has not always required this and some older appraisals of medicines contain other forms of economic analysis such as CEA. All agencies require their committees to consider whether they deem the medicine to be value for money with respect to other the appropriate alternative when making a decision.

5.3 Methods

5.3.1 Sample of decisions

The appraisals/evaluations were selected from reimbursement agencies which were known to make systematic use of economic analysis; had well-established processes; and provided sufficient public documentation to allow relevant data to be collected for the analysis. This reduced the heterogeneity with respect to the type of economic analysis used, although there was substantial variability in the detail of reporting between agencies and within agencies over time.

Because the interest was in the influence of decision-making criteria and methods rather than the medicines themselves, appraisals were selected from two clinical areas. This limited the potential variation that would be seen in a study across disease areas, but the variation within the two disease areas should reflect how the decision-making criteria are applied across the countries. Medicines to treat cardiovascular disease and cancer were included as they provided a large sample of documented evidence for two disease areas that had been captured across all four of the agencies considered. This numerous pharmaceuticals appraised for these diseases reflected the fact that the two disease areas featured in the top 5 causes of death for these countries.

5.3.2 Decision-making factors

The decision-making factors were considered by the characteristics of reimbursement systems considered conceptually important by international decision-makers, (Hutton et al., 2006), consideration of the stated criteria by each of the agencies by reference to their websites and guidelines and the factors that were commonly included across the previous retrospective studies. The research aimed to collect information on all conceptually important quantitative variables across countries but this depended upon sufficient similar documented evidence in the public reports and also how appropriate it was to transform some qualitative aspects of decision-making into quantitative variables. The factors were categorised into three main groups:

1. The first set of factors are described as the 'evidence factors' considered for each technology assessed at the "Individual technology decision level' (Hutton et al., 2006). These include the clinical evidence, economic evidence and budget impact.

2. The second set of factors relate to the policy context of the decision including the health system and country specific characteristics that are not related to the evidence called the 'non

evidence factors'. The non-evidence factors include the disease area, patient views and public interest.

3. The third set of factors relate to the process of decision-making at the individual technology decision level called the 'process factors' that are common across the agencies processes such as review of previous appraisal, patient group involvement and time at which the decision was made.

The definitions of the variables are given in Table A5.1. The dependent variables relate to the recommendation/decision outcome for each of the agencies. The multinomial regression was used to enable classification of the decisions into three categories rather than two (recommended/not recommended) as this was considered to be a more realistic representation of the decision outcome for the four agencies – recommended fully (as per licence), restricted recommendation (restricted to a patient subgroup of the regulatory licence) and not recommended. PBAC and SMC assess and appraise medicines following a single process whereas separate processes operate in SMC and a separate committee in Canada for cancer medicines called the Committee to Evaluate Drugs (CED) which is informed by the CDR but is part of the JODR. NICE has two processes in operation, Multiple Technology Appraisal (MTA) and Single Technology Appraisal (STA). For the NICE, MTAs the recommendation for each medicine and indication was included as a separate decision, and the data relevant to each case was extracted from the reports.

A factor can be considered either as an evidence, non-evidence factor or process factor that may influence the appraisal decision. Influence or impact will be defined as association between a factor measured by an independent explanatory variable and the decision controlling for other factors. Causation is therefore not assumed by this analysis. An 'evidence factor' - a characteristic of the medicines evidence (clinical efficacy, clinical effectiveness and cost-effectiveness), 'non-evidence factor' - other value judgement applied because of a characteristics of the medicine that influences the decision (type of medicine) or 'process factor' – common characteristic shared with respect to the process of assessment within countries reimbursement processes (time period, review/resubmission of medicine). Sixteen explanatory variables were included in the analysis:

1. Evidence Factors:

- Evidence included RCTs

- RCT number
- Evidence included observational studies
- Type of economic analysis
- ICER from economic analysis
- Sensitivity analysis performed

2. Non-evidence Factors:

- Disease Area
- Public Interest

3. Process Factors

- Time since guidance published
- Patient group submission
- Number of patient groups submissions
- Review of previous appraisal
- Country dummy variable (3 dummy variables) to control for other process factors unique to each countries reimbursement system

Evidence factors

Clinical evidence: The number of RCTs used in each technology appraisal was taken from the documentation available for the appraisal. This variable is a proxy for the strength of the clinical evidence and the willingness of the agency to use it to guide the decision-making. This does not necessarily mean the total number of RCTs of the technology, but those RCTs that the agency deemed important and appropriate for reporting in the appraisal. The effect size had been included as a separate factor in other studies but, as this has been captured within the estimate of the ICER value, we deemed this inappropriate and would be related to the CQG.

The clinical evidence has been accounted for in other single country analysis by other variables such as the quality of the evidence and the judgements surrounding the uncertainty of the clinical evidence. However, the inclusion of these variables in this multi country analysis was problematic

for a number of reasons. The lack of reporting of information in the public documentation across these agencies does not allow a consistent objective variable to be constructed that can robustly captures the quality of evidence and uncertainty (with the exception of NICE) across the agencies. In the examination of quality of studies in the case of NICE, (Dakin et al., 2006) found that the variables associated with characteristics of the RCTs, such as the quality, size and significance of effect were not found to be statistically associated with the decision and were also found to be correlated with each other and this could potentially bias the findings of the relative influence. The lack of association may be explained by the association between the quality variables or the fact that many elements of assessing clinical uncertainty require judgements which are difficult to summarise within a number of independent quantitative variables. The use of quality indices for RCTs, such as the Jadad score, has been explicitly discouraged by the Cochrane Collaboration for assessing the quality of trials and risk of bias. The Cochrane handbook (Higgins and Green, 2008) recommends that a domain based approach would be most appropriate for assessing the quality of RCT evidence, but this would be very difficult to introduce into this type of quantitative analysis.

The uncertainty in clinical evidence has been captured explicitly in one other study by a subjective assessment by the authors of the uncertainty present from the documents and classifying this as none, some and considerable (Clement et al., 2009). The construct of such a variable is flawed for a number of reason, firstly, the documentation for each of the countries does not provide sufficient information on the qualitative judgment of uncertainty nor to provide a subjective judgement of the uncertainty, the variable introduces a second level of uncertainty and bias by the researchers interpretation of the public documentation and the category of 'none' in the study is nonsensical because *all* clinical evidence is subject to some level of uncertainty. It was therefore considered inappropriate to construct such a variable across these agencies that would be sufficiently meaningful.

Economic evidence: This study considers the type of economic analysis considered by the agencies in two groups; analyses using cost-effectiveness analysis (CEA) and those that use cost-utility analysis (CUA). CEA is one form of economic analysis where both the costs and consequences of the medicine are examined in the form of CLG or cost per unit of effect. CUA is related to CEA and considers the costs and benefits in terms of quantity and quality of life through the use of the quality adjusted life year (QALY). The type of economic analysis used can be regarded as an indicator of the quality of the outcome data available with three of the agencies stating a preference for cost-utility analyses. The size of our sample enabled an analysis of the differential

influence of (higher quality?) the presence of CUA and CEA. It would be expected that those using CUA would have a higher probability of recommendation or restriction in comparison to those using CEA. A variable was created for two subsamples of those analyses that included CUA and those that included CEA to capture the different ICER values by using the reported CQG and reported CLG.

Value for money is assessed and considered in the deliberations of these national agencies. Chapter 4 identified some evidence of the influence of CQG in countries and the evidence shows that larger ICERs are associated with a higher probability of not recommending for these countries. The pooling of decisions across agencies would expect to show a statistically significant independent effect of a negative association between larger ICER values and the decision to recommend or restrict. However, average effects for each country may be different, indicating different threshold ranges for each of the countries. Higher ICERs might be expected to decrease the likelihood of recommendation in this group of countries with similar income levels, but differing rates of health expenditure and current health service configurations may produce differing decision threshold ranges.

The incremental cost-effectiveness ratio (ICER) selected for use in this study was that ultimately used to make the decision, regardless of the source of the estimate. In Australia, Canada and Scotland the only ICER value is that from the manufacturer's submission to the agency. In the case of NICE, ICER values are presented by the manufacturer and then also either by an assessment group for an MTA or an Evidence Review Group (ERG) for an STA. Many of these ICERs relate to drug doses and patient populations which do not form part of the eventual recommendation. The value used in this study was that for the application of the technology on which NICE made its recommendation. In a number of cases, the specific ICER used for the decision was stated in the "Consideration of Evidence" section of the guidance. Where this was not the case (older NICE appraisals), the assessment group's ICER value was taken. The manufacturer's ICER was only used when there was no other ICER available in the guidance document for the indicated decision.

The above protocol was adhered to in selection of the ICER values. Where the identification of an ICER value was unclear this was discussed by the two researchers extracting data to reach agreement on the appropriate decision ICER. The ICER values were then checked against the guidance by a separate researcher. The CQG and CLG were converted by the exchange rate at the time of the technology appraisal into British pounds (GBP). The analyses used a pragmatic approach of using market prices rather than conversion by Purchasing Power Parity (PPP) for the

ICER values in each country. The decision was made not to convert using PPP's because examination of the PPP's for the four countries revealed that there was small variation in the index for the years of guidance considered. It would be important to consider if the sample had included emerging markets or developing countries where there is generally a large gap between the market and PPP values. A further question which is not addressed here is whether GDP PPP indices are of the appropriate construct for the consideration of international cost-effectiveness estimates.

Sensitivity analysis is a requirement across all of the agencies but there is variation of the reporting of such analysis across the agencies public documents. Ideally, the results of all the sensitivity analysis, summarised into a single quantitative variable to account for the uncertainty in the estimates provided would be the best variable to include. However, due to a lack of public documentation across all agencies reporting the results of sensitivity analysis performed and differential reporting within each country it was only possible to include the reporting of sensitivity analysis. The agencies reporting of sensitivity analysis may be used when committees provide justification for a restricted recommendation or a not recommended decision and its absence may indicate a high degree of confidence in the appraisal for those recommended decisions.

Non-evidence factors:

Disease area and public interest were two non-evidence factors included. Public interest was a new variable identified through qualitative studies in the review in chapter 4 that had not been previously included in quantitative studies. Wirtz et al. focused on the broader personal and political factors which have influenced decision-making but received less attention in previous empirical studies (Wirtz et al., 2005). An understanding of the factors that influence the decision-making environment (policy context) outside of the methods and process for which a medicine is assessed may be influential on national agencies decisions. The study referred to the subjective or political factors that were described as being appropriate and legitimate alongside other rational factors considered. This study aims to focus on public interest/pressure which may be considered a proxy measure for the political influence guiding processes and methods. There has been substantial pressure from manufacturers and patient groups for agencies to approve medicines prior to a reimbursement decision. In some cases there is wider public debate of the issues which may influence decision-making agencies which are ultimately subject to democratic control. A variable was added as a proxy measure of the public pressure for approval of a new medicine for the indication prior to the publication of the decision. This was based on the number of news

reports relating to the disease area and indication for each technology in the period prior to publication of the technology appraisal by the agency. This variable was not concerned with attempts to change a decision once it had been announced but as a proxy measure of the pressure prior to a decision. For each country, the counts were made in a broadsheet and a tabloid newspaper, selected from the highest circulation newspapers of each type. If the agencies were consistently implementing their stated criteria for decision-making there would not be expected to be any association between the public pressure prior to the decision and the actual decision made. However, it could be that medicines that receive substantial media interest prior to the decision may influence the decisions because the decision-makers focus on these decisions in more depth to provide greater justification because the agency and decision-makers are aware that they will be subject to greater public scrutiny.

Process factors:

Seven variables were included to identify aspects of process that may vary for each technology appraisal within each country (time since guidance, patient group submission, number of patient groups and review) and those aspects of process that only vary across the countries reimbursement systems (3 dummy variables for Australia, Canada and Scotland). A new variable called 'review' was added to identify whether the appraisal was either a review variable identified those decisions that were based on either a review of a previous guidance (NICE) or a resubmission by the manufacturer to the (CADTH, PBAC and SMC).

5.3.3 Regression methods

The type of qualitative response regression model used to analyse the factors commonly important in decision-making was the multinomial logit model (MNLM) regression. The model was chosen as it allowed the decision outcome to be categorised as a trichotomous variable - either "recommended", "restricted recommendation" or "not recommended". This is a more realistic representation of decision-making outcomes for national agencies than the dichotomous logistic model. The MNLM requires there to be sufficient observations in each category to ensure sufficient power to make statistical comparison between factors within each comparison group (Greene, 2003). The use of a pooled sample for the two disease areas in this study has the advantage of a larger sample size for each decision outcome. However, additional two-way tabulations were performed to check for perfect prediction of any variable and the dependent

variable (decision outcome) to make sure that there were sufficient observations within each category to produce meaningful results.

The decision outcome will depend on the independent variables including the characteristics of each technology appraisal and the political and country specific factors in which decisions are made. The MNLM requires that decision outcomes are mutually exclusive and that there is no natural ranking for the three decision outcomes. In order for there to be a ranking of decisions a perspective (societal, manufacturer, patient, patient group) would need to be taken and an assessment of the relative desirability of each decision outcome. This analysis adopts a societal perspective and it is not clear that there would be a natural ranking for these decisions – society would require an efficient and equitable decision depending on the evidence. The model also requires the implicit assumption of independence of irrelevant alternatives (IIA). The IIA assumption means that all other things being equal, a choice between two alternative outcomes (decision outcomes) is unaffected by the other (decision outcomes) available. This implies that the relative risk ratios are independent of one another for different comparison groups.

The parameters were estimated using maximum likelihood (ML) estimation in Stata 9.2 SE and robust standard errors were calculated. The result for each factor has been presented as a relative risk which is the ratio of the probability of choosing one decision outcome category over the reference category. The reference case group in the analysis is those decisions which were recommended. This means that the results for the two comparisons are interpreted separately as a comparison between restricted and recommended and not recommended and recommended. There is likely to be some intra cluster correlation between each of the reimbursement agencies in this sample. In other words it is likely that observations on an outcome variable (reimbursement decisions) are independent across groups (reimbursement agencies) but are not necessarily independent within the groups (decisions and factors driving the decisions). This was accounted for by using a cluster command for each of the agencies in Stata.

5.3.4 Data collection

Technology appraisals on cardiovascular and cancer medicines were identified by a systematic search of each of the agencies websites and through contact with the agencies. The data specifications and variable names were clearly specified in a table prior to extraction so that consistent extraction could take place between researchers. The data for each of the variables was extracted from full technology appraisal report documents and, where necessary, the public

appraisal reports that informed the decision process for each medicine. If there were any queries regarding missing documentation of the evidence clarification was gained before noting the information as not reported. Contact was not made with the agencies to consider whether the information reported reflected the information that they had thought they had taken into account in the technology appraisal. Those technology appraisals that were published prior to February 2008 were included within the sample. A record of each was collected within an Excel spreadsheet for all technology appraisals in the sample. The data for the public interest variable was obtained from the Nexis news source database (Nexis, 2008).

5.4 Results

5.4.1 Preliminary data analysis

The pooled MNLM included a total of 189 appraisals of which 17 were reviews of previous technology appraisals. This sample had 48 (25%) decisions that were recommended, 78 (41%) that were restricted, and 63 (34%) not recommended decisions. There were 6 NICE MTA's which resulted in 17 individual medicine appraisals included within the analysis (17 out of 189, 9%). The majority of recommendations were restricted, which demonstrates the importance of a trichotomous decision outcome (dependent variable).

The descriptive statistics are provided in Table 5.1. There were 52 (28%) appraisals for Australia, 19 (10%) appraisals for Canada, 45 (23%) appraisals for England and 73 (39%) appraisals for Scotland. The data included 129 cancer medicine technology appraisals and 60 cardiovascular medicine technology appraisals. The initial analysis showed that there were 34 SMC technology appraisals that did not report a number of the factors. These were either cases where the manufacturer did not submit evidence or cases for the early days of SMC when decisions were less fully reported.

There was a statistically significant higher proportion of cancer medicines not recommended in comparison to cardiovascular medicines ($p=0.05$).

The technologies that were recommended were on average supported by 2 RCTs in comparison to 3 for restricted decisions and 1 for not recommended decisions. Cardiovascular medicines were accompanied on average by 3 RCTs in comparison with cancer medicines which were supported by on average 2 RCTs. There was a statistically significant difference between the mean RCT number for recommended decisions in comparison to not recommended ($p= 0.02$).

The technology appraisals that were recommended were published on average 32 months ago, compared with 33 months for restricted decisions and 24 months for those decisions that were not recommended. The results were statistically significant between recommended and not recommended (p=0.01). On average the cardiovascular technology appraisals were 9 months older than those performed for cancer medicines.

The data show that 85 (45%) of technology appraisals included CUA, and 35 included CEA. Cost-utility values were presented in 78% of analyses for England, 43% for Scotland and 35% for Australia.

Table 5.1: Descriptive statistics for all drug decisions

Variable	Recommended (n=48)	Restricted (n=78)	Not recommended (n=63)	All Decisions (n=189)
Months since guidance released (timesincepub)	32.42 (25.86, 38.97)	33 (28.33, 37.67)	23.7 (20.3, 27.2)	29.8 (26.9, 32.6)
Number of RCTs	2.44 (1.60, 3.30)	2.68 (1.78, 3.58)	1.40 (0.98, 1.81)	2.2 (1.7,2.6)
Proportion of studies: RCT (studyrct)	0.75 (0.62, 0.88)	0.76 (0.66, 0.85)	0.62 (0.50, 0.74)	0.71 (0.64, 0.77)
Proportion of studies: Observational (studyobs)	0.08 (0.002, 0.16)	0.013 (-0.013, 0.038)	0.03, (-0.013, 0.08)	0.04 (0.01,0.06)
Proportion of studies: Not Reported	0.17 (0.06, 0.28)	0.23 (0.14, 0.33)	0.35 (0.23, 0.47)	0.25 (0.19, 0.32)
Economic Analysis: CUA (eccua)	0.54 (0.40, 0.69)	0.45 (0.34, 0.56)	0.38 (0.26, 0.50)	0.45 (0.38, 0.52)
Economic Analysis: CEA (eccea)	0.17 (0.057, 0.28)	0.19 (0.10, 0.28)	0.19 (0.09, 0.29)	0.19 (0.13, 0.24)
Economic Analysis: CMA (eccma)	0.063 (-0.0090, 0.14)	0.14 (0.06, 0.22)	0.05 (-0.006, 0.10)	0.09 (0.05, 0.13)
Economic Analysis: CC (eccc)	0.0 (0.0, 0.0)	0.013 (-0.013, 0.038)	0.015 (-0.016, 0.05)	0.11 (-0.004, 0.025)
Economic Analysis: NR	0.23 (0.11, 0.35)	0.21 (0.11, 0.30)	0.37 (0.24, 0.49)	0.26 (0.20, 0.33)
Sensitivity Analysis (sensanalysis)	0.46 (0.31, 0.61)	0.39 (0.27, 0.50)	0.17 (0.08, 0.27)	0.33 (0.27, 0.40)
ICER value (icercua)	£11,597 (£7,838, £15,357)	£21,496 (£7,160, £35,832)	£26,491 (£17,473, £35,510)	£19,879 (£13,442, £26,315)
Budget Impact (budgetimpact)	0.46 (0.31, 0.60)	0.68 (0.57, 0.79)	0.52 (0.40, 0.65)	0.57 (0.50, 0.64)
Patient group submission (patientgroupsub)	0.38 (0.23, 0.52)	0.30 (0.19, 0.40)	0.19 (0.09, 0.29)	0.28 (0.22, 0.35)
Number of patient group submissions (nopatientgroup)	5.08 (2.80, 7.36)	4.23 (2.24, 6.22)	1.49 (0.09, 2.90)	3.53 (2.42, 4.65)
Public Interest (publicinterest)	16.79 (4.52, 29.06)	7.74 (4.10, 11.39	4.52 (1.72, 7.32)	8.96 (5.4, 12.5)

Note: (95% Confidence Interval), i) n=26, ii) n=35, iii) n=24, iv) n=8

Table 5.2: Cost per QALY by recommendation, country and common medicines and uncommon medicines appraised

Country	Recommended			Restricted Recommended			Not Recommended		
	Mean All	Mean Common	Mean Uncommon	Mean All	Mean Common	Mean Uncommon	Mean All	Mean Common	Mean Uncommon
Australia	£12,270	£12,720	-	£18,778	£14,910	£23,613	£23,475	£28,300	£18,651
England	£13,793	£11,641	£15,358	£19,664	£21,400	£19,086	£34,190	£36,885	£26,105
Scotland	£4,458	£5,687	£3,843	£24,814	£10,991	£32,453	£25,935	£39,281	£7,252
Canada	-	-		-			-		

In the subsample that presented CUA, the average ICER value was £26,491 per QALY for not recommended decisions, in comparison to £21,496 per QALY for restricted recommendations and £11,597 per QALY for recommended decisions. The difference between the recommended CQG mean and the not recommended was statistically significant (p=0.002). The technology which had the highest reported ICER was for an appraisal in Scotland where the reported ICER was £250,000 per QALY for a PAH treatment.

The mean ICER for each country can be found in Table 5.2 by all medicines appraised, medicines appraised commonly by counties agencies' and those that were uniquely appraised by each country agency. The ICER estimates were analysed in these groups to understand the differences across the decision groups. The average ICERs across Australia and England are similar for the all recommended and restricted categories and the common recommended and restricted categories. The main differences occur between the not recommended group between Australia and England where the not recommended ICER across all decisions is £34,190 for England in comparison to £23,475 in Australia. This can be explained by the lower ICERs observed across the mean common medicines ICER and uncommon medicine ICER in Australia. The mean ICER values for Scotland are lower in all the recommended categories in comparison to Australia and England. This is the trend for the restricted ICER of common medicines appraised but a number of high ICERs for uncommon medicines result in a larger restricted ICER for all medicines appraised in Scotland in comparison to Australia and England. The Scottish common and uncommon medicines differ greatly with a mean ICER of £39,281 and £7,252, respectively.

Budget impact was reported in 69% of restricted decisions in comparison with 46% of recommended and 52% of not recommended. There was a statistically significant difference between restricted decisions and recommended decisions (p=0.001).

The analysis shows a higher level of public interest for recommended decisions, 16.8 articles per medicine in comparison with restricted decisions which had 7.7 articles per medicine and not recommended decisions where 4.5 articles per medicine were found. The differences from the reference decision were found to be statistically significant (p=0.03).

5.4.2 Regression model results

The results of three MNLM regressions are presented for the pooled sample of technology appraisals. The first regression included all decisions for the technology appraisals and the second model included a subset of technology decisions excluding the 34 SMC technology appraisals with

limited information discussed previously. The third model included those technology appraisals that included CQG.

The first regression (Table 5.3) included the sample of 189 technology appraisals. The goodness of fit of the model was considered using the McFadden pseudo R^2 and the percent correctly predicted. The pseudo R^2 ranges from 0 to one and higher values indicate a better model fit. The McFadden pseudo R^2 was 0.16 for model 1. The model correctly predicted 74% of restricted decisions, 62% of not recommended decisions and correctly classified 40% of recommended decisions.

A technology appraisal that was performed on a cardiovascular medicine rather than a cancer medicine decreased the likelihood of not recommending by 74% which was statistically significant (p=0.01). There was a similar reduction for restricted decisions with reference to recommended but this was not found to be statistically significant.

The older technology appraisals were associated with a statistically significant reduction in the probability of not recommending in comparison to recommending. The fact that a technology appraisal was a review of a previous decision did not make a statistically significant difference to the mean probability of not recommending or a restricted decision.

An additional RCT statistically significantly reduced the probability of not recommending in comparison to recommending by 21% (p=0.046). The effect of the reduction in the probability of restriction in comparison to recommend was smaller and not statistically significant. Those technology appraisals that were accompanied by observational studies in addition to RCTs were associated with a larger decrease in the probability of not recommending and restriction in both comparisons with recommended decisions.

The nature of the economic analysis supporting the decision was captured by two variables, CUA and CEA. CUA was associated with an increase in the probability of not recommending in comparison to recommending, whereas it was associated with a decrease in the probability of restriction rather than recommending. The use of CEA was associated with both a decrease in both comparison groups' probabilities. None of these effects were found to be statistically significant. The reporting of sensitivity analysis was statistically significant (p=0.03) in reducing the probability of being not recommended in comparison to recommended. This was not statistically significant in the restricted group comparison with recommended.

The reporting of budget impact was associated with a large increase in the probability of restriction in comparison with recommended and was statistically significant (p=0.002). The

budget impact increased the probability of not recommending in comparison with recommending by a smaller magnitude but was not statistically significant.

The public interest variable was found to be statistically significant in the pooled regression. Increases in the measure of public interest show a fall in the probability of not recommending in comparison with recommending (p=0.03) or restricting in comparison with recommending (p=0.07). Two supplementary regressions (results not shown here) were run to test the effect of excluding either public interest or the number of patient group submissions. These showed very small changes to the coefficients and small changes to the significance of the variables included.

In a supplementary regression three dummy variables were included in model 1 to account for the country in which the decision on the technology was made and clustering was accounted for across the three countries (Table 5.5). Dummy variables and adjustment for clustering were introduced for Australia, Scotland and Canada with England as the reference case. The analysis showed both Scotland and Canada were statistically (1% significance level) more likely to make a restricted decision in comparison to a recommended decision and more likely to make a not recommended decision in comparison to a recommended. A number of the variables remained statistically significant and the magnitude of effect did not change greatly across the variables (disease area, public interest, RCT number, study observational). The introduction of country specific variables and adjustment for clustering did influence some of the other factors, making the time since guidance in the comparison of not recommended and recommended and type of economic analysis and budget impact in the comparison of restricted and recommended statistically insignificant. A number of variables in the restricted category in comparison to the recommended became statistically significant at the 5% and 1% level (time since guidance, patient group submission and public interest variable).

The second analysis tested the effect of the limited information provided in the excluded SMC decisions. The second regression correctly predicted 69% of restricted decisions, 57% of not recommended decisions and 46% of recommended decisions. None of the coefficients swapped sign but there was a large change in the CUA coefficient for both outcome comparisons and the budget impact coefficient for the comparison of not recommended with recommended. The significance of some coefficients changed and this may be explained by the resulting reduction in the sample size to 155 (Table 5.3).

The pooled sample included 85 technology appraisals that had estimates of CQG, 26 which were recommended, 35 restricted recommendation and 24 not recommended. A sub-sample

regression (Table 5.4) of those technologies was performed and the regression correctly predicted 60% of restricted decisions, 63% of not recommended decisions and correctly classified 50% of recommended decisions. The pseudo R^2 was 0.2006.

Increases in the CQG estimates were associated with a decrease in the probability of both not recommending and restricting in comparison with recommended. The results were statistically significant in the not recommended versus recommended group at the 10% level but were not statistically significant in restricted recommended versus recommended. Those technology appraisals which reported budget impact, sensitivity analysis and higher levels of public interest were statistically significantly more likely to be restricted than recommended. The older decisions, cardiovascular medicines, those accompanied by sensitivity analysis and those with a patient group submission all statistically significantly reduced the probability of not recommending in comparison with recommended.

The introduction of country specific dummy variables in model 3 changed the coefficients slightly and the CQG became statistically insignificant in the not recommended versus recommended group similar to the restricted recommended versus recommended in model 3. It should be noted that the results should be interpreted cautiously as the standard errors were large for the dummy variables in model 3 owing to few not recommended decisions in NICE decisions for cancer and cardiovascular drugs and the smaller subsample. The pseudo R^2 demonstrated improved model fit with the introduction of the dummy variables in comparison to model 3.

There were too few technology appraisals reporting cost per life-year gained to support a separate analysis of cost-effectiveness per outcome appraisals.

Table 5.3: Model 1 and Model 2 regression results

Variable	Model 1			Model 2		
	Relative Risk Ratio (RR)	Robust s.d.	p-value	Relative Risk Ratio (RR)	Robust s.d.	p-value
Not recommended vs Recommended						
diseasearea	0.2445058	0.1334756	0.010***	0.2584849	0.1629263	0.032**
rctno (number)	0.7941144	0.091661	0.046**	0.8597941	0.0999217	0.194
eccua	1.154654	0.820358	0.840	2.360742	1.787968	0.257
eccea	0.8353286	0.6644449	0.821	1.908197	1.597382	0.44
studyobs	0.1261477	0.1164031	0.025**	0.162627	0.1566555	0.059*
sensanalysis	0.1869046	0.10649	0.003***	0.192696	0.1140577	0.005***
timesinceguidance	0.9701117	0.0114174	0.015**	0.9602064	0.0120886	0.001***
patientgroupsub	0.9678549	0.0364941	0.386	0.9781417	0.0375047	0.564
publicinterest	0.9570102	0.0190524	0.027**	0.953032	0.0226686	0.043**
budgetimpact	2.167374	1.166211	0.151	3.489901	1.978651	0.027**
review	1.099173	0.9066001	0.909	1.246611	1.023834	0.788
Restricted recommended vs Recommended						
diseasearea	0.486853	0.2396647	0.144	0.5087713	0.277806	0.216
rctno (number)	0.9876587	0.0533437	0.818	1.04193	0.0735524	0.561
eccua	0.328006	0.2164812	0.092*	0.6198758	0.4189568	0.479
eccea	0.3847832	0.2989747	0.219	0.8199928	0.6447909	0.801
studyobs	0.0949439	0.1293192	0.084*	0.1072556	0.1448021	0.098*
sensanalysis	0.8540079	0.4284739	0.753	0.8460304	0.4327981	0.744
timesinceguidance	0.997945	0.0100088	0.837	0.9814319	0.0113908	0.106
patientgroupsub	1.025246	0.0249569	0.306	1.03208	0.0254231	0.2
publicinterest	0.9851029	0.0081235	0.069*	0.9850199	0.0069857	0.033**
budgetimpact	4.626985	2.257014	0.002***	6.566758	3.33828	0.000***
review	0.8930886	0.6773815	0.881	0.9117957	0.6832669	0.902
Number of observations	189			155		
Log pseudo-likelihood	-171.68671			-69.989124		
Pseudo R^2	0.1585			0.1746		

Table 5.4: Model 3 regression Model results

Variable	Model 3			Model 3 (Supplementary)		
	Relative Risk Ratio (RR)	Robust s.d.	p-value	Relative Risk Ratio (RR)	Robust s.d.	p-value
Not recommended vs Recommended						
Costperqaly (cqg)	1.000044	0.0000263	0.098*	1.000037	0.0000294	0.203
diseasearea	0.3938765	0.217414	0.091*	0.5270375	0.3873951	0.384
rctno (number)	0.8957413	0.0713806	0.167	0.9887396	0.1003362	0.911
sensanalysis	0.2440817	0.1716249	0.045**	0.3772125	0.2669157	0.168
timesinceguidance	0.9601926	0.0160943	0.015**	1.015886	0.027151	0.555
patientgroupsub	0.9328841	0.0106916	0.000***	1.11299	0.0909948	0.190
publicinterest	0.961838	0.0270538	0.167	0.9510433	0.0305308	0.118
budgetimpact	1.751633	0.7729656	0.204	0.3689346	0.3877018	0.343
review	2.119724	1.824898	0.383	3.283758	2.287823	0.088*
scotland	-	-	-	83.13191	105.3851	0.000***
australia	-	-	-	550.8798	919.7628	0.000***
Restricted recommended vs Recommended						
Costperqaly (cqg)	1.000043	0.0000341	0.205	1.000038	0.0000369	0.308
diseasearea	0.889832	0.1329839	0.435	1.112464	0.4211866	0.778
rctno (number)	1.008062	0.0931994	0.931	1.10356	0.1269025	0.391
sensanalysis	0.9735883	0.3376297	0.938	1.482655	0.6256125	0.351
timesinceguidance	0.9783618	0.0107575	0.047**	1.025357	0.0098049	0.009
patientgroupsub	0.9975973	0.0288034	0.934	1.143655	0.0245178	0.000***
publicinterest	0.989338	0.0037129	0.004***	0.9816605	0.0118023	0.124
budgetimpact	9.869959	4.76514	0.000***	2.995473	0.8216106	0.000***
review	1.855619	2.195938	0.601	2.809609	3.407605	0.394
scotland	-	-	-	27.30291	24.71544	0.000***
australia	-	-	-	165.2192	137.7452	0.000***
Number of observations	85			85		
Log pseudo-likelihood	-73.71167			-68.413167		
Pseudo R^2	0.2006			0.2580		

***= statistically significant at the 1% level, **=statistically significant at the 5% level, *= statistically significant at the 10% level

Table 5.5: Supplementary regression country dummies

Variable	Model 1 (Supplementary)		
	Relative Risk Ratio (RR)	Robust s.d.	p-value
Not recommended vs Recommended			
diseasearea	0.218361	0.170183	0.051*
rctno (number)	0.845214	0.0670763	0.034**
eccua	1.449047	0.9681036	0.579
eccea	1.573341	0.6770083	0.292
studyobs	0.149174	0.1571916	0.071*
sensanalysis	0.184905	0.1742794	0.073*
timesinceguidance	0.979086	0.0167659	0.217
patientgroupsub	1.09263	0.0387232	0.012
publicinterest	0.964431	0.0077073	0.000***
budgetimpact	1.229409	0.2389235	0.288
review	1.084773	1.052287	0.933
australia	23.19655	24.22948	0.000***
scotland	32.38492	20.45078	0.000***
Canada	4.695003	6.226069	0.244
Restricted recommended vs Recommended			
diseasearea	0.440805	0.2527405	0.153
rctno (number)	1.033236	0.0541858	0.533
eccua	0.489922	0.4223648	0.408
eccea	0.708912	0.414761	0.557
studyobs	0.101917	0.1270261	0.067*
sensanalysis	0.921645	0.503212	0.881
timesinceguidance	1.015623	0.0074878	0.035**
patientgroupsub	1.113824	0.0240655	0.000***
publicinterest	0.988429	0.0042842	0.007***
budgetimpact	2.291007	1.618887	0.241
review	0.952992	0.5942747	0.938
australia	13.95652	3.717845	0.000***
scotland	10.70257	5.200454	0.000***
Canada	2.304786	0.781788	0.014**
Number of observations	189		
Log pseudo-likelihood	-162.64696		
Pseudo R^2	0.2028		

***= statistically significant at the 1% level, **=statistically significant at the 5% level, *= statistically significant at the 10% level

5.4.3 Regression diagnostics

A number of diagnostic tests were performed on the regression models and the tests and a brief summary of the results can be found as follows:

- Collinearity between variables was considered using pair wise comparisons and the only variables to show weak correlation were for between number of patient groups/public interest (r=0.21) and CQG/number of RCTs (r=-0.14).
- Multicollinearity between variables was considered using Variance Inflation Factors (VIF). The mean values VIF values of 1.67 for model 1 and 1.43 for model 2 did not indicate multi-collinearity using this test.
- The regression coefficients and statistical significance were not sensitive to changes in the structure of the model such as exclusion of number of patient groups.
- Testing whether the MNML is an adequate specification by testing whether the IIA assumption holds using the Hausman test (Hausman and McFadden, 1984, McFadden et al., 1976) and the Small-Hsaio test (Small and Hsiao, 1985). For model 1 we can conclude that we fail to reject the null hypothesis of IIA but for model 2 and 3 the results are inconclusive and depend on the specification test used. The details of these are reported in Table 5.6.

Table 5.6: Hausman test and Small-Hsaio test

	Test	Omitted outcome	Chi2	P>chi2
Model 1	Hausman Test	Not recommended	-2.152	1.000
		Resticted	-6.379	1.000
	Small-Hsiao	Not recommended	12.482	0.408
		Restricted	12.368	0.417
Model 2	Hausman Test	Not recommended	-4.554	1.000
		Resticted	-9.914	1.000
	Small-Hsiao	Not recommended	91.470	0.000
		Restricted	61.553	0.000
Model 3	Hausman Test	Not recommended	2.454	0.982
		Resticted	3.437	0.944
	Small-Hsiao	Not recommended	374.935	0.000
		Restricted	138.584	0.000

5.5 Discussion

5.5.1 Common factors associated with decisions (non-context specific)

The study found some evidence of the association of common factors with the reimbursement decision outcome across the four national agencies with respect to clinical evidence, two non-evidence factors (disease area and public interest) and process (date of decision and country dummy variables). The results tended to show no common association across countries with respect to the cost-effectiveness estimate for each medicine appraised, although one specification of the model showed a significant result at the 10% level. Forty percent of decisions were categorised as restricted decisions and this proportion was found across the medicines considered for these four agencies demonstrating the importance of considering all three categories of decision rather than a binary categorisation (recommend/not recommend).

The type of clinical evidence, and the number of studies from which it is derived, are commonly important for reimbursement decisions internationally and similarly supports another study of the importance of clinical considerations that considered a univariate analysis of factors in national reimbursement decision-making (Clement et al., 2009). There was on average, two main RCTs supporting the reimbursement decision for medicines appraised by the four agencies and those medicines with a larger number of RCTs were more likely to be recommended than not. Many of the manufacturer's submissions were based on one main RCT and therefore efficacy and modelling of the effectiveness over time. There tended to be a lack of observational data used to monitor the actual effectiveness because many of the decisions concerned the first reimbursement decision for the medicine. The agencies do not consistently review all the medicines and compare the modelled cost–effectiveness (efficacy) and resulting cost-effectiveness at a later point in time. Where recommended decisions are made on health economic analysis supported by one RCT in the processes of single technology appraisal used by the four agencies this will be a partial basis for decision-making (Sculpher et al. 2006). When available, the influence of observational data could reflect that this type of study was complementary to the RCT evidence and allows the committees further understanding of the external validity issues surrounding a new medicine.

The disease area for which the medicine is indicated to treat was found to be associated with the decision. The time element has been controlled for in the regression models so the increased likelihood of cardiovascular medicines being recommended does not reflect the fact that many of the cardiovascular medicines are on average older than the cancer medicines and perhaps more

likely to be approved because of less stringent evidence requirements. The guidance included in this study was published prior to the introduction of new criteria such as the NICE end of life supplementary guidance. It is therefore interesting that across agencies cardiovascular medicines had a greater chance of being recommended in comparison to cancer medicines when there was no priority explicitly given in the agencies stated criteria (pre-2008). There are two possible related explanations for this finding, which relate to the selection of medicines assessed by these national agencies. Firstly, the cardiovascular medicines appraised may have been better at satisfying agencies requirements for demonstrating value in comparison to cancer medicines across these agencies. Secondly, differences in the composition of medicines appraised across the agencies may affect this, for example NICE select the medicines that are evaluated, whereas the manufacturer submits evidence to the CDR, PBAC and SMC for assessment and appraisal.

The level of public interest was a newly introduced non-evidence factor that was found to have a moderate and statistically significant effect on the probability of decision outcome. This is consistent with the idea that political and institutional contexts of a technology appraisal decision are important in determining access to healthcare resources (Goddard et al., 2006, Wirtz et al., 2005). The public pressure may have an impact on the evolution of the processes or the introduction of new factors (as has been seen with the introduction of the NICE end of life supplementary guidance) or could directly impact upon the extent of the deliberations or justification provided for a decision across these agencies. It is important to note that the level of public interest, as measured here, could be accounting for country specific factors which are not included in the analysis. However, it the variable remained statistically significant when country specific variables were introduced into the analysis.

The results indicate that over time the fourth hurdle may have become tougher to pass and gain a recommended decision for cancer and cardiovascular medicines across the four countries. The results show that older medicines were more likely to be recommended in comparison to not recommended across the four agencies. This may reflect a combination of common evolution in the agencies processes and methods used to conduct HTAs including tougher evidence requirements overtime.

5.5.2 Process and health economic analysis within and across countries

There was no common association with the cost-effectiveness estimate and the decision across the four countries and categories in two of three regression models. This study was not designed

to assess the validity of the use of cost-effectiveness thresholds in decision-making, a topic on which there is an extensive literature both for and against (see for example (Birch and Gafni, 2006), (Birch and Gafni, 1992) and (McCabe et al., 2008)). This study concerns the influence/impact that the use of such thresholds might have on decision-making. Previous studies of NICE, pooled estimates of CLG and CQG enable a sufficient sample size to test the influence of the ICER (Dakin et al., 2006, Devlin and Parkin, 2004). This study considered exclusively the effect of the value of the CQG ratio in a sub-sample that reported this information across the national agencies. Although the mean cost per QALY was higher in those appraisals which led to a not recommended decision, when other factors were controlled for, the absolute size of the CQG ratio had a small but statistically insignificant effect on decision-making. Even if agencies were using different thresholds, a positive significant impact between the ICER estimate and the decision would be expected. These results may be explained by the lack of an explicit threshold and differences in the interpretation and weighting of evidence in the countries, the impact of process on the use of health economic analysis and the mix of common medicines and uncommon medicines appraised across the agencies.

NICE is the only agency to be explicit about its threshold range, which it specified to be in the range of £20,000 to £30,000 per QALY gained in 2004. There have been numerous studies on what the threshold is and should be for the NHS in England (Appleby et al., 2009, Culyer et al., 2007, Devlin and Parkin, 2004, Grosse, 2008, McCabe et al., 2008, Williams et al., 2007) but little discussion of the foundations of a threshold and its use in other countries. It has been suggested that other authorities are operating implicit thresholds which are not public (George et al., 2001). However, the absence of a significant relationship would suggest either that the other three agencies in this study were not operating implicit thresholds for cancer and cardiovascular medicines for these medicines or there are factors that are not sufficiently controlled for in the analysis such as variation in process across countries.

Controlling for the influence of process variation that occurs across agencies and systems is more complex in this type of quantitative study because it requires sufficient countries with sufficient similarities and differences in the reimbursement process. This analysis used simple intercept dummy variables to control for process across countries to understand whether this could be important and was found to be associated with the decision for some countries depending on the decision outcome comparison. Therefore the role of economic analysis on decisions may be dependent on the processes. Differences in process across countries may influence decisions in two ways, either independently of other factors such as economic analysis or by modifying the

way in which decision-makers within each reimbursement system consider factors such as economic analysis. The agencies processes may also evolve overtime and differences between agencies processes may converge or diverge depending on the time period at which the decision for the medicine was made.

The inclusion of country specific dummy variables improved the predictive power of the regression and may demonstrate that process factors influence the way in which evidence is considered, even when there are similar evidence requirements, particularly with respect to restricted decisions. There are a number of process differences across the four countries that can be considered by the process variation within the agency providing the decision and variation in the entire reimbursement system process.

The agencies all require the manufacturer to present evidence of the clinical and cost-effectiveness but NICE also has two separate processes of appraisal including an academic assessment group for the MTA process and a evidence review group (ERG) for the STA process to review the evidence. The STA process was designed to speed up the assessment of medicines and has considered a number of new cancer medicines by only requiring a review of the evidence submitted by the manufacturer similar to the other reimbursement agencies. The use of the MTA process may provide decision-makers with more information on the appropriateness and uncertainty surrounding the evidence for committee deliberations and consideration of patient subgroups. This difference in process may result in the consideration of different patient subgroups from the manufacturer and result in different recommendations in comparison to those only considering the manufacturers assessment.

The impact of third party assessment is illustrated in the data when considering the explanation for differences in the mean ICER in the not recommended group for all medicines. The mean ICER of both Australia and Scotland are lower than England which may be due to the fact that the submission is prepared by the manufacturer rather than reviewed by an independent group or provided by an independent assessment group. The wide difference in estimates between the common and uncommon medicines sample for Scotland can be explained by the plausibility of the manufacturers estimate. This was identified by considering the specific SMC guidance for the uncommon medicines, three of which were for cardiovascular medicines and one for a cancer medicine. The cancer medicine was topotecan for the treatment of relapsed small cell lung cancer (SCLC). The economic analysis reported an ICER of £21,582 per QALY but the sensitivity of the ICER to a number of key parameters led the SMC committee to decide that the ICER would potentially be higher than the point estimate provided. The estimates provided in the

cardiovascular medicines SMC guidance were judged not plausible because of assumptions or the structure of the model. The lack of third party assessment and differences in the mix of medicines appraised by the agencies may explain the differences in mean ICER in the sample and also the lack of statistical significance of the common ICER on the reimbursement decision across countries.

The process for cancer medicine reimbursement in Canada has been complex and continues to evolve and may explain cross country differences in decisions for these medicines. There have been a number of changes to the process for oncology medicine appraisal in Canada starting with a one year interim Joint Oncology Drug Review (JODR) process where the CDR provided clinical and pharmacoeconomics reviews for ambulatory new medicines in 2007 which form the basis of the sample in this study (Personal communication: Ministry of Health and Long term care, 2008). It was then expected that the JODR process would be made the responsibility of the CDR after the one year period (CADTH, 2011c). Instead, a new process has begun since 2010 called the pan-Canadian Oncology Drug Review (pCODR) to consider the clinical and cost-effectiveness of medicines after the iJODR demonstrated the cross provincial value to provide decision-making for cancer care. The reviews have begun and the first one will be considered by the Expert Review Committee (pERC) published at the end of October 2011 (pCODR, 2011).

The process by which a committee(s) considers the assessment and appraises the evidence and non-evidence factors varies across the reimbursement systems. There are single committees that assess and appraises the evidence for NICE (Technology Appraisal Committee), CDR (Canadian Expert Drug Advisory Committee) and JODR (Committee to Evaluate Drugs). There are two separate committees in PBAC and SMC, one with the task of providing the technical assessment and the other with providing an appraisal of the evidence and other factors. The PBAC (appraisal committee) is advised by the Economics Sub-Committee (ESC) advises on the economic analyses and technical aspects of these analyses which includes health economists, clinical specialists, epidemiologists, general practitioners, public health academics, Health Scientists, Pharmacologist and one industry representative (PBAC, 2011). The SMC board (appraisal committee) is advised by the New Drugs Committee (NDC) which consists of 21 members including clinicians, pharmacists, health economists, a statistician and two industry representatives. Medical practitioners, pharmacologists, pharmacists and Health economists are represented in at least one of the committees across all of the agencies but the SMC do not include a health economist on the SMC appraisal committee. Members of the public are represented across all committees although patient representatives are only present on the iJODR committee for cancer medicines in Canada.

The separation of the technical and appraisal committees and differences in the composition of committees across the agencies may result in differences in the role that economic analysis plays within each of the processes and subsequently different decisions.

The NICE STA process is distinctive in that a published provisional decision stage occurs before the final decision is made by the agency, where subsequently there is no resubmission opportunity only appeal. The provisional recommendation is made at the Appraisal Consultation Document (ACD) stage and may either be a more 'restrictive recommendation', 'not recommended' or a 'minded not recommended' (NICE, 2008). The minded not recommended allows the manufacturer to submit new cost-effectiveness analyses to reduce the uncertainty surrounding the decision. This is in contrast to the other four agencies processes where manufacturers can only resubmit following the final decision but the manufacturer may have the opportunity to request reconsideration of the recommendation in the CADTH CDR process if the CDR has not followed procedures or the recommendation is not supported in light of the evidence submitted (CADTH, 2010). The difference in NICE process may lead to identification of possibilities where a restrictive recommendation can be made in a subgroup rather than not recommending in comparison to the first decision made by the other reimbursement agencies. This may therefore technically mean that all submissions up to the final submission (whether this is the first submission or a resubmission) should be excluded from any comparison across reimbursement agencies. This is important because the ICERs included for the initial decisions may not have been considered plausible and this would explain the lack of common association between the ICER and the decision

The second set of process differences are with respect to the entire reimbursement or fourth hurdle system in which the reimbursement agencies operate. The systems vary in the number of entities contributing to the reimbursement decision and the nature of the decisions, some containing a separate entity with a process for negotiating price and others allowing the manufacturer the freedom to set price.

The reimbursement systems may provide different incentives for manufacturers submitting to the reimbursement agency that use HTA because of the other institutions involved in the reimbursement systems. Ultimately the final decision on access to a medicine in the systems depends on the decision of the clinician but the systems provide different complex processes by which this final decision is reached. NICE is a single institution that provides mandatory reimbursement decisions for which funds should be made available to provide the medicines in 3 months. The other reimbursement agencies provide advisory recommendations where a second

stage determines the formulary lists of those medicines that can be provided by clinicians, SMC to the health boards in Scotland, CADTH CDR, JODR to the health plans in Canada and PBAC to the Ministry of Health in Australia. The second stage may influence the manufacturers focus and preparation of evidence with respect to patient groups and details of the submissions (relationship between price and reimbursement) and therefore the initial decisions made by these reimbursement agencies.

In England and Scotland manufacturers are free to set the prices of medicines and NICE and SMC signal their demand for the medicine at each price by an explicit indication of the threshold range. There are no explicit thresholds for cost-effectiveness evidence in Australia and Canada. Patented medicines prices are negotiated in Australia. The Pharmaceutical Benefits Pricing Authority (PBPA) makes recommendations to the Ministry of Health after the medicine has been recommended for listing in the Pharmaceutical Benefits Schedule in Australia (Australian Government, 2011b). In Canada prices are reviewed on introduction by the manufacturer by the Patented Medicine Price Review Board (PMPRB) and negotiated when found to be excessively priced. The PMPRB reviews whether a medicine is excessively priced by considering other medicines in the same therapeutic class and a comparison of the price sold in other countries. Further price regulations are in place across the health plans through volume agreements and rebates as a condition of inclusion in the health plans formulary (PMPRB, 2011). In the situation where price is negotiated ex post by a separate institution the result may result in different restrictions on reimbursement to those systems that allow manufacturers the freedom to set price.

Further understanding of the impact of process differences on the decision would need to be explored in a number of single country studies with variables using similar constructs where possible. But of course this is limited by the transparency of the documentation of evidence and other factors reported in the documentation and the ability of a number of quantitative variables to control for some factors that are qualitative in nature.

5.5.3 Limitations

The data show that aspects of clinical evidence, some included non-evidence factors and process factors are commonly associated with the decision to recommend a medicine across countries. However, these findings should be considered cautiously, as the regression models were considered to have low predictive power, although this was similar to other studies using such methods and were better at predicting not recommended decisions and restricted decisions than

recommended decisions. There are potentially multiple reasons for the poor predictive power of the regression and this may be caused by lack of sufficient controls for process differences between countries as discussed previously, unmeasured factors through lack of reporting across countries agencies, qualitative nature of some factors in decision-making and relationships between factors.

The extent of reporting and transparency of each agency limit the analysis of the factors influencing decisions. All the agencies provided some details for the evidence factors but the details varied across the agencies public documentation. NICE is the only agency that provides detailed documentation of the deliberations, stating other non-evidence factors. Therefore non-evidence factors cannot be constructed directly from the public summaries of the decisions across all the agencies and characteristics of medicines or proxy measures such as public interest were used in this study to start to explore the influence of non-evidence factors on decisions.

It would have been useful to explore other characteristics of the evidence that have been included in previous individual agency/country analysis where the quantitative evidence factors are tailored to the information publically available. The inclusion of all these factors was constrained in this study by the lack of common reporting across countries. This study excluded quantitative measures on both the clinical uncertainty (internal validity/external validity) and economic uncertainty (structural uncertainty and parameter uncertainty) and this may explain the lack of predictive power of the regression models. The measurement of such variables would have been included in this study if there had been sufficient public documentation to collect data across all of the countries agencies. However, even if such information had of been available there are further complexities because of the subjective nature of establishing a quantitative variable that can sufficiently and consistently capture the decision-makers deliberations on these evidence factors across the agencies. This is partly illustrated by the differences across agencies with regards to the guidelines for presenting sensitivity analysis (deterministic and probabilistic sensitivity analysis).

A further explanation for the low explanatory power could be due to missing factors that are inherently qualitative in nature and cannot be easily summarised in a quantitative measure. There are some qualitative factors in the deliberations for decision-making that are difficult to summarise in a public document such as the nature of the meeting discussions, order of evidence consideration and balance of input of different decision-makers in deliberations.

Factors that are found to be associated with decisions do not necessarily correspond with influence on decisions. For example, the observation that the conclusions of the economic analysis are associated with the decision outcome does not necessarily mean that the economic analysis has influenced the decision outcome. Buxton describes this with respect to the influence/impact of economic analysis on health policy in the UK. As (Buxton, 2006) emphasises:

> The consistency of subsequent policy with the conclusion of a study does not necessarily indicate that the study has influenced that policy. The consistency may be a happy coincidence, with the evaluation used rather as a drunken man may use a lamp post – more for support than illumination. (p.1134)

There may be situations in which the quantitative variables included in analysis cannot be considered independent and this could undermine the conclusions drawn on the association of factors. Cost-effectiveness and clinical effectiveness were excluded from the analysis because they should be considered endogenous – both will be related to the decision and clinical effect is directly related to the cost-effectiveness estimates through the pricing decision. However, even in those factors initially considered independent, there was for example, a weak relationship between the number of RCTs and the CQG ratio. These factors may be endogenous due to an unobserved variable which is correlated with both of these factors. For example, perceived potential cost-effectiveness of a medicine could increase the willingness to invest in trials.

The main output of the reimbursement agencies in this study was the reimbursement decision outcome but this may be considered an intermediate outcome to the system level objectives. These systems all have the objective of improving the health of the population with respect to other objectives but the way in which the agency influences utilisation and the health of the population may ultimately be considered the final outcome of the agency. The intermediate decision outcome of the reimbursement agency may not necessarily translate to the final outcome in each country because the agency is only one of many entities with different objectives that influence the final outcomes. Research should therefore also consider the influence of economic analysis and other factors on actual use rather than the intermediate outcome of the reimbursement decision.

5.6 Conclusions

The results show that some factors are commonly important across systems and this may be an indication of a degree of international consensus on which elements of HTA are important in

determining reimbursement decisions in the selected countries. In spite of the introduction of non-evidence factors such as public interest the models had low predictive power. However, this was improved by the introduction of country specific dummy variables, indicating the importance of local process differences. Future research will need to focus on country specific models as larger samples of decisions become available to be able to identify process differences between countries. This will need to be coupled with more transparent public documentation by the agencies of the evidence and considerations, to be able to include all factors, to understand further how process can explain differences in decisions across countries.

The desirability of a decision system from a societal perspective will depend on the context and the objectives (access, health maximisation, reducing inequalities, and cost-minimisation) which it has been designed to achieve. In countries with similar decision contexts, systems with similar institutional characteristics may develop with common methods and processes, as a result of similarities in their objectives. On the other hand apparently similar decision processes may reach different decisions if their context and objectives differ. The desire to define the "ideal" process in scientific terms must be tempered by the need for consistency between the system and the political decision context and objectives within which it operates.

Chapter 6: Pharmaceutical Reimbursement Decision-Making: Haute Autorité De Santé (HAS) use of Relative-Effectiveness versus Scottish Medicines Consortium (SMC) Use of Cost-Effectiveness

Abstract

Objectives: Chapter 3 and 4 categorised pharmaceutical reimbursement agencies' objectives, processes and methods of assessment and appraisal found this to vary significantly across countries. The aim of this study is to examine the impact of differences in process and methods upon reimbursement recommendations produced in France and Scotland. There is a particular focus on the contribution of health economic analysis.

Methods: A framework for classifying reimbursement systems was used to analyse the two systems. Recommendations were compared for 2010 and a detailed qualitative analysis of the evidence and the issues reported for common medicines evaluated by both reimbursement agencies. Reasons for discrepancies in recommendations were analysed and case studies selected to illustrate the common reasons.

Results: Thirty-nine common medicines were identified between 2006 and 2010, treating a variety of diseases for which the SMC tended to provide more restrictive, or did not recommend, listing. Similarities in clinical evidence submitted and the respective reimbursement committee's issues were reported. Differences in recommendation can be explained by a combination of the manufacturer's freedom to set price and incentives provided by the formal consideration of economic analysis and quality of life, process for addressing uncertainty in evidence, alongside differences in relevant comparators medicines, relevant outcomes, treatment guidelines, submission of network meta-analysis and the propensity to use such evidence synthesis methods in decision-making.

Conclusion: This study identified some hypotheses and explanations for differences in recommendations such as agency organisational process factors, local differences in clinical guidelines and comparator treatments, methods of evidence synthesis and the use of health economic analysis. However, the differences may be associated with other contextual factors

such as politics, cultural traditions, and local physician prescribing patterns rather than the analytical methods used or the agencies' processes. Further research using larger datasets may allow stakeholders to assess the desirability of differences in some of these factors.

6.1 Introduction

Governments intervene in pharmaceutical markets to promote health and affordable access to pharmaceuticals, whilst balancing the R&D incentive for global pharmaceutical manufacturers to invest in future medicines (OECD, 2008). On the demand side, the collective systems of pricing and reimbursement are one means by which these objectives can be achieved. Health care systems differ in the processes they follow and the evidence they require from manufacturer's when evaluating new pharmaceuticals for inclusion on their public formulary. Chapter 4 identified that many developed countries consider evidence on clinical effects and costs and 20 out of 34 OECD countries report that they require cost-effectiveness analysis in the manufacturer's submission to the reimbursement entity. One exception is the French reimbursement system agency - Haute Autorité de santé (HAS) - which does not require health economic analysis for new medicines and separates pricing decisions from consideration of the clinical efficacy and relative-effectiveness of medicines. The law on financing and social security of 2008 required HAS to consider medico-economic analysis in order to introduce wider methods of appraisal for medicines prior to the reimbursement and pricing decision. The agency established the Commission évaluation économique et de santé Publique (CEESP) to start considering the methods and provide appraisals for selected high priority medicines but is still deemed separate from the first listing assessment and appraisal of the clinical efficacy and effectiveness for new medicines.

A number of studies have considered comparisons of the influences on reimbursement recommendations for systems that use similar processes and evidence requirements (Barbieri et al., 2009, Cairns, 2006, Clement et al., 2009, Lexchin and Mintzes, 2008, Raftery, 2008). This literature has focused on comparisons of decisions at the individual technology assessment level for the evidence informing decisions by the National Institute for Health and Clinical Excellence (NICE) in England, Pharmaceutical Benefits Advisory Committee (PBAC) in Australia and the Canadian Agency for Drugs and Technologies in Health (CADTH) Common Drug Review in Canada. However, there are no studies that directly compare the processes and recommendations of agencies that use health economic analysis with those that do not require such evidence for making reimbursement recommendations.

An understanding of the impact of different reimbursement processes and methods of evaluation will help to evaluate the desirability of such differences across countries and help stakeholders identify best practices for these reimbursement systems given their objectives and health care

system context. The following sections describe the objectives, methods results and conclusions from the study. Limitations of the approach and the need for further research are discussed.

6.2 Objective

This study compared the reimbursement systems for pharmaceuticals in France and Scotland, in order to gain an understanding of the impact of process differences on the listing recommendations produced by each country. There was a particular focus on the contribution of health economic analysis to any differences as, in other respects, the systems are broadly similar with respect to requiring evidence on safety, efficacy and relative effectiveness to provide recommendations for reimbursement. Insights gained into the influence of health economic analysis from this qualitative analysis will be helpful in designing further studies of impending changes to the French and Scottish systems, and in wider studies of other agencies.

6.3 Methods

This study was based on detailed literature and documents, supplemented by consultations with staff members at the respective HTA agencies in Scotland and France - the Scottish Medicines Consortium (SMC) and the Haute Authorité de santé (HAS) and researchers active in the HTA field in France and Scotland. The first step was to obtain a clear picture of the operation of each reimbursement decision-making system from published commentaries and the publicly available documents of the agencies themselves. The differences in process and decision criteria were identified using a framework for describing and classifying reimbursement systems (Hutton et al., 2006). The framework classifies systems at a policy implementation level and technology decision level. From this any differences in processes and decision criteria were identified.

The similarities and differences in listing recommendations for both agencies at the technology decision level were considered by collecting, for both agencies, for new medicine and extension of indications in 2010. This covered a narrower group of medicines assessed by HAS as they assess all medicines and provide reassessment at 5 years. The listing recommendations of both agencies were classified by using a categorisation developed by Raftery *et al.*, which distinguishes between the different types of restriction. The classification included; recommend in line with marketing authorisation, minor restriction (specialist use/monitoring of patient), major restriction (limited to line of therapy, patient subgroup, intolerant to existing treatments) and not recommended

(Raftery, 2006). The classification additionally accounted for the type of HAS recommendation; National Insurance and hospital use or hospital use only and whether additional observational studies were requested.

In order to provide explanations for differences in recommendations between the two agencies the HAS English language translated opinion documents were extracted from the HAS website for recommendations between 2005 and 1st of January 2010 and were matched with SMC advice for the same medicine and patient indication. The HAS agency prioritised the translation of advice by those medicines that had gained a European Marketing Authorisation (EMA) and there were no major changes to the agencies evidence requirements or processes during this period. The data extracted from the SMC and HAS recommendation documents are presented in Table 6.1.

The characteristics of the evidence and committees perceptions of the fitness for purpose of the common medicines appraised were described. A qualitative analysis of the documentation was performed to identify themes for differences in the agencies' recommendations for medicines evaluated. The themes were considered with respect to differences in the clinical evidence and its interpretation and the conclusions resulting from the SMC's consideration of health economic analysis (cost utility, cost effectiveness and cost minimisation analysis). Three medicines were selected to illustrate some of the common themes for discrepancies between the recommendations of the two agencies.

Table 6.1: Data collected from documentation for medicines appraised

Item	Data Extracted:	Notes regarding extracted evidence
Listing Recommendation	• Listing recommendation reported in advice documents • Type of recommendation for France (Hospital use or Social Health Insurance) • Disease area	The recommendations for both agencies were extracted for classification into one common classification provided by Raftery *et al.*
Manufacturers submitted clinical evidence	• Clinical efficacy evidence (trial name and year); • Evidence Synthesis (meta-analysis, network meta-analysis); • Comparators; • Primary Outcome.	Data were collected from the recommendation documents to identify the clinical efficacy evidence and evidence synthesis. Trial names were identified from Cochrane CENTRAL database.
Fitness for purpose of clinical evidence and evaluation of relative-effectiveness:	• Reported issues with clinical evidence submitted • Conclusions regarding relative effectiveness of the medicine • SMR (Medical Benefit) • ASMR (Improvement in Medical Benefit)	The fitness for purpose of the manufacturer submission was considered by collecting data on the committees' issues with the evidence with respect to study design, quality, relevance to practice and robustness of network meta-analysis. The conclusions regarding the relative-effectiveness through the description provided by the SMC and the HAS judgement of the ASMR resulting from the evidence.
Manufacturers health economics submission	• Type of economic analysis; • Cost-effectiveness estimate reported;	The estimates of cost-effectiveness analysis were recorded for those specific to the indication recommended in the advice document.
Fitness for purpose of health economic analysis.	• Reported issues with health economic analysis submitted to the SMC; • Conclusion regarding cost-effectiveness.	The fitness for purpose of the economic analysis was considered by the main issues reported in the documentation produced by the SMC.

6.4 Results

The results are presented in two sections; the description of the two reimbursement systems using the framework for classifying reimbursement systems, Hutton *et al.* (Part 1) and an analysis of the recommendations and characteristics for a series of medicines evaluated by both reimbursement agencies (Part 2).

6.4.1 Part 1: Comparison of reimbursement systems

A comparison of the two reimbursement systems is provided in Table A6.1 by using the data collected from chapters 3 and 4.

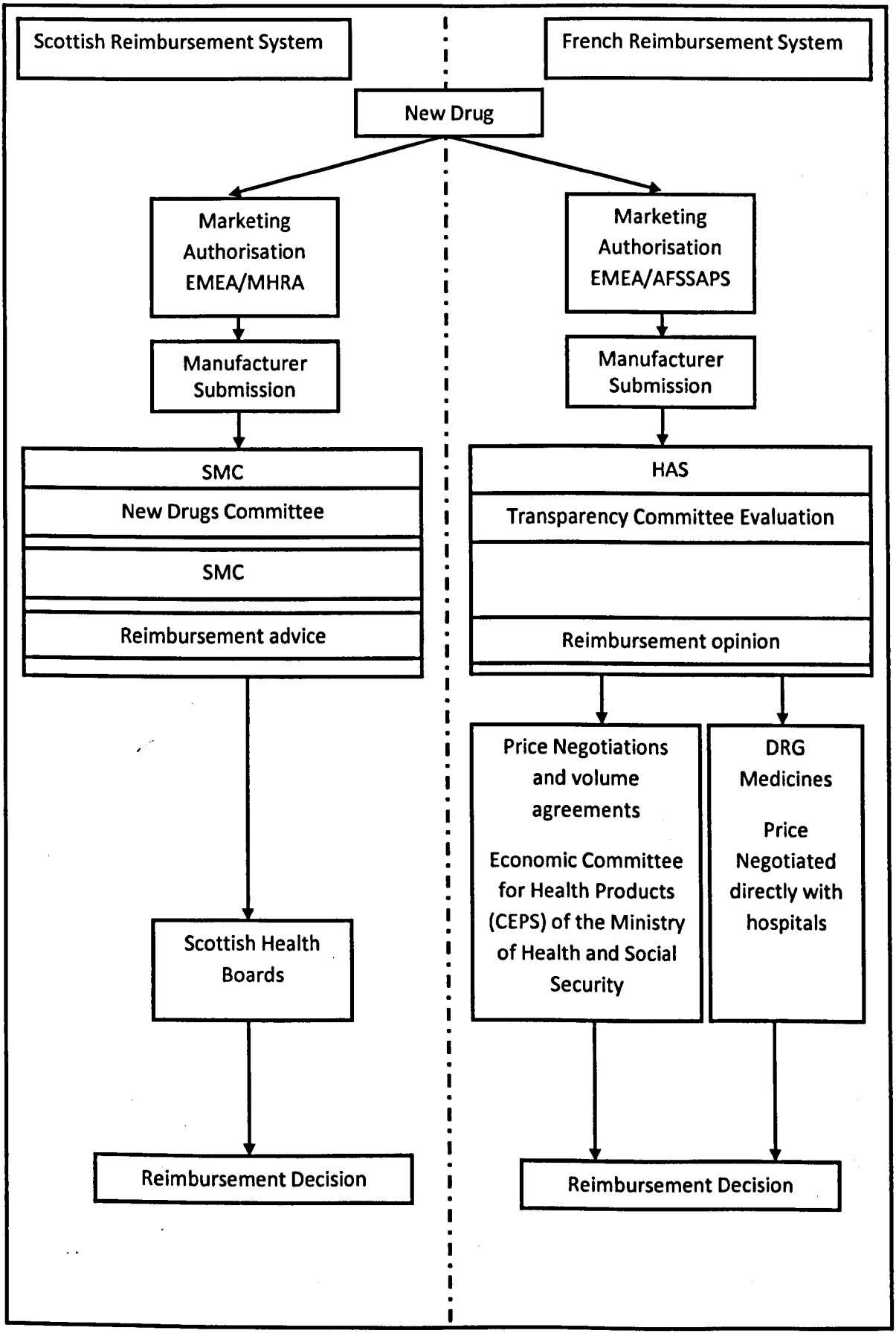
Policy Implementation Level

The Scottish health care system provides universal coverage, is mainly financed through taxation and national insurance contributions and a fixed £3 prescription charge is for those required to pay the charge (set to be abolished in Scotland from April 2011). In contrast, the French system is mainly financed through social health insurance (approx 78%) paid for by the employer and employees and co-insurance rates vary for prescription medicines based on the review of effectiveness where between 0% and 100% is paid by the social health insurance fund. Prices for branded medicines are set freely within the Scottish reimbursement system prior to evaluation of the medicines' cost-effectiveness at the list price but are restricted by ex-post profit controls and price reductions through the UK wide Pharmaceutical Price Regulation Scheme (PPRS) (Department of Health, 2008). In France the HAS opinion informs the pricing and volume agreements that are negotiated between the manufacturer and the Economic Committee for Health Products (CEPS) for outpatient medicines and medicines on top of DRG. Prices for those medicines for hospital use included in the DRG are negotiated directly with the individual hospitals (Ministry of Health, 2010).

The reimbursement systems of the two countries are compared in Figure 6.1. The most notable differences are the number of stages and remit of the agencies. The SMC only appraises medicines whereas the HAS remit is wider including medical device opinions, professional practices, certification of health facilities and guiding the management of long term illnesses. The two systems include agencies whose processes include HTA to provide advice on the reimbursement of medicines: SMC established in 2001 by Health Boards in Scotland and the HAS established in 2004 by the Ministry of Health and Solidarity in France. The French system includes

a second stage in which advice is produced by the CEPS department on the negotiation of price with the manufacturer using the assessment of clinical evidence provided by HAS. The agencies similarly provide advisory recommendations. The final reimbursement decisions are made by the 15 Health Boards in Scotland and pricing and reimbursement decisions are made by CEPS and the Ministry of Health and Social Security in France. An Area Drug and Therapeutic Committee (ADTC) formulary list is produced by each Scottish Health Board and a positive formulary list is provided in the Official Journal of France (HAS, 2011c, SMC, 2011a).

Figure 6.1: French and Scottish reimbursement systems



Technology decision level

1. Assessment of evidence

HAS considers all pharmaceuticals whereas the SMC considers all newly licensed medicines, new formulations of existing medicines and new indications for established products (SMC excludes assessment of vaccines, branded generics, non-prescription-only medicines (POMs), blood products, plasma substitutes and diagnostic medicines) once marketing authorisation has been granted by the respective regulatory agencies. There is a fee charged to the manufacturers for submission of a dossier to HAS (2,875 EURO) but no fee required for submission of the New Product Assessment Form (NPAF) to the SMC. The two agencies similarly require the manufacturer to submit evidence of clinical efficacy, comparative safety and demonstrate the relative-effectiveness of the medicines but judge the evidence and associated uncertainty through different approaches. The SMC also includes a subgroup called the Public and Patient Involvement Group (PAPIG) which is comprised of members of the SMC and public partners. The PAPIG main purpose is to ensure that the patient/carer perspective is taken into account in all SMC advice. Patient interest groups can provide submissions for each medicine appraised by the SMC committee and a template and guidance is provided on the website (SMC, 2011e). Neither agency has a process for comments from external stakeholders on the assessment of evidence.

(i) Efficacy and relative-effectiveness assessment

The SMC requires the manufacturer to provide evidence assembled systematically for the indication(s) of the medicine including details of RCTs (active controlled most relevant), meta-analyses, and most relevant effects of a medicine. The manufacturer provides evidence of clinical efficacy and is required to consider the medicine in terms of the applicability to clinical practice in Scotland, guidelines and relevant protocols for the most relevant active comparator medicines. In the absence of head to head evidence a network meta-analysis is required by the SMC. The network meta-analyses should be described with reference to a systematic review for studies included and the search strategy for trials included and clinical/statistical heterogeneity between data sources (SMC, 2011b).

HAS requires the manufacturer to submit all relevant studies for the clinical efficacy of the medicine but there are no requirements for these to be identified by a systematic review of the evidence. In the absence of head to head trials a network meta-analysis is permitted. The HAS performs a separate literature review of the evidence.

(ii) Cost-effectiveness assessment

The responsibility for demonstrating the cost-effectiveness and any further analysis relevant to Scottish practice rests with the manufacturer and failure to submit cost-effectiveness automatically results in a not recommended decision. A reference case is not provided but the SMC specifies that cost-utility analysis is the preferred form of economic evaluation and health effects should be expressed in Quality-Adjusted Life Years (QALYs). Modelling is the main framework used to synthesise data of clinical and cost-effectiveness, in the absence of real-life effectiveness data. Manufacturers are required to provide sensitivity analysis in the form of single and multi-way analysis to allow the committee to explore the uncertainty in the estimates.

HAS and SMC both provides summaries of the assessment of evidence within the document detailing the appraisal of evidence on their respective websites. HAS documents are known as 'HAS Opinions' and the SMC documents are known as 'SMC advice'. The agencies do not provide the original manufacturer submission on their websites (HAS, 2011, SMC, 2011a).

2. Decision process

(i) Appraisal of clinical evidence

The HAS committee is called the Transparency committee and considers the dossier from the manufacturer and a review of the literature. There are two committees in the SMC, the New Drugs Committee (NDC) that considers the evidence submitted and reports to the SMC Committee that makes the final recommendation decision. The NDC and Transparency committee solely receive a submission from the manufacturer of the relevant evidence and in contrast to NICE in England, do not commission a third party to provide a separate review of the clinical evidence and economic evidence (in the case of SMC). Both committees consider the fitness for purpose of the clinical efficacy evidence, relative-effectiveness and its generalisability to French and Scottish practice.

The two committees report different outcomes from their respective appraisals; the NDC reports a qualitative description of the relative-effectiveness considerations, which has been taken from asking six standard questions from independent experts. In contrast, the Transparency committee is informed by a literature review and the manufacturer's submission and reports a medical benefit (SMR) and the Improvement in Medical Benefit (ASMR) (including a manufacturer's claimed score for both these criteria). A detailed summary of these considerations can be found in Table I. The SMR is determined by the absolute clinical effect and

the importance to public health and this determines whether the medicine should be reimbursed and the rate at which it should be reimbursed.

The appraisal of the ASMR by the Transparency committee has implications for the price that is negotiated between the manufacturer and CEPS. A separate ASMR may be awarded to a medicine that has different benefits in different indications or patient subgroups. Medicines receiving an ASMR I-III are allowed free pricing relative to the maximum average of UK, Germany, Italy and Spain by the CEPS. Prices of medicines with an ASMR of IV and V are negotiated resulting in a price similar to or less than the comparator in France, along with a price-volume agreement. When there is uncertainty in the evidence, HAS requires the manufacturer to collect further observational data as a condition of the opinion for listing.

(ii) Appraisal of economic evidence

The SMC aims to maximise health gain from a fixed NHS budget and cost-effectiveness provides a summary of these economic considerations (SMC, 2011a). Similar to consideration of the clinical evidence the committees must consider the fitness for purpose of the economic evidence and the interpretation of the estimate of cost-effectiveness in the context of the medicine's use in practice. The health economic analysis is one criterion considered in the draft advice by the NDC to the SMC and the threshold range reported in the NICE guide to appraisal is considered in the context of other criteria (NICE, 2008). Since 2009, manufacturers have been able to submit a Patient Access Scheme (PAS) to improve the cost-effectiveness of a medicine by reducing the cost of the new medicine and allowing patient access to clinically effective medicines. These schemes essentially provide a discount on the price whilst maintaining the list price of the medicine.

Outputs and Implementation

The details of the recommendations are provided in an advice document for the SMC within 120 days (non-legally binding) and an opinion document for the HAS in 90 days (legally binding). Neither of the agencies publishes the manufacturer submission. Three categories of advice are provided by the SMC to the Area Drug and Therapeutic Committees (ADTC) for listing; accepted

for use; accepted for restricted use and not recommended[2]. In contrast, HAS opinions are either positive or negative (conditions may also be imposed for additional studies or a target patient population) and are produced for the CEPS of the Ministry of Health where decisions are made on the price for outpatient medicines and hospital medicines that are not covered within the DRG (Ministry of Health, 2010).

Manufacturers may resubmit to the SMC in the light of new evidence or a new analysis of existing evidence but the SMC does not periodically review existing advice. In contrast, HAS can self-refer medicines in the presence of new evidence, reviews all medicines at 5 years post-listing and assesses the evidence from any post-listing studies. The recommendations at the 5-year review may result in the SMR being revised and an opinion for de-listing the medicine. Manufacturers may submit new evidence for medicines at any point in a new dossier and the Transparency committee will provide reassessment of the medicine.

6.4.2 Part 2: SMC and HAS recommendations for 2010

The HAS published a total of 410 opinions on their website, reflecting the wider remit of medicines assessed by HAS including reassessment of SMR and renewal of registration but excluding those medicines following a simplified process (generics or different presentations of a medicine already listed). The SMC published 86 advices in 2010 on their website (including abbreviated submissions). The SMC considered 57 and HAS considered 122 new medicines including new indications and extensions of indications in this year. The HAS recommended listing in 115 (96%) and the SMC recommended listing for 32 (56%) of these medicines. Table A6.2 provides a tabulation of the listing recommendations and characteristics of the medicines assessed by each agency.

6.4.2.1 Similarities and differences in medicine recommendations

There were 39 English translated submissions that were matched between 2005 and the start of 2010. The matched medicines were for treatment of a variety of diseases such as neoplasms, diseases of the nervous system, infection and parasitic, circulatory system, endocrine, nutritional and metabolic, skin and musculoskeletal system. The details of the recommendations can be

[2] There is the facility for the SMC to designate an innovative medicine for a condition where there are no other treatment options as "unique". In the event that such a medicine for a specific condition was accepted by SMC, NHS Boards would be required to introduce it to an agreed national programme.

found in Table 6.2 and Table 6.3 and 6.4 present the medicines and diseases treated. The proportion of medicines recommended for listing for this selected sample of medicines were 85% for the SMC and 100% for HAS. The SMC recommended in 33%, minor restriction in 13%, major restriction in 39% and were not recommended in 15%. The HAS opinions were recommended in 59%, minor restrictions in 28% and major restrictions in 13%. There were 14 concordant decisions made between the two agencies (Kappa Statistic=0.11), which can be interpreted as poor agreement between the two agencies recommendations. In eight of the submissions, six concordant and two discordant decisions, the Transparency committee requested additional observational data as a condition of the recommendation to be presented for reassessment. There were some similarities with the disease areas treated by medicines appraised in 2010, although there were a more diverse number of diseases in this year and a higher rate of not recommended for both agencies in comparison to the matched sample.

6.4.2.2 Manufacturers' clinical evidence submissions

The majority of submissions contained one or two key trials that informed the submission for clinical efficacy and evidence of clinical effectiveness. There was at least one commonly reported trial in both the SMC and HAS recommendation document for the same medicine. In twelve of the recommendations there were additional studies presented by the manufacturers. There were six cases where no common comparators were shared between the submissions for SMC and HAS. Network meta-analyses were submitted on eight occasions to the SMC and three occasions to HAS. The manufacturer similarly submitted such analyses to both agencies in two common submissions. Few details were provided in the documents produced by both agencies with respect to the network meta-analyses such as trials included, whether the analysis was a mixed treatment comparison or indirect comparison and the type of statistical analysis.

Table 6.2: Cross tabulation of matched SMC advice and HAS opinions

	HAS advice				
SMC advice	To list advice	To list Minor Restriction	To list Major Restriction	To not List	Total (SMC)
List advice	8	3	2	0	13 (33%)
List Minor Restriction	1	4	0	0	5 (13%)
List Major Restriction	11	2	2	0	15 (39%)
To not Listed	3	2	1	0	6 (15%)
Total (HAS)	23 (59%)	11 (28%)	5 (13%)	0 (0%)	39 (100%)

Table 6.3: Cross tabulation of medicines for matched SMC advice and HAS opinions

	HAS advice			
SMC advice	**To list advice: 23 (59%)**	**To list Minor Restriction: 11 (28%)**	**To list Major Restriction: 5 (13%)**	**To not List: 0 (0%)**
List advice: 13 (33%)	C003: docetaxel (H) C004: candesartan cilexetil (NHI &H) C005: solifenacin succinate (NHI & H) C018: posconazole (H) C026: levetiracetam (NHI, H) C032: nebivolol (NHI & H) C050: levetiractem (NHI & H) C051: palonosetron (NHI & H)	C002: ribavirin (NHI & H) C016: pegylated interferon alfa 2a (NHI & H) C028: adalimumab (NHI & H)	C015: ibrandronic acid (NHI & H) C040: testosterone undecanoate (NHI & H)	
List Minor Restriction: 5 (13%)	C027: exemestane (NHI & H)	C011: capecitabine (H) C014: sildenafil citrate (H)) C043: rituximab (H) C048: rituximab (H)		
List Major Restriction: 15 (39%)	C009: lanthanum carbonate (NHI & H) C023: tipranavir (NHI & H) **C024: infliximab (H)** C030: voriconazole (H) C033: daptomycin (H) C036: tigecycline (H) C037: tigecylcine (H) C045: ivabradine (NHI & H) C046: natalizumab (H) C049: levetiracetam (NHI & H) C052: posaconazole (H)	C010: omalizumab (H) **C013: erlotinib (NHI & H)**	C038: pegaptanib (NHI & H) C047: parathyroid hormone (NHI & H)	
To not Listed: 6 (15%)	C001: botulinum type A (H) C007: rasagiline (H) **C008: rasagiline (NHI & H)**	C025: sodium oxybate (H) **C029: sorafenib (H)**	C034: alglucosiuidase alfa (H)	

Table 6.4: Common medicines

No.	Drug	Indication	ICD-10 Disease Category
1	botulinum toxin type A	Focal Spasticity	Diseases of the nervous system
2	ribavirin	Children with Chronic Hepatitis C	Certain infectious or parasitic diseases
3	docetaxel	Node-positive Breast Cancer	Neoplasms
4	candesartan cilexetil	Heart Failure	Diseases of the circulatory system
5	solifenacin succinate	Incontinence	Diseases of the genitourinary system
6	rasagiline	Parkinson's Disease Indication1	Diseases of the nervous system
7	rasagiline	Parkinson's Disease Indication 2	Diseases of the nervous system
8	lanthanum carbonate	Chronic Renal failure	Diseases of the genitourinary system
9	omalizumab	Asthma Control	Diseases of the respiratory system
10	capecitabine	Colon Cancer	Neoplasms
11	erlotinib	NSCLC	Neoplasms
12	sildenafil citrate	Pulmonary arterial hypertension	Diseases of the circulatory system
13	ibandronic acid	Osteoporosis	Diseases of the musculoskeletal system
14	peginterferon alpha-2a	Chronic Hepatitis B	Certain infectious or parasitic diseases
15	posaconazole	Invasive Fungal Infection	Certain infectious or parasitic diseases
16	tipranavir	HIV	Certain infectious or parasitic diseases
17	infliximab	Psoriasis	Diseases of the skin and subcutaneous tissue
18	sodium Oxybate	Narcolepsy	Diseases of the nervous system
19	levetiracetam	Epilepsy	Diseases of the nervous system
20	exemestane	Breast Cancer	Neoplasms
21	adalimumab	Psoriatic Arthritis	Diseases of the skin and subcutaneous tissue
22	sorafenib	Renal Cell Carcinoma	Neoplasms
23	voriconazole	Candidemia	Certain infectious or parasitic diseases
24	nebivolol	Chronic Heart Failure	Diseases of the circulatory system
25	daptomycin	Soft Tissue Infections	Diseases of the skin and subcutaneous tissue
26	alglucosidase alfa	Pompe Disease	Endocrine, nutritional and metabolic diseases
27	tigecycline	Soft Tissue Infections	Diseases of the skin and subcutaneous tissue
28	tigecycline	Intra-abdominal infections	Diseases of the digestive system
29	pegaptanib	Age-related macular degeneration	Diseases of the eyes and adnexa
30	testosterone undecanoate	Testosterone Deficiency	Endocrine, nutritional and metabolic diseases
31	rituximab	Lymphoma	Neoplasms
32	ivabradine	Chronic Stable Angina	Diseases of the circulatory system
33	natalizumab	Multiple sclerosis	Diseases of the nervous system
34	parathyroid hormone	Osteoporosis	Diseases of the musculoskeletal system
35	rituximab	Rheumatoid arthritis	Diseases of the musculoskeletal system
36	levetiracetam	Epilepsy	Diseases of the nervous system
37	levetiracetam	Epilepsy	Diseases of the nervous system
38	palonosetron	Cancer Chemotherapy	Neoplasms
39	posaconazole	Invasive Fungal Infection	Certain infectious or parasitic diseases

6.4.2.3 Fitness for purpose and relative-effectiveness

The two committees reported issues with the clinical evidence in 77% (30/39) submissions. The common issues reported by both committees were lack of direct comparison with active comparators (n=14), selection of trial patient population (n=9), submission of uncontrolled studies (n=1) and lack of long-term efficacy data (n=1) (Table A6.7). The Transparency committee considered all the network meta-analysis submitted to be unreliable due to the lack of exchangeability between trials. In contrast, the SMC considered all of the network meta-analyses and these were used in the economic models submitted to the SMC. The source of a few meta-analyses reported for the SMC were those previously informing NICE decision-making.

The Transparency committee considered 64% (24/39) of medicines submitted to demonstrate relative-effectiveness (ASMR = [1, 2, 3 innovative], 4) in comparison to French practice (Table 6.5). The SMC provided a description of the clinical-effectiveness and it was inferred from the description that the SMC judged improvement in relative-effectiveness with respect to the clinical outcome and health related quality of life for 30 medicines.

Table 6.5: HAS medicine ASMR level

ASMR	Number of Medicines
1 – Major	2
2 – Important	6
3 – Modest	11
4 – Minor	5
5 – Inadequate	15
Total	39

6.4.2.4 Health economic evidence submitted

The SMC reported issues with the economic evidence in 21 submissions. The main reasons for concerns with the economic evidence were consideration of a limited number of comparators (n=5), costing and resource use (n=5), model assumptions (n=4) and the use of appropriate clinical data (n=3).

The manufacturer submitted cost-utility analysis in 31 cases claiming an improvement in health benefit in comparison to usual practice in Scotland. The manufacturer targeted a subgroup of the licensed population in 11 of the submissions. When costs had been modelled the estimates provided for the cost-utility analyses ranged from dominant (QALY benefit and cost-saving) to £318,283 per QALY. There was one submission including a cost-effectiveness analysis and 8 submissions including cost-minimisation analysis.

6.4.2.5 Qualitative analysis of reasons for differences in recommendations

The reasons for differences in the recommendations are contained in Table A6.4 and Table A6.5. The most common reasons were differences in the comparators and committees judgement of the uncertainty in the evidence (n=4); both committees agreeing on uncertainties in the clinical evidence but uncertainties in the economic evidence leading SMC to be more restrictive or not recommend (n=4); both agreeing on equivalent relative-effectiveness but the use of cost-utility analysis resulting in either HAS or SMC being more restrictive (n=4); both agreeing on

improvement in relative-effectiveness but manufacturer submits in a subgroup where the SMC advises a major restriction (n=3); both agreeing on improvement in relative-effectiveness and manufacturers submission to the SMC demonstrates cost-effectiveness but either agency providing a minor restriction (n=3); both agreeing on improvement in relative-effectiveness but the price was too high to enable cost-effectiveness in Scotland (n=2) and other reasons (n=5).

The following three case studies focus on the left hand side four quadrants of Table 6.3 where the SMC was more restrictive in comparison to HAS and illustrate some of the main common issues that may explain differences in the recommendations between HAS and SMC.

Infliximab: Synthesis of evidence using network meta-analysis

The Transparency opinion included judgements on two extensions of indications (psoriatic arthritis and psoriasis). The matched SMC advice focused on a single indication for the treatment of moderate to severe psoriasis in adults who have failed to respond to, or who have a contraindication to, or are intolerant of other systematic therapy. The clinical evidence submitted to the SMC and HAS contained the same clinical efficacy evidence for two double blind RCTs and one additional double blind RCT. Both submissions included an indirect comparison, which was judged by the Transparency committee to be unreliable due to the dosage of methotrexate in the included trials, other treatments, lack of tests for heterogeneity, length of follow-up and lack of a systematic review. The Transparency committee concluded that infliximab shared the same moderate improvement in actual benefit as etanercept (ASMR=3) for those patients with severe psoriasis. The Transparency committee additionally requested a representative observational study of the benefit in practice over 5 years. The SMC judged the indirect comparison submitted (previously been used in NICE decision-making) to be useful for the economic model but noted that there could be heterogeneity between trials. The results of the indirect comparison presented in the submission demonstrated infliximab to have a higher PASI75 response than etancercept and efalizumab. These estimates were included in the economic model producing an estimate of £27,354 per QALY for severe psoriasis. The SMC judged that the economic case had been made and advised a major restriction to this subgroup.

Sorafenib: Clinically-effective and free pricing versus negotiation

Sorafenib is indicated for the treatment of patients with advanced renal cell carcinoma who have failed prior interferon alpha or interleuken 2 based therapy or considered unsuitable for such therapy. The same clinical efficacy evidence was submitted to the agencies which included one

Phase II RCT placebo controlled and one Phase III placebo controlled RCT. The trials demonstrated a progression free survival of approximately 3 months in comparison to placebo (relevant comparator in both countries), although evidence was unavailable at the time of recommendations for improvement in overall survival. HAS acknowledged this uncertainty and judged the medicine to be an important improvement in actual benefit (ASMR=2) and recommended listing. The SMC committee similarly judged an improvement in relative-effectiveness and considered the manufacturer's Markov model to be well conducted, which produced a base case estimate of £35,523 per QALY. The committee were concerned with the uncertainty in the extrapolations from the available trial data and substantially reduced the confidence that could be placed in the longer-term estimates of cost-effectiveness. The SMC judged that in light of the uncertainty and price supplied by the manufacturers' cost-effectiveness had not been demonstrated.

Erlotinib – Formal consideration of quality of life versus ASMR

Erlotinib is indicated for the treatment of patients with locally advanced or metastatic Non-Small Cell Lung Cancer (NSCLC) after failure of at least one prior chemotherapy regimen (EGFR positive patients only). Both of the submissions included a Phase III double blind placebo controlled trial, in addition the submission to HAS included two phase I dose ranging studies and one phase II non-comparative study of efficacy and safety. The primary outcome of overall survival demonstrated a 2 month improvement in actual benefit in comparison to placebo, but the main comparators in France and Scotland are docetaxel and pemetrexed for second line. The absence of evidence for these relevant comparators, led the Transparency committee to advise to recommend with no improvement in actual benefit for second line therapy. The SMC manufacturer's submission presented the economic case for those that would be eligible for docetaxel monotherapy. The submission presented a cost-utility analysis that was informed by the synthesis of evidence by an indirect comparison to enable a comparison with docetaxel. The analysis found a quality of life improvement in contrast to the Transparency committee, which could not judge the impact in the absence of direct comparisons. The estimate of £4,800 per QALY in the basecase was subject to uncertainty regarding the appropriate number of cycles for which expert advice considered 4 to be appropriate resulting in an estimate of £22,500 per QALY. The medicine was recommended in this restricted group.

6.5 Discussion

The agencies share similarities in their objectives of providing information and advice to their respective authorities to make final reimbursement decisions on the use of medicines but have different remits for medicines appraised. The HAS agency recommended listing in the majority of cases whereas the SMC was more likely to not recommend or place restrictions on the medicine in 2010. In those common medicines covering a variety of disease areas the trend remains, although there is a slightly higher proportion of listing recommendations for both agencies in this selected sample. The qualitative analyses show that similarities exist in the clinical trials submitted by the manufacturer and consideration of issues relating to the studies submitted (relative efficacy). Differences in recommendation may be explained by a combination of the manufacturer's freedom to set price and the incentives provided by the consideration of economic evidence by the SMC, alongside differences in relevant comparator medicines, relevant outcomes, country specific treatment guidelines, submission of network meta-analysis and the propensity to use such evidence synthesis methods in decision-making.

Pricing approaches differ in both countries - price negotiations are performed by the CEPS after the HAS makes a judgement on the SMR and relative-effectiveness in France (ex-post price negotiation). In contrast, in Scotland prices are set freely (ex-ante free pricing) and an economic evaluation provided in addition to the clinical evidence. The systems provide different demand curves for global profit maximising manufacturers who consider the impact of the local listing price on international price referencing. In the common medicines evaluated there were cases where HAS recommended the medicine (obtaining a set maximum price defined by the ASMR) and the manufacturer chose to submit the cost-effectiveness evidence for a targeted subgroup to the SMC. This may suggest a high price was more important for international price reference purposes than the potential local revenue maximising position for the manufacturer given that the UK represents a relatively small 3.5% (Scotland represents c10% of this proportion) of the global market (OECD, 2008).

The consideration of economic evidence by the SMC rather than a score relating to improvements in relative-effectiveness (HAS) provides differences in the perceptions of value of some new medicines depending upon the medicines' characteristics. The requirement for manufacturers to present an economic evaluation may explain some of the variation in recommendations because in combination with free pricing it has provided incentives for the manufacturer to target a patient population, quantify and understand the uncertainty of the relative-effectiveness

estimates in combination with the cost of the medicine and formally quantify the health related quality of life benefits for the medicine.

The assessment of the medicines improvement in actual benefit using the primary clinical outcomes by HAS produced some examples where the HAS committee judged the medicine to have no improvement based on the same clinical evidence and relevant comparators. In these cases the manufacturer had presented cost-utility analysis to the SMC, and the committee judged this to be robust demonstrating modelled improvements in overall health related quality of life. The formal consideration of health related quality of life in some SMC submissions was rewarded by a premium price. In contrast, the Transparency committee judged no improvement (ASMR=5) leading to no premium price because there was no formal analysis of health related quality of life (HRQOL) provided.

The SMC and HAS both assess the evidence around the point of marketing authorisation and HAS sometimes requires the manufacturer to collect additional observational evidence when the evidence is uncertain for the reassessment at 5-years. Network meta-analyses were more frequently submitted to the SMC and included in the respective economic analysis that included sensitivity analysis to explore the uncertainty in the treatment effect. This type of analysis maybe more frequently submitted to the SMC because of its use in the economic evaluation or because the Transparency committee tends to judge such analyses submitted by the manufacturer to not be sufficiently robust. The Transparency committee dealt with these uncertainties by judging and categorising the medicine as no improvement in relative-effectiveness; with the implications being that the price resulting would be similar or lower than the existing treatments. In contrast, the SMC considered the sensitivity and scenario analysis around the estimates of cost-effectiveness and provided a restricted recommendation or not recommended decision depending on the degree of uncertainty. There were a few examples where the Transparency committee placed restriction on the use due to uncertainty in the clinical evidence on the first recommendation. The differences between the systems make price the main adjustment variable in France, as opposed to quantity in Scotland.

There were examples where the maximum price setting and negotiation in France allowed the medicine to be available in France but not in Scotland because the medicines were not cost-effective at the list price. Since 2009, a patient access scheme process has been made available to manufacturers in Scotland. This now enables manufacturers to propose a pricing discount that does not affect the list price, but improves the cost-effectiveness of a new medicine allowing

reimbursement. These clinically effective medicines may have been recommended if such a scheme had existed then.

The reimbursement processes (free pricing, number of stages, medicines assessed, reassessment of decisions) could be just as important in explaining differences in decisions as the methods for evaluating the technologies at the technology decision level (use of economic evaluation). At launch, the Scottish system uses economic evaluation to understand the uncertainties and may restrict or not recommend when the committee judges there to be too much uncertainty given the price set by the manufacturer. Economic analysis is essential to control access where prices cannot be negotiated. The French system tends to more often recommend the medicine and will provide a price at launch that is reflective of the judgements of clinical efficacy and uncertainty in the evidence. The French process then requires the manufacturer to collect further real life evidence in the presence of uncertainty for reassessment of listing. This provides access to new medicines for patients, but lower financial incentives to innovative global manufacturers.

This study provides some hypotheses and explanations for the differences observed in recommendations for a selected sample of medicines but does not identify whether one reimbursement system is better than the other in delivering health benefits, controlling health care costs or incentivising innovation. This would require further quantitative analysis of a larger sample of medicines for the two agencies and observation of utilisation rates and patient outcomes. Further research could explore the balance between the manufacturer (producer surplus) and patients (consumer surplus) by an analysis of prices and reimbursement decisions over the life cycle of the medicines in the two countries. Even if this were possible a study design which controlled for all system differences would be difficult to achieve. A further limitation is that the study relies on the documented evidence available where some of the considerations may not have been documented. Additionally, the HAS recommendations for which English translations are available may not be representative.

In December 2010, consultations were published in both countries for changes to the evaluation of medicines. The Department of Health in England[3] has published a consultation on a new value based approach (VBP) to the pricing of branded medicines in the UK (Department of Health, 2010) consequently a number of suggestions have been made for the operation of VBP in the UK (Claxton et al., 2011, NICE, 2011f, Office of Fair Trading, 2007, Office of Health Economics, 2011). The HAS published a consultation on the procedures and methods for economic evaluation for

[3] The PPRS is a voluntary agreement between manufacturers in operation for over 50 years and works in conjunction with other measures to encourage cost-effective prescribing of medicines. The Department of Health in England consulted on a proposal to modify this scheme through value based pricing for the entire UK.

technologies (HAS, 2010). The consultations propose the introduction of price negotiation for the SMC and the introduction of economic evaluation for HAS appraisal of medicines, which may result in more similarities between the two reimbursement systems in the future. The potential process changes may reduce the differences in recommendations and access to medicines in both countries using VBP informed by economic evaluation. The Scottish system will need to determine the details of price negotiations, agencies involved, other factors to be taken into account and reassessment of the price and any new evidence for medicines. The French system will need to determine whether health economic evaluation is used at launch and/or at reassessment, the opportunity cost of health care resources and other factors. The forthcoming details of these process changes will influence the extent to which variation in recommendations is reduced and health is maximised in each country given their respective budget constraints.

Chapter 7: Summary and Conclusions

7.1 Overview summary

In the earlier years of the development of health economic techniques, critics pointed out the difficulties that health economists had found in making an impact upon decision-making and developing techniques to be used by decision-makers (Loomes and McKenzie, 1989, Ashmore et al., 1989). Sociologists wrote a book about Health Economists in the late 1980s with a pessimistic outlook for the application of health economic techniques for practical purposes and wrote the following:

> '....few applied social scientists are likely to work in an environment as generally advantageous as that enjoyed by contemporary British Health economists. While their achievements should, quite legitimately, encourage other applied social scientists, their disappointments and failures must stand as a warning to us all of the inherent difficulty of using academic social science as a basis for practical assistance of others.' (p.3 (Ashmore et al., 1989))

The development of health economic analysis since then has gained prominence in the appraisal and evaluation of health technologies. In the course of this thesis I have explored the contribution of health economic analysis to medicine reimbursement decision-making in a number of OECD reimbursement systems. One of the main aims of the thesis was to understand the similarities and differences in the use of health economic analysis and the influence upon reimbursement decisions for pharmaceuticals. The novelty of this thesis covers four main interlinked topics:

1. The thesis identifies the current evidence base with respect to the influence of factors on OECD countries' reimbursement decisions. Chapter 2 identified few quantitative studies addressing the influence of factors on reimbursement decisions and even fewer country comparisons of reimbursement agencies and systems. There were a number of limitations with these studies. The studies focused on the evidence factors and fewer non-evidence factors and process factors were taken into account.
2. There was little known about the operation of many OECD countries' entire reimbursement systems and the place of reimbursement institution(s) using HTA in the systems. The novelty of chapter 3 and 4 was to use a framework to systematically categorise OECD countries' reimbursement systems to identify the policy environment and process in which health economic analysis is used. Reimbursement systems are very

heterogeneous but some are more similar with respect to the evidence considered. Health Economic analysis is used in many reimbursement systems but there is variation in the extent of its use, the operation of a threshold range, committees and institutions involved in the system and the alignments with each system's policy objectives.

3. Chapter 5 provides a comparison of reimbursement systems using formal health economic analysis. The chapter tests the hypothesis that some countries' reimbursement agencies using similar evidence requirements would display common association with the decision even though there is some heterogeneity in the process. The chapter considers factors across four established reimbursement agencies requiring similar clinical effectiveness and cost-effectiveness evidence using, regression analysis. There were elements of clinical evidence, non evidence factors and process factors that were correlated with decisions. Cost-effectiveness was not found to be statistically associated with the decisions and the magnitude of effect was small and surprisingly a measure of public interest was found to be associated with the decision. The findings require further research because some evidence factors could not be completely controlled for because of lack of reporting across the agencies and the methodology's lack of sufficient control for the process differences across the agencies.
4. Chapter 6 provides a comparison of a reimbursement system using health economic analysis and one without the use of health economic analysis. The chapter contributes to the current knowledge on the contribution of health economics by comparing two reimbursement agencies' matched decisions, the SMC in Scotland and the HAS in France that provide advisory reimbursement decisions. There were differences in the recommendations for the same medicines with the SMC tending to restrict or not recommend in comparison to HAS. The chapter finds that the observed differences in the recommendations may be explained by price setting and process for dealing with uncertainty, relevant comparator medicines, relevant outcomes, treatment guidelines, use of network meta-analysis and formal consideration of HRQOL in the health economic analysis.

The task of assessing the contribution of health economic analysis has required the use of both quantitative and qualitative methods of analysis and required consideration of new factors that may influence medicines' reimbursement. Contribution can be considered in a number of ways and the thesis identified past research that had considered the contribution through the use of Health Economic analysis or by the association with decisions. The thesis has found the that there is a differential contribution through how Health Economic analysis is used at the policy

implementation level and the individual technology decision level and has explored the influence on decisions in a comparison of Health Economic systems and the contribution through comparison with a system that does not use health economic analysis. Finally, the contribution through impact on the final outcomes in the reimbursement systems is discussed.

7.2 The contribution identified in previous research

7.2.1 Contribution through use of health economic analysis

Chapter 4 categorised medicines at the individual technology decision level and considered the use of health economic analysis in the decision process. If the contribution of health economic analysis is to be judged upon its use in reimbursement decision-making then it has made significant contribution in many systems. Health economic analysis is widely required across countries and a stated decision factor across twenty of the OECD countries studied. Cost-utility analysis is a preferred type of analysis across many of the countries using such evidence in decision-making. This has required Health Economists to be present on committees to interpret and make decisions in over half of those OECD countries committees where health economic analyses are required. There is variation with respect to the means of communication of the assessment to the committee and the documentation of the assessment of evidence. NICE in England and Wales is the only agency to communicate the manufacturer's submission on the website after the first appraisal meeting. Some agencies state the use of health economic analysis but do not provide documentation of the assessment of evidence for the medicine. This makes it difficult to interpret the contribution of such analysis to reimbursement decision-making in these countries. In contrast the willingness of the decision-maker to pay for independent analysis in a few of the countries such as NICE in England, PHARMAC in New Zealand and IQWIG in Germany (although there are no actual examples) may indicate the significant importance and value of such analysis to the decision-maker.

7.2.2 Contribution through the association with reimbursement decisions

Chapter two systematically reviewed the empirical studies that have considered the influence of health economics analysis and other factors on reimbursement decisions within and across countries. The majority of quantitative analysis focused on the correlation or association of the estimates of cost-effectiveness (cost per QALY, cost per effectiveness) and other factors on a cross sectional sample of decisions. The majority of evidence identified includes quantitative and qualitative studies for NICE decision-making in England, PBAC decision-making in Australia and CDR decision-making in Canada. There is limited evidence for the influence of factors for other

OECD countries' reimbursement decision-making and a lack of cross country comparisons of decisions and factors. Cost-effectiveness was the most frequently explored factor across studies when this was included. This was the only factor to have a consistent construct and studies across and within countries found the same direction of effect but the magnitude of effect was not always comparable because of the different methodologies used. Some studies provided estimates of the cost-effectiveness threshold from the analysis of retrospective decisions but some authors did not produce an estimate. Many of the studies included factors with respect to the clinical and economic evidence and few included other factors such as the influence of reimbursement process. Mixed evidence of the influence within reimbursement systems and across systems was found with respect to other factors, clinical evidence factors, non-evidence factors and process factors when these were included in the studies within countries and across countries (when included). There were a number of qualitative factors that were identified that had not been explored in the quantitative research which mainly related to the non-evidence factors and agencies' processes of decision-making.

The samples of medicines included were generally only assessed and appraised at one point in time by the reimbursement agencies. The quantitative studies did not always define the meaning of influence, were often based on small samples of reimbursement decisions, and did not always explore the potential relationships between factors and the regression model specifications. The second chapter illustrated the need for both quantitative and qualitative studies for those single country analyses of the influence of factors when this had not been previously studied in OECD countries. There were few comparisons of reimbursement systems that identified the influence of health economic analysis and process factors. One cross country comparison identified reimbursement process as a potential explanation but did not correlate differences directly with decisions or elucidate all the process factors potentially explaining differences in decisions (Clement et al., 2009).

7.3 Differential contribution of health economic analysis through its use in systems

7.3.1 Health economic analysis use at the policy and individual technology level

Chapters three and four set out to understand and categorise the reimbursement systems using a framework to understand the institutions involved and the process of reimbursement decision-making (Hutton et al., 2006). The aims of these chapters were to help to understand the similarities and differences between the reimbursement systems before any empirical studies of factor influence were undertaken of reimbursement decisions across countries. Chapter 3

categorised the systems at the policy implementation level and found varying objectives, types of financing and numbers of institutions involved in decision-making. The potential differences in principal objectives of the systems may explain the reimbursement processes and methods used at the individual technology decision level. The use and contribution of Health Economic analysis is most evident in NICE in England and Wales and this was established within the context of increasing health spending where the aims of such analysis were to reward innovation whilst gaining value for money. In contrast where the principal objective is cost containment such as Spain other primary methods and processes of reference pricing and price cuts are being used rather than health economic analysis and HTA. The principles primary objectives are important for the use and impact of such analysis across countries. However, these principle objectives vary overtime and depend on the political environment and those systems that frequently change the objectives and methods make study of the linkage of objectives and the use of health economic analysis challenging.

Chapter 3 categorised systems by their implementation of decisions and found this can take place through a variety of mechanisms and a large number of the systems either operate through a social insurance sickness fund, through a Ministry of Health scheme or at a regional level where another decision-making body is responsible for the final decision and implementation. The variation in the mechanisms of implementation and other institutions involved affects the adherence to the recommendations made by the agencies and the ultimate impact of health economic analysis and HTA. Accountability of the reimbursement agencies was not well documented across the reimbursement systems. The accountability of reimbursement agencies was addressed by the existence of a formal appeal and consultation process or by reporting measures of performance against the objectives of the reimbursement agency. The performance of systems was often demonstrated by the reimbursement agency through the volume of decisions published and the rates of recommendations for medicines. Only the PHARMAC agency in New Zealand was identified to set targets for each year with respect to the influence of decision-making for medicines on health outcomes in a document that they call a 'statement of intent'. The agency estimates the health gain in terms of QALYs by considering the average values of the funding options available to them called the prioritisation list and comparing this with the average value of the funding decisions actually made. This attempt to consider the additional value is possible for PHARMAC in New Zealand because it is legally required to manage its spending within a community medicines budget unlike other systems where agencies are advisory or decisions are implemented by a different institution. The use of health economic analysis

through the explicit and formal consideration of medicines impact on health of the population allows reimbursement agencies to be accountable for the decisions made.

Chapter 4 identified variation in the application of HTA and the means by which Health Economic analyse are used in the reimbursement process with respect to the type of medicines requiring such analysis, process of assessment and appraisal, use of cost-effectiveness analysis in the appraisal alongside other stated factors. Manufacturers are required to produce clinical evidence and economic evidence for many of the countries and a few countries provide independent assessments of the medicine. These approaches have practical implications for the judgements regarding the nature of the cost-effectiveness threshold and the assumptions in the context of decision-making.

Threshold ranges for cost-effectiveness have been explicitly stated in agency documentation in England and Wales, Scotland and the Netherlands but other criteria are applied differently during the appraisal of the medicine. The application of the cost-effectiveness is described as central to NICE decision-making and the impact with respect to other factors has evolved overtime with the introduction of supplementary guidance at the end of life. Factors such as degree of uncertainty, lack of capture of health improvement and innovative nature of the technology are taken increasingly within set ranges. The consideration of end of life is considered supplementary for this but implies a threshold even though a range is not stated explicitly. The SMC consider cost-effectiveness as a central criterion similar to NICE but states that the NICE threshold is considered but there is no strict upper limit in the decision and refers to modifiers of the decision where a higher cost-effectiveness ratio may be accepted. In contrast health economic analysis is one of four principal factors (multiple criteria) in the Netherlands when considering cost-effectiveness analysis produced for CVZ and there are separate committees one for considering the therapeutic value a second and a medicines reimbursement committee. A further new committee called the appraisal committee is tasked with matters where wider social considerations should be addressed. The CVZ tend to include criteria that affect the strength by which the cost-effectiveness criteria should be considered in decision-making, less strict consideration is taken for medicines that are for high burden of disease, rare and have a public health risk whereas cost-effectiveness is a stricter criterion such as high budget impact, uncertainty about the appropriateness of the intervention. Details of the application of these multiple criteria are not explicitly provided in the decision documents as would be required if formal methods of Multiple Criteria Decision Analysis were applied (MCDA) (Goetghebeur et al., 2011, Devlin and Sussex, 2011). Other authors have reported the importance of being explicit about other factors such as

equity considerations in decision-making (Williams and Cookson, 2006, Shah et al., 2011). This raises a question of whether these factors should be considered for each individual medicine by the committees responsible by providing explicit principles of equity that are determined by the political process or whether these should be made at the policy implementation level through the design of the systems processes to ensure that the objectives and the systems institutions are accountable. For example the involvement of stakeholders in the consultation of evidence, entitlement to appeal decisions and the grounds established for appeal.

There are then those systems where implicit thresholds have been identified in the literature for Australia, Canada, Ireland, New Zealand, Korea and Sweden. Although there is debate on whether some of these countries actually appraise decisions using a cost-effectiveness threshold in mind because of other important factors. This calls into question the appropriateness of providing quantitative analyses of past decisions in these countries. The decision documentation tends to account for the evidence in these countries and statements of the other non-evidence considerations are generally lacking.

7.3.2 Comparison of health economic analysis reimbursement systems

The previous chapters considered the current evidence base and the categorisation of systems to allow more detailed analyses of the influence of factors across reimbursement systems. Chapter 5 attempted to control for new factors in a larger sample in a pooled analysis across systems using similar evidence requirements from the manufacturer and found association with respect to the clinical evidence, non-evidence factors and within country process factors. Surprisingly there was a correlation with the number of citations of the medicine in the media prior to the decision across countries but no statistical correlation with the cost-effectiveness estimates. The introduction of specific dummies to control for country differences in the process and reimbursement systems improved the regression fit but these results remained.

There are two possible explanations for these findings. The first explanation is that the influence of health economic analysis in these countries for the medicines studies is not as influential as believed by health economists in these countries and other factors can explain actual decision-making. The second explanation is that it was inappropriate to pool countries because of the process differences across countries that cannot be sufficiently controlled for in this type of quantitative analysis. Through the different approaches used in this thesis I would tend to find the second explanation more plausible. There is a fundamental problem with these types of regression analyses in the consideration of past decisions that influence has only been studied

with respect to the correlation rather than causal association of a reduced set of factors that are provided by the agencies. It is likely that a number of factors are missing from the analyses because they have not been measured or there is an insufficient sample size to control for many other important factors that may explain differences in decisions within and across countries. This was one main problem in this analysis where there was sufficient information to produce new variables for NICE but insufficient to add these across all the other countries agencies. Differences in process across countries may influence decisions in two ways, either independently of other factors such as economic analysis or by modifying the way in which decision-makers within each reimbursement system consider factors such as economic analysis. The chapter identified a number of process differences that may moderate the use and interpretation of the health economic analysis such as the use of third party independent assessment by NICE, the process of implementation of decisions and interpretation of decision outcomes between the countries differs and is highly complex for some medicines in Canada, the number of committees involved in assessing and appraising the evidence and the composition of the committees, the use of provisional stages and incentives provided by the pricing of medicines and interaction with the provision of cost-effectiveness evidence. A second means to explore the influence of the use of health economic analysis is to consider a comparison of two systems decisions The understanding of such processes require qualitative study in comparisons of systems to understand the influence of process.

7.3.3 Comparison of the use of health economic analysis versus no health economic analysis

The final empirical chapter contributed to the knowledge on contribution of health economic analysis by comparing two reimbursement systems and matching reimbursement for those medicines considered for the same indication (Bending et al., In press). The analysis compared recommendations of an agency that uses health economic with one that does not require economic analysis for decision-making. The French agency HAS considers safety, clinical efficacy and relative effectiveness but not consider health economic analysis at the first listing decision. There were similarities and differences identified in the policy implementation level and reimbursement processes of the two agencies. Medicines that were commonly assessed and appraised by the two agencies available in English language were compared with respect to the recommendations and evidence. There was poor agreement between the decisions made by the two agencies for the sample of medicines that were appraised by both agencies. The SMC tended to provide more restrictive listing or did not recommend in comparison with HAS in France. The observed differences in the matched recommendations may be explained by the process of price

setting and dealing with uncertainty, relevant comparator medicines, relevant outcomes, treatment guidelines, use of submitted network meta-analysis in the appraisal and formal consideration of HRQOL in health economic analysis by the SMC. The use of health economic analysis would appear to be important against a system that does not use such analysis because it provides differences in the perceptions of value of some new medicines depending upon the medicines characteristics. In combination with free pricing it can be observed that some differences in recommendations may be explained by the incentives for the manufacturer to target a patient population, quantify and understand the uncertainty of the relative effectiveness estimates in combination with the cost of the medicine and explicitly quantify the HRQOL benefits of a new medicine.

7.3.4 Contribution through influence on final outcomes rather than the intermediary decision

This thesis has identified the current evidence base and has attempted to add to the current knowledge on the use and contribution of health economic evidence and other factors in heterogeneous reimbursement systems. The chapters have focused on the contribution of health economic analysis and other factors upon the intermediate outcome of the reimbursement decision in countries. One weakness of this thesis is the implicit assumption that final outcomes such as utilisation and improved health outcomes given the resources available are causally influenced by the decisions made by the agencies reimbursement decisions. For example, if the plausible estimate of a medicine is judged to be cost-effective against a threshold range and this subsequently leads to a recommended decision does this lead to appropriate use and an improvement in health outcomes. Chapter 3 and 4 displayed the complexities by which some systems operate and the different decision outcomes, the interpretation and review of medicines within the systems. This makes the complexity of understanding the consistency of the agency decision, health economic analysis and other factors very difficult to analyse empirically. Further there has to be a good understanding of the objectives of the system at the time of the analysis because these will define the final outcomes that should be considered (cost-effectiveness/health improvement, access or cost containment). Studies have made assessment of the influence of decisions in England and Scotland. This would require a study conducted in two stages, firstly considering the consistency of the decision with the decision outcomes and the resulting consistency of the intermediate decision outcome with medicines utilisation and price. Little empirical evidence is known about the impact of decisions on final outcomes such as utilisation for decisions outside of the UK (Bennie et al., 2011, Sheldon et al., 2004). The recent study of

SMC decision-making in Scotland found that the effect of a not recommended decision is variable but suggests a number of limitations to the collection of prescribing data in Scotland. This study demonstrated the complexity in implementing advice from a reimbursement agency using health economic evidence and the changes in actual practice.

Health economic analysis has contributed to the reimbursement system alongside the need of government agencies to be transparent by providing a framework to consider many aspects of the assessment and appraisal. The technique provides a means for agencies to measure the consequences of certain decisions and to be able to justify the value of considering evidence and other factors to the Ministry of Health which they are ultimately accountable. There are many factors influencing the end utilisation of medicines and the reimbursement agencies do not act alone in the process such as conflicting clinical guidelines, clinical decision-making and the potential for other countries decisions to influence use. Health Economic analysis has therefore been widely used in OECD reimbursement systems, there is evidence that it is associated with decisions in some countries and has provided structure by which other factors can be explicitly taken account and the agencies held accountable. But this only tells half of the story and the potential contribution to the end outcome of use and the impact of health outcomes is largely unknown in all systems. Using this criterion, there is some evidence suggesting the very opposite and potential lack of its end contribution to final decision-making.

7.4 Policy implications: Lessons for the use and implementation of VBP in countries

This thesis has identified a number of key lessons for the implementation of VBP in those countries that have recently chosen to formally implement such methods of determining reimbursement and price of medicines. The key lessons are with respect to the objective of each reimbursement system, documentation of decision-making, use in the reimbursement process and the plans for implementation of VBP.

The first lesson is with respect to the objective(s) of each system. There needs to be clarity of the reimbursement institution(s) objective (maximisation of health, other objectives) and how all the institutions involved within the process work together to be accountable for the objective(s) of the system. It is clear that a lot more work needs to be done on the accountability of each of the agencies and how they contribute to the final outcomes of the system (for example has the decisions made by the agency improved health). This will be easier to consider in some systems more than others but this is likely to improve over time with the developing use of information technology to track decisions and use of the medicines by each population.

Once the objectives are clearly provided the criteria used in VBP need to be clearly stated and the decision-making clearly described within the guidance documentation. The criteria are likely to have some commonalities across countries because the review identified a number of common factors common to each country alongside the health economic analysis. But the review also identified a number of uniquely defined factors in each country some more easily quantifiable than others (need, severity, fairness in decision-making). A deliberative process is still important in systems but it is crucial that more subjective elements of decision-making are documented so that appropriate signals can be provided for manufacturers and accountability to the countries general public. This will not only help with accountability to the general public of each reimbursement system but also enhance the understanding of the decision-making and the desirability of the methods and processes of reimbursement decision-making. The formal use of MCDA would assist with this.

The third key lesson from this thesis is that process is very important and this will effect the implementation of VBP. The framework analysis of each system would appear to suggest that the stakeholders involved may be very important. For example the balance between expert participation (and professional background of the expert) and public participation may not only be important factors in explaining differences in decisions across countries but also for identifying and mediating the criteria used for decision-making. The involvement of policy makers and stakeholders in design of the VBP scheme will be critical for the political sustainability of the institutions involved in providing the decisions. A number of different processes may result in different countries depending on the criteria used in VBP such as the stages by which criteria are considered, the setting of threshold values for certain criteria and the number of decision outcomes in each country.

Finally, this thesis has found that many of the agencies have evolved their processes with respect to the use of HTA evidence and it appears some agencies have learnt a great deal over the years. It is therefore likely that an incremental process of implementation rather than a step change in process will allow each system to learn from practical experience. This will allow better accountability of the system to the public, provide stability in the signals of value to manufacturers and help to understand further how evidence improves the welfare of citizens in each country choosing to implement VBP.

7.5 Limitations: What could have been done differently?

A number of limitations have been identified in the previous chapters and this section summarises the main weaknesses that became apparent as study was undertaken.

- Language: There was decision documentation available in other countries that were not taken into account in comparisons in this thesis because of the requirement for translation of this documentation. The thesis therefore only identified use for many OECD countries and conclusions regarding the influence of factors on decisions can only be drawn for a subset of the OECD countries.
- Factor Causation: This study has identified no evidence that the association observed between factors and decisions are causal and ultimately whether this links to the final outcomes of the system. Although some studies have stated that they are natural experiments but it is questionable whether certain policy changes (third party assessment) are exogenous to the system or related to the processes and objectives of the system. There is no evidence on whether the contribution of Health Economic analysis is causal, although in some countries there is consistency between the association with the decision and the impact stated by decision-makers in qualitative studies. The use of the framework has attempted to identify the main similarities and differences between countries to allow comparison taking into account different aspects of the reimbursement system.
- Interview and questionnaire methodology: The study has not used a series of questionnaires and interviews to obtain responses directly from the decision-makers' in OECD countries. This has been studied in detail for the United Kingdom but there is scope to provide interviews in other countries where these were not identified in the current evidence base of Chapter 2. This would of required interviews and questionnaires in a number of languages to add sufficiently to the current body of evidence that exists for the United Kingdom.
- Reflexivity: On reflection many of the studies considering the influence of health economic analysis have been conducted by individuals with an Economics, Health Economics, Health Sciences and the author of this thesis holds two degrees in Economics and is a student in Health Sciences. The author of this thesis has tried to be as objective in the construct of variables and avoid many subjective judgements made by other authors in the construct of variables in the quantitative analysis and interpretation of the findings.

However, it is likely that the perspectives of the researchers have affected the conclusions drawn.

7.6 Further research recommendations

The following further research recommendations have been identified:

1. Individual Country Studies

There is an opportunity for more individual country studies where a number of factors are considered in those countries where a lack of quantitative or qualitative studies identified in Chapter 2. The increased requirement for transparency across countries reimbursement systems may make this possible.

2. Comparisons across countries

Future research could conduct both qualitative and quantitative comparisons of decisions made by other reimbursement agencies that produce documented decisions such as in Sweden (TLV) and the Netherlands (CVZ). In order for there to meaningful quantitative comparisons across countries there needs to be consensus on the construct of variables used in future quantitative analyses. Many variables are formed from the data that is available by the agency requiring an assessment and appraisal. This will enable an understanding of the influence of the many different processes on the final decision outcome alongside the other factors such as Health Economic analysis.

3. OECD country interviews

A future study could interview decision-makers in systems where few studies were identified in Chapter 2 of the importance of health economic analysis and other factors.

4. Implementation

Previous chapters identified that the mechanisms of implementation and pricing vary across the OECD countries. Further study of the influence of health economic analysis and other factors should not only focus on the reimbursement decision but other outcomes such as the price and use of the medicine following the recommendation.

5. Contribution to health outcomes

The value of using HTA and Health Economic analysis has not been assessed with respect to the improvement in health outcomes from limited resources in many of the systems. This

must be the ultimate purpose of such techniques and therefore further attempts such as that being undertaken in New Zealand are important to assess its contribution and value.

Appendices

Chapter 1 appendix

There are no appendices for chapter 1.

Chapter 2 appendix

Box A2.1: Study inclusion/exclusion sheet

Systematic Review: The Influence of Factors in Pharmaceutical Reimbursement Decision-making

Study ID:

Study Name:

INCLUDE **EXCLUDE**

Exclusion Reason:

Further Studies Found in Reference List:

Study Group inclusion:

Box A2.2: Excluded study references

Aaserud, M., Trommald, M., Oxman, A. D. & Innvaer, S. 2002. [Evaluation of reimbursement applications for new drugs]. *Tidsskrift for Den Norske Laegeforening,* 122, 2619-23.

Anell, A. 2004. Priority setting for pharmaceuticals. The use of health economic evidence by reimbursement and clinical guidance committees. *European Journal of Health Economics,* 5, 28-35.

Barham, L. 2008. Single technology appraisals by NICE: are they delivering faster guidance to the NHS? *Pharmacoeconomics,* 26, 1037-43.

Buxton, M. 2001. Implications of the appraisal function of the National Institute for Clinical Excellence (NICE). *Value in Health,* 4, 212-6.

Claxton, K., Sculpher, M., McCabe, C., Briggs, A., Akehurst, R., Buxton, M., Brazier, J. & O'Hagan, T. 2005. Probabilistic sensitivity analysis for NICE technology assessment: not an optional extra. *Health Economics,* 14, 339-47.

Cohen, J. P., Niezen, M. & Stolk, E. 2008. Role of budget impact in drug reimbursement decisions. *Journal of Health Politics, Policy and Law,* 33, 225-247.

Dear, J., O'Dowd, C., Timoney, A., Paterson, K. R., Walker, A. & Webb, D. J. 2007. Scottish Medicines Consortium: an overview of rapid new drug assessment in Scotland. *Scottish Medical Journal,* 52, 20-6.

Drummond, M., Evans, B., LeLorier, J., Karakiewicz, P., Martin, D., Tugwell, P. & MacLeod, S. 2009. Evidence and values: requirements for public reimbursement of drugs for rare diseases--a case study in oncology. *Canadian Journal of Clinical Pharmacology/Journal Canadien de Pharmacologie Clinique,* 16, e273-81; discussion e282-4.

Eddama, O. & Coast, J. 2009. Use of economic evaluation in local health care decision-making in England: a qualitative investigation. *Health Policy,* 89, 261-70.

Harris, A., Buxton, M., O'Brien, B., Rutten, F. & Drummond, M. 2001. Using economic evidence in reimbursement decisions for health technologies: Experience of 4 countries. *Expert Review of Pharmacoeconomics and Outcomes Research,* 1, 7-12.

Hill, S. R., Mitchell, A. S. & Henry, D. A. 2000. Problems with the interpretation of pharmacoeconomic analyses: a review of submissions to the Australian Pharmaceutical Benefits Scheme. *JAMA,* 283, 2116-21.

Ikegami, N., Drummond, M., Fukuhara, S., Nishimura, S., Torrance, G. W. & Schubert, F. 2002. Why has the use of health economic evaluation in Japan lagged behind that in other developed countries? *Pharmacoeconomics,* 20 Suppl 2, 1-7.

Jonsson, B. 1997. Economic evaluation of medical technologies in Sweden. *Social Science & Medicine,* 45, 597-604.

Laupacis, A. 2002. Inclusion of drugs in provincial drug benefit programs: Who is making these decisions, and are they the right ones? *Canadian Medical Association Journal,* 166, 44-47.

Miners, A. H., Garau, M., Fidan, D. & Fischer, A. J. 2005. Comparing estimates of cost effectiveness submitted to the National Institute for Clinical Excellence (NICE) by different organisations: retrospective study. *BMJ,* 330, 65.

Persson, U. & Ramsberg, J. 2007. [Health economics evaluations are of great significance for Pharmaceutical Benefit Board's decisions]. *Lakartidningen,* 104, 3046-50.

Russo, P. 2008. Pharmacoeconomic evaluations in the Italian regulatory context: A quali-quantitative analysis of pricing and reimbursement dossiers. [Italian]. *PharmacoEconomics - Italian Research Articles,* 10, 59-75.

Sloan, F. A., Whetten Goldstein, K. & Wilson, A. 1997. Hospital pharmacy decisions, cost containment, and the use of cost-effectiveness analysis. *Social Science and Medicine,* 45, 523-533.

Summerhayes, M. & Catchpole, P. 2006. Has NICE been nice to cancer? *European Journal of Cancer,* 42, 2881-6.

Box A2.2: Excluded study references Continued..../

Van Wilder, P. B. & Dupont, A. G. 2009. Reimbursement of medicines in Belgium: role of evidence-based medicine. *Acta Clinica Belgica,* 64, 120-8.

Williams, I. P. & Bryan, S. 2007. Cost-effectiveness analysis and formulary decision making in England: findings from research. *Social Science & Medicine,* 65, 2116-29.

Box A2.3: Search strategies

Medline Search:

HTTP/1.0 200 OK
Date: Tue, 06 Jul 2010 09:49:58 GMT
Server: OvidHTTPD/1.1.67 [libwww-perl-daemon/1.33]
Database: Ovid MEDLINE(R) <1950 to June Week 4 2010>
Search Strategy:

---

1 (reimbursement or payer).ti,ab. (13271)
2 Reimbursement mechanisms/ (9041)
3 pharmaceutical benefits advisory committee.ti,ab. (33)
4 pbac.ti,ab. (124)
5 committee for drug reimbursement.ti,ab. (0)
6 danish medicines agency.ti,ab. (28)
7 haute autorit$ de sant$.ti,ab. (40)
8 french national authority for health.ti,ab. (19)
9 "reimbursement and medicinal products".ti,ab. (0)
10 edaf.ti,ab. (3)
11 "ministry of social affairs and health".ti,ab. (19)
12 italian medicines agency.ti,ab. (5)
13 agenzia italiana del farmaco.ti,ab. (4)
14 aifa.ti,ab. (19)
15 health insurance review agency.ti,ab. (18)
16 national cent$ of excellence in health technology.ti,ab. (0)
17 centro nacional de excelencia tecnologica en salud.ti,ab. (0)
18 cenetec.ti,ab. (0)
19 pharmaceutical management agency.ti,ab. (10)
20 pharmac.ti,ab. (168)
21 health technology assessment agency.ti,ab. (2)
22 aotm.ti,ab. (2)
23 (ministry of health adj20 slovak republic).ti,ab. (8)
24 (dental adj6 pharmaceutical benefits board).ti,ab. (0)
25 (pharmaceutical adj20 tlv).ti,ab. (2)
26 (social insurance agency adj20 turkey).ti,ab. (0)
27 (medicare adj20 coverage advisory committee).ti,ab. (9)
28 "Institute for Quality and Efficiency in Health Care".ti,ab. (20)
29 Institut fur Qualitat und Wirtschaftlichkeit im Gesundheitswesen.ti,ab. (5)
30 iqwig.ti,ab. (38)
31 (national health insurance fund administration adj20 hungary).ti,ab. (9)
32 national centre for pharmacoeconomics.ti,ab. (1)
33 ncpe.ti,ab. (23)
34 ("ministry of health" adj5 "labour and welfare" adj20 Japan).ti,ab. (106)
35 direction de la sant$.ti,ab. (5)
36 national insurance health boards.ti,ab. (0)
37 college voor zorgverzekeringen.ti,ab. (1)
38 (cvz adj20 netherlands).ti,ab. (2)
39 norwegian medicines agency.ti,ab. (13)
40 statens legemiddelverk.ti,ab. (0)
41 "national institute for pharmacies and medicines".ti,ab. (0)
42 instituto nacional da farmacia e do medicamento.ti,ab. (0)

Box A2.3 Search strategies Continued..../

43 agencia d'Avaluacio de tecnologia i recerca mediques de catalunya.ti,ab. (0)
44 (federal office of public health adj20 switzerland).ti,ab. (18)
45 (national institute adj6 clinical excellence).ti,ab. (811)
46 scottish medicines consortium.ti,ab. (15)
47 smc.ti,ab. (5532)
48 nice.ti,ab. (2673)
49 drug coverage.ti,ab. (427)
50 drug approval/ (7704)
51 decision$.ti,ab. (142933)
52 allocation$.ti,ab. (17615)
53 advice.ti,ab. (23015)
54 list.ti,ab. (37580)
55 lists.ti,ab. (15589)
56 recomend$.ti,ab. (80)
57 recommend$.ti,ab. (279492)
58 apprais$.ti,ab. (20381)
59 or/1-49 (29297)
60 or/50-58 (512770)
61 59 and 60 (3833)
62 (comment or editorial).pt. (591648)
63 61 not 62 (3754)
64 Animals/ (4590194)
65 Humans/ (11286508)
66 64 not 65 (3409968)
67 63 not 66 (3747)
68 limit 67 to yr="1990-Current" (3423)

Embase Search

Date: Tue, 06 Jul 2010 09:21:51 GMT
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Database: EMBASE <1980 to 2010 Week 26>
Search Strategy:
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1 (reimbursement or payer).ti,ab. (9616)
2 Reimbursement mechanisms/ (13206)
3 pharmaceutical benefits advisory committee.ti,ab. (37)
4 pbac.ti,ab. (124)
5 committee for drug reimbursement.ti,ab. (1)
6 danish medicines agency.ti,ab. (27)
7 haute autorit$ de sant$.ti,ab. (43)
8 french national authority for health.ti,ab. (18)
9 "reimbursement and medicinal products".ti,ab. (2)
10 edaf.ti,ab. (1)
11 "ministry of social affairs and health".ti,ab. (16)
12 italian medicines agency.ti,ab. (10)
13 agenzia italiana del farmaco.ti,ab. (5)
14 aifa.ti,ab. (35)
15 health insurance review agency.ti,ab. (10)
16 national cent$ of excellence in health technology.ti,ab. (0)

Box A2.3 Search strategies Continued..../

17	centro nacional de excelencia tecnologica en salud.ti,ab. (0)
18	cenetec.ti,ab. (0)
19	pharmaceutical management agency.ti,ab. (12)
20	pharmac.ti,ab. (168)
21	health technology assessment agency.ti,ab. (3)
22	aotm.ti,ab. (1)
23	(ministry of health adj20 slovak republic).ti,ab. (16)
24	(dental adj6 pharmaceutical benefits board).ti,ab. (0)
25	(pharmaceutical adj20 tlv).ti,ab. (0)
26	(social insurance agency adj20 turkey).ti,ab. (0)
27	(medicare adj20 coverage advisory committee).ti,ab. (8)
28	"Institute for Quality and Efficiency in Health Care".ti,ab. (49)
29	Institut fur Qualitat und Wirtschaftlichkeit im Gesundheitswesen.ti,ab. (6)
30	iqwig.ti,ab. (96)
31	(national health insurance fund administration adj20 hungary).ti,ab. (8)
32	national centre for pharmacoeconomics.ti,ab. (1)
33	ncpe.ti,ab. (20)
34	("ministry of health" adj5 "labour and welfare" adj20 Japan).ti,ab. (77)
35	direction de la sant$.ti,ab. (2)
36	national insurance health boards.ti,ab. (0)
37	college voor zorgverzekeringen.ti,ab. (1)
38	(cvz adj20 netherlands).ti,ab. (3)
39	norwegian medicines agency.ti,ab. (12)
40	statens legemiddelverk.ti,ab. (0)
41	"national institute for pharmacies and medicines".ti,ab. (0)
42	instituto nacional da farmacia e do medicamento.ti,ab. (0)
43	agencia d'Avaluacio de tecnologia i recerca mediques de catalunya.ti,ab. (0)
44	(federal office of public health adj20 switzerland).ti,ab. (18)
45	(national institute adj6 clinical excellence).ti,ab. (887)
46	scottish medicines consortium.ti,ab. (16)
47	smc.ti,ab. (5111)
48	nice.ti,ab. (2465)
49	drug coverage.ti,ab. (333)
50	drug approval/ (15475)
51	decision$.ti,ab. (114476)
52	allocation$.ti,ab. (13673)
53	advice.ti,ab. (18741)
54	list.ti,ab. (30524)
55	lists.ti,ab. (11512)
56	recomend$.ti,ab. (227)
57	recommend$.ti,ab. (242911)
58	or (15770)
59	or/1-49 (26989)
60	or/50-58 (435739)
61	59 and 60 (4142)
62	(comment or editorial).pt. (259359)
63	61 not 62 (4063)
64	Animals/ (55517)
65	Humans/ (7099174)
66	64 not 65 (38607)

Box A2.3 Search strategies Continued..../

67 63 not 66 (4063)
68 limit 67 to yr="1990-Current" (3837)

EconLit

Date: Tue, 06 Jul 2010 13:34:51 GMT
Database: Econlit <1969 to June 2010>
Search Strategy:
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1 (health adj20 drug).ti,ab. (303)
2 (health adj20 medicine).ti,ab. (199)
3 (reimbursement or payer).ti,ab. (794)
4 (drug adj20 pay$).ti,ab. (72)
5 (medicine adj20 pay$).ti,ab. (16)
6 pharmaceutical.ti,ab. (1612)
7 (health adj20 agency).ti,ab. (131)
8 drug coverage.ti,ab. (42)
9 decision$.ti,ab. (42658)
10 allocation$.ti,ab. (15528)
11 advice.ti,ab. (1432)
12 list.ti,ab. (1740)
13 lists.ti,ab. (677)
14 recomend$.ti,ab. (14)
15 recommend$.ti,ab. (7948)
16 apprais$.ti,ab. (2861)
17 or/1-8 (2919)
18 or/9-16 (68771)
19 17 and 18 (412)
20 limit 19 to yr="1990-Current" (401)
21 from 20 keep 1-401 (401)

HMIC

Database: HMIC Health Management Information Consortium <May 2010>
Search Strategy:
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1 (reimbursement or payer).ti,ab. (619)
2 (drug adj20 pay$).ti,ab. (75)
3 (medicine adj20 pay$).ti,ab. (131)
4 pharmaceutical.ti,ab. (2324)
5 (health adj20 agency).ti,ab. (1099)
6 drug coverage.ti,ab. (15)
7 decision$.ti,ab. (10299)
8 allocation$.ti,ab. (2656)
9 advice.ti,ab. (5522)
10 list.ti,ab. (4451)
11 lists.ti,ab. (2706)
12 recomend$.ti,ab. (20)
13 recommend$.ti,ab. (12260)
14 apprais$.ti,ab. (2232)

Box A2.3 Search strategies Continued..../

15 or/1-6 (4169)
16 or/7-14 (35406)
17 15 and 16 (749)

NHSEED

Search Name: NHSEED Search 06072010
Comments:
Save Date: 2010-07-06 09:30:21

ID	Search	Hits	
#1	(reimbursement):ti,ab,kw		754
#2	(payer):ti,ab,kw	228	
#3	MeSH descriptor Reimbursement Mechanisms explode all trees	793	
#4	(drug coverage):ti,ab,kw		170
#5	(decision*):ti,ab,kw		8590
#6	(allocation*):ti,ab,kw		25023
#7	(advice):ti,ab,kw		2129
#8	(list):ti,ab,kw		5906
#9	(lists):ti,ab,kw		5906
#10	(recommend):ti,ab,kw	14428	
#11	(apprais*):ti,ab,kw		2344
#12	(#1 OR #2 OR #3 OR #4)	1616	
#13	(#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11)	55167	
#14	(#12 AND #13)		233

REPEC

Reimbursement and decision – 104 studies

Table A2.1: Study data collection table

		Study Details
Study Detail	Study Name:	
	Study ID:	
	Review author ID:	MWB
	Citation:	
	Agency name:	
	Country:	
	Study design:	Quantitative / Qualitative
Study Methods	Total number of reimbursement decisions/interviews	
	Decision time period	
	Study type	
	Decision outcomes	
	Factors included	
	Clinical evidence factor definition (quantitative)	
	Economic evidence factor definition (quantitative)	
	Non-evidence factor definition (quantitative)	
	Process factor definition (quantitative)	
	Other factor definition (quantitative)	
	Definition of influence	
Study Results	Factors considered important	

Table A2.2: Study exclusion reasons

Study	Exclusion Reason
(Anell, 2004)	Description of the use of evidence rather than data on decisions and factors. (No data on decisions)
(Anis, 1998)	Description on the influence of provincial decision-making.
(Barham, 2008)	Length of time to complete the appraisal not investigated in relation to decision outcome (Factor not related to decision outcome)
(Buxton, 2001)	Discussion paper with no data on decisions (No data on decisions)
(Claxton et al., 2005)	Discussion paper with no data on decisions (No data on decisions)
(Dear et al., 2007)	The timing of production of guidance is not related to the influence on decisions (Factor not related to decision outcome)
(Drummond et al., 2009)	Discussion paper with no data on decisions (No data on decisions)
(Eddama and Coast, 2009)	Local decisions and health policy which do not relate to medicine formulary decisions. (Local level decision making)
(Harris et al., 2001)	A summary of potential influence without direct reference to decisions and data (No data on decisions)

Table A2.2: Study exclusion reasons Continued...../

(Hill et al., 2000)	This is a critique of past manufacturers submission without relation to decisions (Factor not related to decision outcome)
(Ikegami et al., 2002)	This is summary of systems rather than data on decisions (No data on decisions)
(Jonsson, 1997)	Summary of the Swedish system without data on decisions (No data on decisions)
(Laupacis, 2002)	This is an essay on the Canadian system rather than an empirical study of decisions (No data on decisions)
(Miners et al., 2004)	This study contains empirical analysis on the differences between the presentation of results by the manufacturer and assessment group for the economic analysis (Factor not related to decision outcome)
(PausJenssen, 2003)	Qualitative description of the factors influencing Ontario provincial decision-making in Canada.
(Cohen et al., 2008)	This study is a discussion of the theoretical use of budget impact analysis (Factor not related to decision outcome)
(Scobie et al. 2010)	This study considered a qualitative review of CDR decisions but did not directly consider the factors influencing decisions. The study considered the timeliness of CDR recommended and restricted decisions with respect to the decisions made by the provinces.

Table A2.2: Study exclusion reasons Continued...../

(Sloan et al. 1997)	The use of economic analysis in the pharmacy setting (No data on decisions)
(Summerhayes and Catchpole, 2006)	The influence on one medicine decision (One medicine decision studied)
(West, 2002)	Qualitative study of the factors influencing reimbursement decisions in 5 provinces.
(Williams and Bryan, 2007)	Qualitative study on local formulary decisions.
(Aaserud et al., 2002)	Not in English language
(Persson and Ramsberg, 2007)	Not in English language
(Russo, 2008)	Not in English language
(Van Wilder and Dupont, 2009)	Not in English language

Table A2.3: Quantitative studies data extraction

Study	Country	Agency	Number of reimbursement decisions/Interviews	Decision period/Study type	Decision outcomes	Factors considered	Analysis	Results: Factors considered important
(Clement et al., 2009)	England, Australia and Canada	National Institute for Health and Clinical Excellence (NICE), Pharmaceutical Benefits Advisory Committee (PBAC), Common Drug Review CADTH CDR.	CDR- n=121, NICE-n=199, PBAC-n=282, Total n=602 Common submissions al three-n=19	2001-2008 Mixed Method Retrospective analysis of decisions	Listed, not listed	• Resubmissions • Life threatening disease • Clinical evidence • Clinical Uncertainty • Economic evidence • Economic uncertainty	Statistical differences across decisions by Chi2 tests.	The three agencies face common issues with respect to the strength of experimental evidence. The results of the evaluation process are influenced by the context, agency processes, ability to engage in price negotiation and differences in the social values.
(Chim et al., 2010)	Australia	Australia (PBAC)	PBAC: 243	2005-2008 Quantitative Retrospective Analysis	Approval, rejection/deferral	• Medicine type • Application type • Estimated cost to the PBS • Economic model estimate	Logistic regression of (cancer vs non cancer)	The study aimed to assess whether cancer medicines were less likely to be approved than other medicines, controlling for other factors. The multivariable regression found that application type (new indication/ new drug), estimated cost to the PBS per year and economic model estimate were statistically significantly associated with the decision. There was no statistical difference in the odds of approving cancer medicines.
(George et al., 2001)	Australia	Pharmaceutical Benefits Advisory Committee (PBAC)	n=355, CUA=26, CELG=9	1991-1996 Quantitative Retrospective Analysis	Recommended Reject Defer	• Cost-effectiveness analysis and cost-utility analysis were considered with respect to the decision outcome.	Mann-Whitney test to identify difference between the CLG/CEA for recommend/Reject	The study found that decisions to recommend drugs at a proposed price are associated with a lower cost per life year gained than decisions to reject is consistent with the use of economic efficiency as a criterion. The criteria of efficiency alone cannot describe adequately the decisions, for example, uncertainty, scientific rigour of the evidence, lack of alternatives, perceived need in the community, drug is to be used in a hospital setting and seriousness of intended indication.

(Harris et al., 2008)	Australia	Pharmaceutical Benefits Advisory Committee (PBAC)	n=103 (CUA)	1994-2004 Quantitative Retrospective Regression Analysis	Listed Not Listed	• The variables included were the ICER • Cost to government, • Clinical significance, • Precision of clinical evidence • Level of evidence • Quality of studies • Relevance of evidence • Life threatening • Economic model validity • Modelled outcome, • Modelled cost • No alterative acceptable therapy, • Uncertainty given by the upper most sensitivity analysis • Whether the drug had been previously considered.	Probit regression model of	The study found that the ICER, budget impact, clinical significance, relevance of evidence, life threatening, highest ICER, previously considered and life threatening interacted with clinical significance had statistically significant effects upon the decision. The study concludes that the importance of the clinical effect. cost-effectiveness, budget impact are important factors influencing decisions. The study concludes that there was no evidence of a single threshold. The authors acknowledge that the small sample size may be too small to identify some differences across some of the variables included in the study.
(Scuffham et al., 2008)	Australia	Pharmaceutical Benefits Advisory Committee (PBAC)	n=49 (CUA)	2002-2004 Quantitative Retrospective analysis	Recommended, Rejected Deferred	• The approach to elicit QALY weights through either a multi attribute utility instrument (MAUI), health state valuation (HSV) or non preference measure.	Descriptive statistics of decisions	The rejection rates were greatest for those submissions including non-preference based approaches, HSVs were more likely to be recommended whereas MAUIs were more likely to be deferred.
(Van Wilder and Dupont, 2008)	Belgium	National Insurance Agency	N=824, class I submissions=67	2002-2004 Quantitative	Positive Negative	• The extent of the acquired evidence with the compound • The approval of added value for class I submissions only	Pearson chi square	The percentage of positive decisions to reimburse is significantly lower for the limited (68.4%) as compared to the extended evidence group (92.5%). The approval of the added value-label is highly predictive of a positive decision. The authors conclude that both factors play a role in decision making.

(Dakin et al., 2006)	England	National Institute for Health and Clinical Excellence (NICE)	N=94, N=60 for CEA	1999-2005 Quantitative Retrospective analysis	Recommend Restricted recommend Not recommended	• Date of decision • Patient group submission • Number of RCTs • RCT size • RCT quality • RCT relevance • RCT significance • Observational data • Systematic review • CUA estimate • CER and CQG estimate • No alternatives • Budget impact • Intervention type	Multinomial logistic regression.	The study found that the decisions were related to the number of RCTs, pharmaceuticals, the number of systematic reviews and the cost-effectiveness and there was a differential impact between the decision outcomes. For example higher cost-effectiveness was only found to be important in the comparison between not recommended and recommended for restricted use but did not significantly affect the decision between recommended and restricted use. The study suggested that there was a differential impact of factors on the three decision outcomes.
(Devlin and Parkin, 2004)	England	National Institute for Health and Clinical Excellence (NICE)	N=33	1999-2002 Quantitative Retrospective analysis	Recommended Not recommended	• ICER value • Uncertainty • Alternative treatment options • Other factors • Burden of disease • Budget impact	Logistic regression	Cost-effectiveness, uncertainty and burden of disease were demonstrated to explain decisions. The results suggested a threshold of between £34,000 and £47,000 considering the model that included these explanatory factors. It was not possible to consider the budget impacts contribution to the decision because of the small sample size. The model assumes that the documented evidence is what NICE actually believed to be important in the decision making.
(Devlin et al., 2010) [conference abstract]	England	National Institute for Health and Clinical Excellence (NICE)	N=184	1999-2009 Quantitative Retrospective analysis	Recommend in patient subgroup/indication or Not recommend in patient subgroup/indication	• Clinical evidence • Economic evidence • No alternatives • Type of disease • Children • Date of guidance • Involvement of stakeholders • STA process	Logistic regression	Not reported – work in progress.

(Mason and Drummond, 2009)	England	National Institute for Health and Clinical Excellence (NICE)	N=56 (38 appraisals)	2000-2008 Quantitative Retrospective analysis	Positive Restricted Negative	• The impact of time period on decisions made by NICE for cancer treatments	Generalised Fisher exact test	The results showed that relative to period 1 the proportion of negative recommendations increased in period 2, irrespective of whether the data was analysed by appraisal or by drug assessment. The study found similarities in the issues reported for restricted decisions but found a large variation in those citing the ICER as a reason for restriction between period 1 (27%) and period 2 (100%) and NICE being unsure whether the drug represented value for money, period 1 (20%) than in period 2 (80%). The study concludes that the change to the STA process explains part of the observed changes, it is clear that the nature of the evidence base for cost-effectiveness has shifted from an absence of evidence to evidence of absence.
(Tappenden et al., 2007)	England	National Institute for Health and Clinical Excellence (NICE)	N=664 (16 respondents completing 18 choice scenarios)	2007 Quantitative	Recommended Not recommended	• The study explored preferences for using the incremental cost effectiveness • The degree of uncertainty surrounding the ICER and health outcomes • The age of beneficiaries • Baseline health related quality of life • The availability of alternative therapies.	Logistic binary regression model	The results suggest that increases in the ICER, a high level of uncertainty and the availability of other therapies are associated with a statistically significant reduction in the odds of adoption. The results were seen to support a probabilistic adoption/rejection curve, rather than the operation of a single fixed threshold. The results show that the committee is unlikely to adopt technologies that have unfavourable economic profiles, unless other factors are present. The study suggests that further research should consider the criteria used in other health care systems.

(Koopmanschap et al., 2010)	Netherlands	The use of evidence in reimbursement decision making	Mixed methods: N= 66 for DCE Focus group	2007-2008 Quantitative	Recommend Not recommended	• Budget impact (national additional medical cost) • Productivity saving (savings in costs for absence from work) • Disease severity prior to treatment • Economic analysis (ICER-cost per QALY) • The number of QALYs gained per patient • The composition of the health gain (longer life expectancy, purely improved QoL, 50:50 of these scenarios) • Uncertainty and risk aversion through the cost per QALY doubling from the average scenario.	Discrete Choice Experiment using Multinomial Logistic Regression Models (MNLM)	The regression model observed sign for each of the coefficients was as expected, an intervention with a higher budget impact, higher cost per QALY and more uncertainty was less likely to be preferred, whereas disease severity and the amount of individual health gain were positively linked with the probability of choosing the intervention. Productivity savings were not significant. There was near significance between the interaction of budget impact and higher cost-effectiveness. There were some subgroups that attracted more weight in decision making with particular emphasis on disease severity. The study found that respondents were generally more risk averse towards health effects than costs. The results were consistent with the low and high disease severity thresholds in the Netherlands of EURO80,000 and $10-$15,000 for low severity diseases. There were other factors identified that were not captured in the analysis, the number of patients covered by the intervention, health care cost per person, relative impact on budget and risk behaviour relating to the disease.
(Neumann et al., 2005)	USA	Medicare	N=69 of which n=5 medications	1999-2003 Quantitative	Determination : Completely covered Covered with conditions Local contractor discretion No national coverage	• Level clinical evidence – well designed, well conducted studies in representative populations. • Limitations of evidence, limited number of studies, limited number of patients, lack of controls, relevance of outcomes, selection bias, lack of randomisation, length of study and other.	Descriptive Statistics and narrative description of documented evidence.	The study considered commonly reported limitations that included a limited number of patients in studies and lack of controls. The majority of cases were covered with conditions (61%), no national coverage (32%), local contractor discretion (6%) and completely covered (1%). The technologies with good evidence were more likely to be covered than those with poor and fair evidence (RR=1.46, p=0.004).The cost is not explicitly considered in coverage decisions but it has been acknowledged that those with a high budget impact receive a more careful evidence review. Cost-effectiveness analysis was not used to influence decisions.

Table A2.4: Qualitative studies data extraction

Study	Countries compared	Agencies compared	Number of reimbursement decisions/Interviews	Decision period/Study type	Decision outcomes	Factors considered	Analysis	Factors considered important
(Barbieri et al., 2009)	England and Scotland	National Institute for Health and Clinical Excellence (NICE) and Scottish Medicines Consortium (SMC)	n=25 comparisons of the same medicines	2001-2006 (supplementary information provided). Qualitative Retrospective analysis of decisions	Raftery classification for Recommended, Recommended with restriction.	• Impact of Third Party Assessment (MTA vs STA) • Length of process • Clinical effectiveness • Cost-effectiveness evidence • Uncertainty in cost-effectiveness evidence • Consideration of subgroups • Characteristics of the technology considered.	Narrative description of 25 case studies	The study identifies a trend in 25 decision comparisons where NICE guidance tends to be more restrictive due to more information available for subgroups considered. The article argues that third party review may be important for reaching decisions when the evidence base is under the control of the manufacturer, manufacturer is unable to implement appropriate methods and failed to reflect all uncertainties. There may be situations where the use of a hybrid approach is most appropriate depending on the technology.
(Cairns, 2006)	England and Scotland	National Institute for Health and Clinical Excellence (NICE) and Scottish Medicines Consortium (SMC)	n=21 comparisons of the same medicine	2001-2005 Qualitative Retrospective analysis of decisions	Recommended, restricted recommendation and not recommended.	• Timing • Length and detail of process • Quality of manufacturer submission • Cost-effectiveness • Clinical-effectiveness • Stakeholder involvement	Narrative description of 21 case studies	The decisions that were made by both agencies were similar and the authors suggested that this indicates that the work of NICE and SMC are complementary.
(Clement et al., 2009)	England, Australia and Canada	National Institute for Health and Clinical Excellence (NICE), Pharmaceutical Benefits Advisory Committee (PBAC), Common Drug Review CADTH CDR.	CDR- n=121, NICE-n=199, PBAC-n=282, Total n=602 Common submissions al three-n=19	2001-2008 Mixed Method Retrospective analysis of decisions	Listed, not listed	• Resubmissions • Life threatening disease • Clinical evidence • Clinical Uncertainty • Economic evidence • Economic uncertainty	Statistical differences across decisions by Chi2 tests.	The three agencies face common issues with respect to the strength of experimental evidence. The results of the evaluation process are influenced by the context, agency processes, ability to engage in price negotiation and differences in the social values.

(Lexchin and Mintzes, 2008)	Canada, Australia and Scotland	Common Drug Review CADTH CDR, Pharmaceutical Benefits Advisory Committee (PBAC), Scottish Medicines Consortium (SMC)	CDR-n=47, PBAC=31, SMC=29 Common submissions by all three –n=22	1999-2006 Qualitative Retrospective analysis of decisions	Listed, restricted list, not listed	• Clinical evidence • Quality of Pharmacoeconomic studies, • Price and effectiveness of competing products • Prevalence of disease • Perceived need for treatment • Composition of the panel making the decision	Statistical differences in decisions considered Chi2 test and kappa scores	There was no difference across the proportion of all drugs recommended by the CDR and the other two agencies. However, when individual drugs were compared there was poor to moderate agreement between CDR and the other 2 agencies, as well as between PBAC and SMC. The poor level agreement was attributed to analyses of the pharmacoeconomic data by the agencies. Other considerations such as prevalence of disease, perceived need for treatment and composition of the panel making the decision was suggested but not directly tested with the data.
(Raftery, 2008)	England, Australia and New Zealand	National Institute for Health and Clinical Excellence (NICE), Pharmaceutical Benefits Advisory Committee (PBAC), Pharmaceutical Management Agency (PHARMAC)	n=10 common decisions for NICE top 10 least cost-effective drugs	1996-2007 Qualitative	Listed, Listed with major restrictions, Listed with minor restrictions, not listed.	• Clinical effectiveness • Cost effectiveness • Uncertainty • Nature of condition • Innovative technology • Precedents • Budget impact • Rule of rescue • Health benefits • Direct cost to users • Availability of alternative treatments	Narrative comparison of 10 case studies	The drugs deemed least cost-effective by NICE between 1996 and 2005 were all approved for funding in the England, six were approved in Australia and five in New Zealand. It was suggested that it was difficult to avoid a conclusion that the reason that these drugs had been funded was because of the nature of the disease and it proved politically difficult not to fund them. Mechanisms such as patient access schemes were introduced to enable the funding of these drugs. The decision to fund drugs in the final decision depends on their political and social acceptability which are brought around by the public's perceptions.
(Hailey, 1997)	Australia	Pharmaceutical Benefits Advisory Committee (PBAC)	n=12	Not Reported Qualitative Case studies	Listed Restricted listing Not listed	• Clinical effectiveness • Safety • Cost effectiveness • Availability of alternatives • Budget impact • Minister over rule • Price negotiations • Lobbying efforts by support groups	Case Study narrative description	The study concluded that economic evaluation had played a valuable input and is used routinely in the decision making process. There have been other factors that have influenced the decisions such as political views, existing policies, administrative feasibility, budget impact and political and societal factors.

(Rocchi et al., 2008)	Canada	Common Drug Review CEDAC	N=62 – documented evidence N=17 – focus group	2003-2007 Qualitative	Positive Negative	• Type of clinical outcome (surrogate, intermediate, final) • Magnitude of benefit versus comparators • Choice of comparator • Trial duration • Generalisability of trial population • Trial size • Comparative safety • Price • Quality of model • Effectiveness used in model versus efficacy • Historical factors • Type of disease • Prevalence of disease • Equity • Rule of rescue • Lack of alternatives • Budget impact • Appropriateness of utilisation • Innovative drug	Documented narrative and focus groups	In 37 submissions the only economic consideration mentioned was the price of the drug. Economic evidence beyond price was considered in 25 out of the 62 cases. This included 12 negative recommendations and 13 positive recommendations. The ICER value was not routinely reported across the documented evidence for these decisions. There was no clear indication of whether the panel found the ICER attractive or not attractive. The study considered a subset of oncology drugs that were deemed to be an interesting subset. The ICERs for oncology drugs constituted the upper limit of ICERs for recommendations ($80k per QALY). In the round table focus groups the use of economic evidence provoked strong disagreement. The majority of participants thought that economic evidence contributed to decision-making but clinical evidence was considered more important. The concept of equity is not addressed across decisions as in cancer not all health gains are valued equally. (Hierarchy of diseases)
(Andronis et al., 2009)	England	National Institute for Health and Clinical Excellence (NICE)	n=15 (reimbursement decisions) n=28 semi structured interviews	2003-2004 Qualitative Retrospective analysis of documented evidence Interview	Recommended Not recommended	• The impact of uncertainty and the use of sensitivity analysis to explore this uncertainty and the impact on the decision outcome. • The impact of parameter uncertainty and structural uncertainty. • The identification of subgroups using sensitivity analysis.	Retrospective narrative	In two decisions, the impact of uncertainty of the cost-effectiveness estimates was discussed with regards to the decision. The documents appear to indicate that uncertainty is explicitly considered for decision making with a focus on parameter uncertainty. The interviews suggested that PSA was important for decisions and is an important factor for consideration when NICE makes decisions

(Bryan et al., 2007)	England	National Institute for Health and Clinical Excellence (NICE)	N=28 semi structured interviews	2003-2004 Qualitative Semi-structured interviews	Not reported directly but consideration of impact on coverage decision.	• The impact of economic analysis in NICE decision-making • Use of economic analysis • Understanding of CE analysis • Cost-effectiveness threshold	Descriptive narrative	The interviews confirmed that economic analysis is used in a direct way to inform decisions for new technologies with barriers to the use of research grouped under accessibility of the research evidence (difficulties in accessing information, interpretation and skills required) and acceptability of the research evidence (whether decision makers are inclined to adopt the recommendations of the economic analysis). The study questions whether health maximisation is the only objective of the decision maker, and suggests that a number of other conflicting objectives which must be traded off in the decision making process. For example, the situation in which equity concerns were evoked or raised in decision-making given the unclear nature of the equity concerns.
(Raftery, 2006)	England	National Institute for Health and Clinical Excellence (NICE)	N=117 (86 guidance published)	1999-2005 Qualitative	Yes, routinely, Yes with major restrictions Yes with minor restrictions Not recommended	• Clinical evidence (insufficient evidence for use) • Economic evidence (do not use because of poor cost-effectiveness).	Narrative description	There were 22 (19%) no decisions, 27 yes decisions (23%), 38 yes with major restrictions (32%) and 30 yes with minor restrictions (30%). The negative decisions were explained by insufficient evidence in two thirds of the decisions and unacceptable cost-effectiveness in a third of the decisions. The highest ICER that NICE had accepted during this period was £39,000 per QALY. In this period there had been 25 appeals of which 15 were dismissed, 5 led to minor word changes and 5 were referred back to the appraisal committee. The study concluded that NICE rejections had been fairly rare and they were more likely to recommend.

(Raftery, 2009)	England	National Institute for Health and Clinical Excellence (NICE)	N=11	1999-2009 Qualitative	Not recommended decisions	• The impact of end of life guidance on previous decisions to not recommend a treatment	Narrative description	Process changes resulted with respect to NICE because of legal action by patients, media publicity and political discomfort. This resulted in specific criteria. The study found that most of the previous studies would fail to meet the criteria of no alternative treatment with comparable benefits existing. Only two of the drugs would qualify if best supportive care were taken to indicate a lack of alternatives. It was concluded that the new arrangements were unlikely to improve the availability of new cancer drugs. The identification one group now sets precedence for other groups to be identified.
(Williams et al., 2008)	England	National Institute for Health and Clinical Excellence (NICE)	Systematic review of influence of economics on decision making. Local formulary case studies (n=4) Documentary evidence of decisions (n=7) Interviews with decision makers (n=30) Workshops (n=2)	2002-2004 Qualitative	Coverage decision as determined by the participant	• To determine the influence of economic information in health policy decision making in England, considering local formulary decisions and national NICE decision making.	Systematic Literature Review, Case studies, Semi-structured interviews and workshops	The study found that at a local level the use of economic analysis was an exception to inform formulary decisions. The local level focused on clinical benefit and the cost implications. In contrast, at the national level economic analysis was seen to be highly integrated with an ordinal approach to consideration of clinical and cost-effectiveness information. The analysis provided a framework for considering the decision problem but concern was raised about understanding of the economic analysis. The study concluded that further assessment is required into clarification of the objectives that society seeks from investments in health care.

(Williams and Bryan, 2007)	England	National Institute for Health and Clinical Excellence (NICE)	N=4 case studies N=30 semi structured interviews	2002-2004 Qualitative	Coverage decision as determined by the participants	• The influence and use of health economic evaluation in the decision making process.	Narrative description of case studies and semi structured interviews	The study found that there was an ordinal approach to how the evidence and analysis were considered, the clinical evidence followed by the economic evidence. A concern with cost-effectiveness was not apparent unless a clinical value had been demonstrated. The economics provided an analytical framework for the consideration of evidence, it is not just the overall outcome of the evaluation but it allows the discussion to be structured around the important aspects of the evidence and deliberations can be made. The study highlights that it is important to guard against one group on a committee being granted a dominant position. The use of one disciplines approach may mean that decisions are not aligned to social values.
(Wirtz et al., 2005)	England	National Institute for Health and Clinical Excellence (NICE)	N=20 interviews on three drug therapies.	2002 Qualitative	Coverage decision as determined by the participants	• Cost-effectiveness • Equity considerations • Personal factors • Political factors	Narrative description of interviews	The interviews captured two aspects of decision-making which are not usually captured in the rationales usually cited. The first dimension was 'subjectivity' which includes personal factors which influence the kind of evidence, and interpretations of the evidence, such as personal experiences related to the disease or the novelty of the benefit of the technology. The second relate to the overall social and political functions of decision making which relate to the importance of maintaining relationships, the achieving of politically and legally defensible decisions and the reduction of organisational burden. The researchers did not imply by referring to these dimensions that they were inappropriate rather the opposite. The authors believe that including these type of factors helps to articulate the fuzzy elements of decision making. The study concludes that the factors identified were often buried under the rationales given to legitimise the decisions made. The authors suggest that personal and political factors should be recognised as a dimension of decision-making is done within a discourse of reasonableness.

(Vuorenkoski et al., 2003)	Finland	Pharmaceutical Pricing Board	N=18 interviews	2001 Qualitative	As determined by the stakeholders interviewed.	• Disease areas prioritised for special higher reimbursement categories, 75% for chronic and serious diseases, 100% for severe and long term diseases. • Clinical effectiveness • Economic evaluation • Roles of stakeholders and influence in the reimbursement process • Pharmaceutical companies, patient organisations and medical speciality associations • Price and potential budget impact	Semi-structured interviews analysed using a thematic framework approach.	The system in Finland in 2001 was to provide explicit prioritisation of disease areas. The nature of inclusions is believed to be of a technical nature but there are at least two non-scientific rationales used explicitly in decision making due to fiscal constraints and the difficulty of removing drugs in the higher reimbursement categories. The study found that it is difficult to base prioritisations solely on the wording of legislation and scientific data. The unofficial stakeholders were viewed to be conducive to provide a positive channel between stakeholders and public administration and may divert public policy to their narrow interests making the work of the public administration more difficult. However they were seen to have restricted influence. It is crucial to recognise stakeholders lobbying resources, interests and means of exerting influence so that decisions do not favour any particular individuals or groups of society.
(Niezen et al., 2009)	Netherlands	CVZ – Health insurance Board and Ministry of Health	N=11 semistructured interviews	2006 Qualitative	Recommendations for a new intervention	• Clinical effectiveness • Cost effectiveness • Severity of illness • Budget impact • Other implicit decision making factors	Narrative description of the interview themes.	The interviews found that policy makers often rely on information gathered from cost-effectiveness analysis to justify their decision rather than explaining how budget impact had an effect on the decision. Budget impact is seldom used in an argument for denying a drug reimbursement outright or imposing conditions on reimbursement. The justifications for the use of budget impact collected from a literature review were opportunity costs, loss aversion and endowment effects, uncertainty and equal opportunity. Budget impact was found to play a role in decision making.

(Pronk and Bonsel, 2004)	Netherlands	CVZ – Health Insurance Board and Ministry of Health	N=139	1999-2002 Qualitative	Outpatient drugs recommended either for: List 1a subsititutable List 1b unique Other Refusal	• Therapeutic value • Budget impact • Burden of disease • Efficiency • Dynamic nature of decision making.	Descriptive statistics and narrative description of the decisions by the Ministry of Health	New drugs in the Dutch system in 1991 are excluded unless they pass legal requirements for clinical criteria and are grouped into two lists, DPRS-list 1a for substitutability with accepted drugs implying a reimbursement maximum, DPRS-list 1b which are unique and valuable with liberal price setting and those that are rejected as lack of value. The 85 DPRS-list Ib applicants were evaluated for the criteria finding therapeutic value, budget impact and burden of disease being important criterion.
(Anell and Persson, 2005)	Sweden	Pharmaceutical Benefits Board LFN	N=107	2002-2005 Qualitative	Unconditional reimbursement Conditional reimbursement Rejected	• The principle of human dignity, whereby health care is provided equally for all individuals • The principle of need and solidarity, according to those with the greatest medical need are provide more health care resources than others. • The cost-effectiveness principle, according to which the costs of a pharmaceutical preparation must be reasonable. • The marginal utility principle which is a component of the cost-effectiveness principle..	Narrative description of the documented agency decisions	82 out of the 107 cases the drugs received unconditional reimbursement, 12 cases there was conditional reimbursement and 13 cases where the drug was rejected. There were orphan drugs that were approved unconditionally even though their cost-effectiveness was weak. Those pharmaceuticals approved for limited reimbursement were found in the treatment of large patient populations where there was a large budget impact. The rejected applications were for low priority or deemed not to have demonstrated a clinically significant difference in benefit to receive a price premium. Reimbursement is limited to relevant subgroups when there is a high budget impact and varying cost-effectiveness. There were often rejections where the manufacturer had not proved the benefits in comparison to existing alternatives.

(Jansson, 2007)	Sweden	Pharmaceutical Benefits Board LFN	N=107 documented decisions N=23 interviews	2002-2005 Qualitative	Unconditional subsidy Conditional subsidy Rejected	• Human dignity • Need and solidarity • Cost-effectiveness • Based on the three above principles Health care is divided into four priority groups, priority I for life threatening diseases or conditions, priority II for prevention and rehabilitation, priority III for health care of less severe acute and chronic diseases and injuries and priority IV for health care for other reasons than disease or injury. • Stakeholder involvement such as patients, pharmaceuticals and patient associations	Descriptive statistics and narrative description of documented evidence and interviews.	87 out of 107 received unlimited subsidy, 9 out 107 received limited subsidy and 11 out of 107 were rejected. The analysis of the public documents and interviews confirmed that cost-effectiveness had played an important role in decision making. In those pharmaceuticals that received unconditional subsidy the cost-effectiveness was at an acceptable level. The economic analysis required for orphan drugs was seen to be less stringent. The conditional subsidy have been found in those treatments with potentially large patient populations. The rejections were based on the absence of supporting evidence and low priority. In the case studies individual actors have been found to directly influence decision makers through lobbying, contact to the LFN and official letters. Six appeals have been made out of the eleven rejected applications.

Table A2.5: Summary of quantitative studies

Study Authors	Country(s) (Institutions)	Number of Decisions	Methodology (Statistical)	Decision Outcomes	Time period of decisions	Factors Considered in statistical analysis
(Clement et al., 2009)	Canada (CADTH CDR) England (NICE) Australia (PBAC)	CDR: 121 NICE: 199 PBAC: 153	Univariate Chi Square tests for characteristics	Binary (List/Do not list)	CDR: 2004-2008 NICE: 2001-2008 PBAC: 2005-2008	Resubmission Life threatening disease Clinical evidence Economic evidence
(Chim et al., 2010)	Australia (PBAC)	PBAC: 243	Logistic regression (cancer vs non-cancer)	Binary (Approval, Rejection/Deferral)	PBAC: 2005-2008	Medicine type Application type Estimated cost to PBS Economic model estimate
(George et al., 2001)	Australia (PBAC)	PBAC: 35	Univariate Mann Whitney test	Binary (Recommended, Not recommended) Defer decision discarded.	PBAC: 1991-1996	Economic model estimate
(Harris et al., 2008)	Australia (PBAC)	PBAC: 103	Probit regression	Binary (Recommended, not recommended)	PBAC: 1994-2004	Clinical evidence Economic evidence Total financial cost Patient population characteristics History of drug submission
(Scuffham et al., 2008)	Australia (PBAC)	PBAC: 49	Univariate comparison	Binary (Recommend, other)	PBAC: 2002-2004	Type of QALY weights
(Van Wilder and Dupont, 2008)	Belgium (CRM)	CRM:824	Univariate Chi Square tests	Binary (positive, negative)	CRM: 2002-2004	Clinical evidence Added therapeutic value
(Dakin et al., 2006)	England (NICE)	NICE: 94	Multinomial Logistic regression	Multinomial (recommend, restrict, not recommend)	NICE: 1999-2003	Economic evidence Clinical evidence Budget Impact Characteristics of patient group Type of technology Other alternative Time of decision Stakeholder involvement

(Devlin and Parkin, 2004)	England (NICE)	NICE: 33	Logistic regression	Binary (recommended, not recommended)	NICE: 1999-2002	Economic evidence Other alternative Burden Budget Impact Other factors
(Devlin et al., 2010) [Conference abstract]	England (NICE)	NICE: 184	Logistic regression	Binary (recommended, not recommended)	NICE: 1999-2009	Clinical Evidence Economic evidence Characteristics of disease Characteristics of patients Patient group submission
(Mason and Drummond, 2009)	England (NICE)	NICE: 56	Fisher-Freeman-Halton test for comparison between two periods	Multinomial (Recommended, restricted, not recommended)	NICE: 2000-2006	STA process
(Neumann et al., 2005)	US (Medicare)	Medicare: 69 (5 medicines)	Univariate Comparison	Multinomial (Completely covered, covered with conditions, local contractor discretion, not covered)	Medicare: 1999-2003	Quality of clinical evidence Net benefit Time to medicine decision
(Tappenden et al., 2007)	England (NICE)	NICE decision makers: 37	Discrete choice experiment using logistic regression analysis	Binary (Recommended, not recommended	NICE: 2005	Economic evidence Age Baseline Health related QOL Availability of other therapies
(Koopmanschap et al., 2010)	Netherlands (CVZ)	Decision makers (including CVZ) 66	Discrete choice experiment using logistic regression analysis	Binary (Reimbursement, not reimbursement)	CVZ: 2007-2008	Additional medical cost per year Absence from work cost saving Disease severity Economic evidence Number of QALYs Composition of health gain

Table A2.6: Characteristics of revealed preference quantitative studies in Australia

	(Chim et al., 2010)	(George et al., 2001)	(Harris et al., 2008)	(Scuffham et al., 2008)
Institutions (Year)	PBAC (2005-2008)	PBAC (1991-1996)	PBAC (1994-2004)	PBAC (2002-2004)
Decision outcome (Number)	Binary: List/Do not list (n=243)	Binary (Approval/Rejection, Defer) (n=35)	Binary (List, not list) (103)	Binary (List, not list) (n=49)
Influence (Statistical analysis)	Univariate and Multivariate analysis. Correlate association between factor and decision outcome (Logistic regression)	Correlate association between past decisions and cost-effectiveness (Univariate analysis)	The factors associated with the decision outcome. (Probit regression)	The association of QALY weights and recommendation (univariate analysis).
Sample of Medicines	All major submissions	All submissions	Submissions including a CUA only	Submissions including a CUA only
Clinical evidence definition				
Comparator Claim	Accepted or rejected/partial			
Clinical Claim	Accepted or rejected/partial			
Clinical significance			Did the committee consider size of treatment effect to be significant (Y/N)	
Precision of clinical evidence			Statistical reliability of the measure of treatment effect using 0.05 cut off	
Level of evidence			Head to head, indirect RCT, non randomised	
Quality of studies			12 item checklist used for quality	
Relevance of evidence			Comparator and population appropriate (Y/N)	
Economic evidence definition				
Economic Claim	Accepted or rejected/partial			
Type of economic analysis	Binary category: CMA/no economic evaluation or CEA/CUA	Cost per life year or Cost per QALY	Cost utility analysis ONLY	
Type of QALY weights used				Categorical: Non-preference based approaches
Cost-effectiveness estimate	Categorical CMA or none, CEA, CUA<AUS$45,000, CUA between AUS$45,000 to AUS$75,000, CUA>AUS$75,000	Ranking of individual cost per life year and cost-effectiveness estimates.	Incremental cost per QALY	
Economic analysis validity			Categorical variables for model structure, modelled outcome & modelled cost (critically flawed, some flaw, reliable)	
Uncertainty of cost per QALY			Upper limit in model sensitivity analysis	
Budget impact	Categorical (<A$10m or >A$10m)		Annual predicted cost of listing A$	
Non-evidence factors definition				
Number of patients per year	Three categories (<10,000, 10,000-100,000, >100,000)			
Medicine Type	Cancer medicine/non-cancer			
Presence of alternatives			Last line or not last line	
Life threatening			Premature mortality (Y/N)	
Process factors definition				
Resubmission	Categorical: Resubmission or first time.		Categorical: Previous considered (Y/N)	

Table A2.7: Characteristics of revealed preference quantitative studies in England and Wales

	(Dakin et al., 2006)	(Devlin and Parkin, 2004)	(Devlin et al., 2010)	(Mason and Drummond, 2009)
Institutions (Year)	NICE (1999-2003)	NICE (1999-2002)	NICE (1999-2009)	NICE (2000-2006)
Decision outcome (Number)	Multinomial: Recommended, restricted, not recommended (n=94)	Binary (Recommended, not recommended) (n=33)	Binary (List, not list) (184)	Multinomial (Recommended, restricted, not recommended) (n=56)
Influence (Statistical analysis)	Correlate association between factors and decision outcome (Multinomial logistic regression)	Correlate association between factors and decision outcome (logistic regression)	Correlate association between factors and decision outcome (logistic regression)	The association of change in process on the decision outcomes (Univariate analysis)
Sample of Medicines	All technologies appraised	All technologies appraised	All technologies appraised	All cancer medicines appraised
Clinical evidence definition				
Number of RCTs	Total number of RCTs reported in the guidance.		Number of RCTs including CIC trials	
RCT size	Mean number of patients in RCTs applicable to guidance		Mean number of patients in RCTs	
RCT quality	Jadad score assessment of quality of RCTs			
RCT relevance	Proportion of RCTs using a comparator deemed relevant			
RCT significance	Proportion of RCTs showing the intervention to have a significant effect.			
Observational study	Number of observational studies			
Systematic Review	Number of systematic reviews or meta-analyses			
Economic Evidence definition				
Type of economic analysis	The presence or absence of a cost-utility analysis			
Cost-effectiveness estimate	The cost per QALY gained or cost per life year gained	Cost per QALY or the cost per life year gained.	Cost per QALY estimate	
Budget impact	The potential budget impact if recommended.	The impact on the NHS budget of approving the treatment.		
Uncertainty in cost-effectiveness		Calculated as a range of cost-effectiveness ratio divided by the mean.		

Table A2.7: Characteristics of revealed preference quantitative studies in England and Wales Continued..../

Non-evidence factors definition				
Type of technology	Pharmaceutical or other technology			
No alternatives	Presence or absence of alternatives	Other alternative therapy present	The technology is the only treatment available	
Other factors		Severity of condition, short duration of life.		
Burden of disease		The burden of disease represented by number affected.		
Type of disease			The technology is for the treatment of cancer or not.	
Children			The technology is for use in children or not	
Process factors definition				
Date of guidance	Number of months since guidance was published.		Number of months since the guidance was published	
Involvement of stakeholders	Presence/absence of patient group submission.		Presence of a patient group submission	
Appeal	Presence of an appeal - Categorical: no appeal, appeal entirely upheld, appeal partially upheld, all grounds dismissed			
STA process			Appraisal conducted by a Single Technology Appraisal (STA) or Multiple Technology Appraisal (MTA)	Introduction of the STA process in August 2006.

Table A2.8: Description of each factor and direction of association

Factor Considered	Studies	Countries Considered	Influence/Impact on Reimbursement decision
Clinical Evidence Factors			
Clinical uncertainty (type of trial, comparator and endpoint)	(Clement et al., 2009)	AU, CA, ENG	Mixed - Lower probability of listing for CA and AU, But no association for ENG
Added therapeutic value	(Van Wilder and Dupont, 2008)	BE	Proven added value was positive associated with a listing decision
Relevant clinical endpoint	(Clement et al., 2009)	AU, CA, ENG	Increased probability of listing
Number of RCTs	(Dakin et al., 2006)	ENG	One additional RCT reduced the probability of being restricted or not listed in comparison to listing.
Size of treatment effect	(Harris et al., 2008)	AU	A large clinical effect was associated with a higher probability of listing
Number of QALYs gained per patient	(Koopmanschap et al., 2010)	NL	A positive association between the number of QALYs and choice of intervention (listing)
The composition of health gain	(Koopmanschap et al., 2010)	NL	There was a preference for listing interventions with quality of life improvements over extension of life with no improved quality of life
Clinical claim (accepted/rejected or partially accepted)	(Chim et al., 2010)	AU	The acceptance of the manufacturers clinical claim is statistically associated with a positive listing.
RCT significance	(Dakin et al., 2006)	ENG	No association
RCT size	(Dakin et al., 2006)	ENG	No association
Precision of treatment effect	(Harris et al., 2008)	AU	No association
Type of evidence (RCT)	(Harris et al., 2008)	AU	No association
RCT quality (Jadad score)	(Dakin et al., 2006)	ENG	No association
Quality of studies (12 item checklist)	(Harris et al., 2008)	AU	No association
Quality of evidence (Well designed and conducted RCTs)	(Neumann et al., 2005)	US	Technologies with good evidence were more likely to be listed in comparison with poor evidence
Comparator and population appropriate	(Harris et al., 2008) (Dakin et al., 2006)	AU, ENG	No association
Comparator claim (accepted/rejected or partially accepted)	(Chim et al., 2010)	AU	The acceptance of the comparator claim is statistically associated with a positive listing.
Non randomised studies	(Dakin et al., 2006)	ENG	No association
Number of systematic reviews	(Dakin et al., 2006)	ENG	The number of systematic reviews was positively associated with listing in comparison to not listing

Economic Evidence Factors			
Type of economic analysis (CUA)	(Dakin et al., 2006) (Chim et al., 2010)	ENG	The use of CUA increased the probability of not listing in comparison to listing (ENG). Those with a CMA/no economic evaluation in the preliminary submission were more likely to lead to a positive listing than those with a CEA/CUA analysis (AU).
ICER (cost per QALY)	(Clement et al., 2009) (Harris et al., 2008) (Tappenden et al., 2007) (Koopmanschap et al., 2010) (Chim et al., 2010)	AU, CA, ENG, NL	A negative association between higher ICER values and listing (AU, CA, ENG, NL)
ICER (cost per LYG)	(George et al., 2001)	AU	A negative association between higher ICER values and listing
ICER (cost per LYG and cost per QALY)	(Devlin and Parkin, 2004) (Dakin et al., 2006)	ENG	Mixed - A negative association between the ICER values and listing. A negative association found between higher ICER values and restricted in comparison to not recommended
Economic claim (PBAC committee accept the manufacturers economic claim)	(Chim et al., 2010)	AU	The PBAC accepting the manufacturers claim was associated with a positive recommendation.
Economic uncertainty (major flaws in model, assumptions and mapping)	(Clement et al., 2009)	AU, CA, ENG	Mixed - Lower probability of listing for CA and AU, But no association for ENG
Degree of uncertainty concerning costs and effects	(Tappenden et al., 2007)	ENG	A high level of uncertainty is associated with a reduction in the probability of listing
Probability that costs per QALY will be at least doubled as compared to the average CE	(Koopmanschap et al., 2010)	NL	A higher level of uncertainty was negatively associated with listing choice.
Range of cost-effectiveness divided by base case ICER	(Devlin and Parkin, 2004)	ENG	A negative association between a larger ratio and listing
Upper limit in model sensitivity analysis	(Harris et al., 2008)	AU	A higher upper cost per QALY was positively associated with listing
Non preference based measure used for QALY weights	(Scuffham et al., 2008)	AU	Non preference based measures were associated with a lower probability of listing
Model Structure appropriate	(Harris et al., 2008)	AU	No association
Translation of clinical outcomes to quality of life	(Harris et al., 2008)	AU	No association
Modelled cost issues	(Harris et al., 2008)	AU	No association

Budget impact – cost to government	(Harris et al., 2008) (Dakin et al., 2006) (Koopmanschap et al., 2010) (Chim et al., 2010)	AU, ENG, NL	Mixed - A negative association between higher budget impact and listing in AU and NL. No association in ENG.
Savings in costs of absence per year	(Koopmanschap et al., 2010)	NL	No association observed.
Non Evidence Based Factors			
Severity/Life threatening	(Clement et al., 2009) (Harris et al., 2008) (Koopmanschap et al., 2010)	AU, CA, ENG, NL	Mixed -No association observed for listing AU, CA, ENG. AU study found life threatening drugs to be positively associated with listing. NL study found severity to be positively linked to choice of intervention.
Burden of disease	(Devlin and Parkin, 2004)	ENG	A positive association between a higher burden of disease and listing
No alternative therapy	(Harris et al., 2008) (Devlin and Parkin, 2004) (Dakin et al., 2006) (Tappenden et al., 2007)	AU, ENG	Mixed - No association found in AU. Two studies in ENG found an alternative therapy lowers the probability of listing and one found no association.
Type of intervention, pharmaceutical or other	(Dakin et al., 2006)	ENG	A pharmaceutical reduced the probability of not listing in comparison to listing
Medicine type (cancer, non-cancer)	(Chim et al., 2010)	AU	No statistical association between cancer medicine and recommendation.
Number of patients per year	(Chim et al., 2010)	AU	No statistically significant association with recommending
Mean age of population who will benefit	(Tappenden et al., 2007)	ENG	No association observed.
New medicines/indications in comparison with line extensions	(Van Wilder and Dupont, 2008)	BE	Line extensions were more likely to be listed than new medicines and indications
Baseline HRQoL	(Tappenden et al., 2007)	ENG	A very low to a high baseline HRQoL was negatively associated with listing
Reimbursement Process Factors			
Patient group submission	(Dakin et al., 2006)	ENG	The presence of a patient group submission decreased the probability of a restricted listing in comparison to listing.
Previously considered (resubmission)	(Harris et al., 2008) (Chim et al., 2010)	AU	Mixed evidence for AU. A previously considered drug had a higher probability of listing. There was no association found in a second study.
STA process impact on cancer medicines	(Mason and Drummond, 2009)	ENG	Between 2006 to 2008 NICE, were more restrictive in comparison to 2000 to 2006.

Date of decision	(Dakin et al., 2006)	ENG	A positive association was found between later guidance and not listing in comparison to listing
Appeal	(Dakin et al., 2006)	ENG	No association with probability of recommending a medicine.

Table A2.9: Model specification tests reported

Study	Type of model specification test
(Clement et al., 2009)	No statistical specification tests reported.
(Chim et al., 2010)	Goodness of Fit test: Hosmer and Lemeshow Sensitivity analysis: Exclusion of factors from the regression model.
(George et al., 2001)	No statistical specification tests reported.
(Harris et al., 2008)	Goodness of fit: Pseudo R^2 and Receiver Operating Characteristics (ROC) Regression model assumptions: Variance Inflation Factor (VIF) to consider potential multicollinearity. Omitted Relevant Variables: Dummy variable included to test for structural change. Consideration of outlier observations.
(Scuffham et al., 2008)	No statistical specification tests reported.
(Van Wilder and Dupont, 2008)	No statistical specification tests reported.
(Dakin et al., 2006)	Goodness of fit: Pseudo R^2 and regression predictive classification of decisions. Sensitivity analysis: robust versus conventional standard errors and impact of dropping factors. Regression model assumptions: multicollinearity considered between the variables.
(Devlin and Parkin, 2004)	Goodness of fit: Pseudo R^2.
(Devlin et al., 2010)	Conference abstract: Not reported.
(Mason and Drummond, 2009)	No statistical specification tests reported.
(Neumann et al., 2005)	No statistical specification tests reported.

Table A2.10: Summary of quantitative reimbursement factors influence

	Characteristics and Validity	Treatment effect and precision	Quantity of clinical evidence	Quality of clinical evidence	Clinical uncertainty and judgement	Economic analysis type and results	Appropriate economic analysis	Economic evidence uncertainty	Other Economic evidence factors	Non-evidence factors	Process factors	Validity of results				
												Influence Definition	Study type	Statistical method	Sample (d) = decision (p) = participant	Model Specification tests
AUS	(Clement et al., 2009)				1	1		1		1		Correlation	Revealed	Univariate Chi2	153 (d)	No
	(Chim et al., 2010)				2	3			1	2	1	Correlation	Revealed	Logit regression	243 (d)	Yes – 2
	(George et al., 2001)					1						Correlation	Revealed	Univariate Mann Whitney	35 (d)	No
	(Harris et al., 2008)	2		1	1	1	3	1	1	2	1	Correlation	Revealed	Probit regression	103 (d)	Yes – 4
	(Scuffham et al., 2008)						1					Correlation	Revealed	Univariate comparison	49 (d)	No
BE	(Van Wilder and Dupont, 2008)	1								1		Correlation	Revealed	Univariate Chi2	824 (d)	No
CA	(Clement et al., 2009)				1	1		1		1		Correlation	Revealed	Univariate Chi2	121 (d)	No
ENG	(Clement et al., 2009)				1	1		1		1		Correlation	Revealed	Univariate Chi2	199 (d)	No
	(Dakin et al., 2006)		5	1	1	2				2	2	Correlation	Revealed	Multinomial Logit	94 (d)	Yes – 3
	(Devlin and Parkin, 2004)					1		1		2		Correlation	Revealed	Logit regression	33 (d)	Yes – 1
	(Mason and Drummond, 2009)										1	Correlation	Revealed	Univariate Fisher/Freeman	56 (d)	No
	(Tappenden et al., 2007)					1		1		3		Correlation	Stated	Logit regression	37 (p)	No
NL	(Koopmanschap et al., 2010)	2				1		1	2	1		Correlation	Stated	Logit regression	66 (p)	No
USA	(Neumann et al., 2005)			1								Correlation	Revealed	Univariate	69 (d)	No
Total Number of times a factor studies per country		5*	5	3	7*	13	4	7	4	16	5					

(Devlin et al. 2010) as a conference abstract and the results could not be directly included with respect to direction of effect on the reimbursement decision. *3 factors were stated but influence was not reported and therefore not included in the count.

Table A2.11: Comparison of quantitative and qualitative studies by country

Country/Type of evidence	Australia	Belgium	Canada	England	Finland	Netherlands	New Zealand	Scotland	USA
Reimbursement agency	PBAC	National Insurance Agency	CDR	NICE	Pharmaceutical Pricing Board (PPB)	Health care insurance board (CVZ)	PHARMAC	SMC	Medicare
Quantitative studies Factors Considered	• Size of clinical effect • Precision of clinical effect • Quality of studies • Comparator claim • Clinical claim • ICER • Economic claim • Type of Economic analysis • Weight of clinical evidence • Clinical uncertainty • Relevant clinical endpoint • Comparator appropriate • Economic uncertainty • Uncertainty evaluated by sensitivity analysis • Type of utility elicitation • Budget Impact • Severity of disease • Resubmission • Number of patients per year • Medicine type	• Size of clinical effect • New medicine line extension	• Clinical uncertainty • Weight of clinical evidence • Relevant clinical endpoints • ICER • Type of economic analysis • Economic uncertainty • Life threatening • Resubmission	• Clinical uncertainty • Weight of clinical evidence • Relevant clinical endpoint • Baseline HRQoL • Number of RCTs • Number of Systematic reviews • Number of observational studies • RCT significance • RCT size • RCT quality (Jadad) • Comparator appropriate • Uncertainty evaluated by sensitivity analysis • ICER • Type of economic evaluation • Economic uncertainty • Life threatening • Resubmission • Appeal • Burden of disease • Type of medicine • Patient group submission • Date of decision • Lack of alternative therapy	No studies identified	• ICER • Uncertainty evaluated by sensitivity analysis • Budget impact • Disease severity • Number of QALYs gained • Distribution of QoL improvement	No studies identified	No studies identified	• Quality of clinical evidence

Table A2.11 – Comparison of quantitative and qualitative studies by country Continued..../

Qualitative Studies Factors Considered	• Clinical-effectiveness • Cost-effectiveness • Composition of the decision panel • Prevalence of disease • Severity of disease • Patient lobbying • Budget impact		• Clinical benefit • Cost-effectiveness • Quality of model • Comparative effectiveness, type of outcome, comparator choice, trial duration, trial size & comparative safety • Composition of the decision panel • Prevalence of disease • Availability of other therapies • Budget Impact	• Third party independent assessment • Cost-effectiveness • Severity of disease, rule of rescue • End of life process • Approach to decision making, ordinal • Sensitivity analysis and uncertainty in economic analysis • Stakeholder involvement in decision making	• Process categorisation of severe diseases • Price • Budget impact	• Clinical effectiveness • Cost-effectiveness • Burden of disease • Budget impact • Severity of disease	• Cost-effectiveness • Proven marginal benefit • Cost-effectiveness in subgroup • Disease type, Orphan drug • Lack of alternative therapies • Stakeholder lobbying	• Manufacturer submission • Cost-effectiveness • Composition of the decision panel • Prevalence of disease	No studies identified

Chapter 3 appendix

Table A3.1: Policy implementation summary

Country and agency/institution	Establishment of system	System Institutions	Agency/Institution responsible for assessment	Agency/Committee responsible with appraisal and deliberation	Reimbursement institution funding	Annual Report
Australia (PBAC)	Pharmaceutical Benefits Scheme (PBS) began in 1948 and provides a list of medicines that are publically funded. PBAC is required to provide advisory recommendations to the Ministry of Health and since 1993 required an economic analysis. All Australian residents with a Medicare card are eligible and a copayment (up to $34.20 for PBS Medicines and $5.60 for concessions). Public system predominately funded by taxation. PBAC only reviews medicines (Australian Government, 2011b).	Requires a review by 1. Pharmaceutical Benefits Advisory Committee (PBAC), an independent statutory body that assesses new medicines established in 1954; 2. Price negotiation by the Pharmaceutical Benefits Pricing Authority; 3. Final decision to list in the PBS by the Ministry of Health and Ageing (Australian Government, 2011a). *Price: Negotiated by separate institution called the PBPA.*	PBAC (statutory body)	PBAC (statutory body) & Ministry of Health	Ministry of Health and Ageing through taxation (Department of Health and Ageing, 2011).	Not identified
Austria (HEK/HBV)	The regulation regarding pharmaceutical reimbursement is the responsibility of the Federal government specifically the Federal Ministry of Health, Family and Youth (BMFGJ). The health system is funded by social insurance based on the principles of statutory insurance, solidarity and self-governance, which includes 22 social security institutions. The Medicines Evaluation Committee (HEK) was established in 2005 and provides advice to the Federation of Social Security Institutions (HBV). The Federation makes final reimbursement decisions. The	A traffic light system operates in the Reimbursement Code, "green", "yellow" and "red zone". The reimbursement code is determined by the rules of procedure (351g ASVG 2004). The Reimbursement Code aims to provide physicians with a transparent and clear understandable set of medicines that are available for general reimbursement. The process maybe initiated by the Federation of by the manufacturer submitting an application for marketing authorisation. The Federation will review the application for completeness and the manufacturer will be required to provide the	HEK	Main Association of Austrian Security Institutions (HBV)	Committee provides recommendation to the Main Association of Austrian Social Insurance Institutions (PPRI, 2007a).	Not identified

	BMFGJ takes the advice of the pricing committee (PK) for pricing decisions. The medicine maybe listed on the positive list for outpatient medicines called the reimbursement Code (EKO) or maybe included in the negative list (Federation of Social Security Institutions (HBV), 2011) .	information within 14 days otherwise the application will be rejected. The Independent Pharmaceutical Commission (UHK) functions as an appeal court for when a manufacturer's medicine is not approved for reimbursement, (PPRI, 2007a) *Price: Separate Pricing Committee*				
Belgium (CRM)	The Committee for Reimbursement of Medicines (CRM) was established in 2001 in a legal act (Royal Decree 21 December 2001). It is responsible for formulating proposals for the admission of pharmaceuticals for the list of reimbursable pharmaceuticals, advise the Minister on aspects of the policy on reimbursement of pharmaceutical products, formulate the insurance committee proposal interpretive rules for the reimbursement of pharmaceuticals. The CRM is located in the National Institute for Health and Disability Insurance which is a non-governmental public body. The NIHDI is a federal institution, which organises, manages and supervises the correct application of compulsory insurance in Belgium (NIHDI, 2011).	The CRM formulates advice to the Minister of Health and Social Affairs whose decision may differ because of budget or social considerations (Adriaens and Soete, 2010). *Price: Separate Pricing Committee at FPS Economy for maximum prices.*	Committee for Reimbursement (CRM) in the NIHDI	Minister of Health and Social Affairs	Not identified. (Emailed institution for funding source. National Institute for Health and Disability Insurance (NIHDI))	Not identified
Canada (CADTH, CDR)	CADTH was established in 1989 and the Common Drug Review (CDR) started accepting submissions in 2003 to standardise reviews across the country. CADTH is funded by the federal, provincial and territorial governments as an independent not for profit agency. The Common Drug	The manufacturer submits to the CADTH CDR. The CEDAC committee provides the appraisal of evidence and the manufacturer may reduce the price during the process. The CDR process provides advisory recommendations to the drug plans. The provincial drug plans make the final decision on	CADTH	CADTH – CEDAC and Provincial drug plans	Federal, provincial and territorial governments (CADTH, 2010b).	Yes – 2009 – Quantity of reports, transparency and number of website hits (CADTH, 2009).

	Review (CDR) undertakes reviews of Drug Submissions and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial (F/P/T) Drug Plans with the exception of Québec. The drug plans make their own decisions based on the recommendations and plans mandate, priorities and resources. (CADTH, 2011b).	reimbursement (CADTH, 2011a). *Price: Monitoring at the national level and provincial health plan negotiations.*				
Denmark (DMA)	The Danish Health Act of 2005 Sections 144(1-3) and 152 (2&4) decides whether to grant reimbursement for medicinal products. The Danish Medicines Agency is an agency under the Ministry of Interior and Health and provides final reimbursement decisions and is advised by the reimbursement committee which is an independent authority. The Reimbursement Committee (MTN) was established in 2003 by the Danish Minister for the Interior and Health to provide advice to the DMA (Danish Medicines Agency, 2008).	The recommendations provided by the Reimbursement Committee appointed by the Ministry of Health are advisory and the Danish Medicines Agency makes the final decision (Danish Medicines Agency, 2008). *Price: Agreement between the Danish Association of Pharmaceutical industry and the Ministry of Health*	Danish Medicines Agency & Reimbursement Committee	Danish Medicines Agency	The income for the Danish Finance Act, fees set by the Danish Minister for Interior and Health and income from work carried out for the European Medicines Agency (Danish Medicines Agency, 2010).	Yes 2007 annual report (Danish Medicines Agency, 2007).
Finland (PPB)	Pharmaceutical manufacturers have the freedom to set price and a patient can receive reimbursement through the KELA, the social security institution (sometimes referred to as social insurance institution even though predominantly funded through taxation). This can take place once the Pharmaceutical Pricing Board has made a decision on the reimbursement status and price under the Health Insurance Act (1224/2004). The conditions set out	The PPB makes the final decision and patients can then receive reimbursement from the Social Insurance Institute, KELA for either basic reimbursement or special reimbursement (Ministry of Social Affairs and Health, 2011). *Price: The PPB sets the statutory maximum price and reimbursement.*	PPB	PPB	Government Department	-

	in the payment of reimbursement under the health insurance act for a medicinal product is that the medicine must have a reimbursement status confirmed by the Pharmaceutical Pricing Board (PPB) (Ministry of Social Affairs and Health, 2011).					
France (HAS)	The HAS was created in the health insurance Act of August 13 2004. HAS is an independent public scientific authority to assess medical technologies (HAS, 2011b).	The manufacturer submits to the HAS agency. The HAS provides one of the two stages of advice regarding the case for reimbursement which includes consideration of clinical evidence. Economic considerations made by the Economic Committee for Health Products (CEPS). The HAS opinion informs the pricing and volume agreements that are negotiated between the manufacturer and the Economic Committee for Health Products (CEPS) for outpatient medicines and medicines on top of DRG. Prices for those medicines for hospital use included in the DRG are negotiated directly with the individual hospitals, (Rochaix and Xerri, 2009). *Price: This is negotiated by a separate committee called the CEPS.*	HAS (independent authority/agency)	HAS – Transparency Committee & Ministry of Health	The budget of HAS is €62M in 2009 and is 15% funded by government subsidies, Primary state social health insurance fund contributes 50% and 26% by French Social Security Agency. (HAS, 2011a)	Yes – 2009 – quantity of guidance produced and other tasks discussed (HAS, 2009).
Germany (G-BA)	The Federal Joint Committee (G-BA) is a legal decision-making body in a self regulated statutory health insurance (SHI) system under the German Social Law (SGB V). It was established on 1st January 2004 as mandated by a federal health reform law (GKV Modernisation Act – GMG). The directives issued by the G-BA are legally binding for insured persons as well as for the providers and payers	The manufacturer sets price (can be prescribed) and then submits to the G-BA and the social insurance system covers fully the medicine. The G-BA will consider the early benefit assessment and employs IQWIG to provide the assessment of the dossiers. If the medicine is deemed to have no additional benefit the price of the medicine is set in the reference price. If the medicine has additional benefit the	IQWIG (independent authority)	G-BA (decision-making body) – Federal Joint Committee	The Federal Joint Committee is funded by system surcharges. These are composed of a surcharge for each billable hospital visit and from an additional increase in fees	Not identified

	of health care: physicians, hospitals and sickness funds. A new body was created in 2004 called the Institute for Quality and Efficiency in Healthcare (IQWIG) an independent scientific body which is responsible for the assessment of new medicines at the request of the G-BA. The Act for the Restructuring of the Pharmaceutical Market in Statutory Health Insurance (AMNOG) in 2011 has greatly changed the reimbursement system. G-BA aims to regulate SHI-wide issues of access, benefits and quality for medical technologies (Federal Joint Committee, 2010, Leverkus, 2011)	price is negotiated with the sickness funds at 6 months. No agreement on price results in an arbitration committee that will agree price. On dissatisfaction of the arbitration price, the manufacturer or funds can request IQWIG to provide an efficiency frontier analysis. The reimbursement price is valid from one year onwards (Leverkus, 2011). *Price: FJC agrees maximum price but on failure to agree prices are negotiated with the sickness funds.*			for outpatient's medical and dental care. The G-BA fixes a surcharge each year (Federal Joint Committee, 2011b).	
Ireland (Corporate unit and NCPE)	There is no legal agreement applicable for reimbursement decisions in Ireland. There is an agreement between the Health Service Executive and Pharmaceutical industry called the Irish Pharmaceutical Healthcare Association agreement. The HSE is a public organisation which is accountable to the Minister of Health and Children. There is a General Medical Services (GMS) scheme and a Drugs Payment Scheme (DPS) provide reimbursement for those eligible in Ireland. The Health Service Executive is responsible for the operation and management of the public health services in Ireland on behalf of the Department of Health and Children. The HSE reports directly to the Minister for Health. The Corporate Pharmaceutical Unit	The CPU may request the NCPE to provide an economic analysis for those medicines that are high budget impact. The recommendation is provided to the CPU which makes the final decision for reimbursement (IPHA, 2006, NCPE, 2011, Tilson et al., 2010). *Price: A separate agreement is provided between the Irish Pharmaceutical Healthcare Association (IPHA) and the Irish government.*	NCPE – (independent body)	HSE (public body)	Ministers of Health and Children and Department of Health and Children through taxation (Health Service Executive, 2010) The National Centre for Pharmacoeconomics (NCPE) is funded by the Department of Health and Children.	Yes 2010 – Broader remit and medicines only mentioned in accounts (Health Service Executive, 2010).

	of the HSE makes final recommendations on the reimbursement and pricing of medicines. The final decision is informed by recommendations from the National Centre for Pharmacoeconomics (NCPE) established in 1998 (CPU, 2011, IPHA, 2006, NCPE, 2011).					
Israel (Medical Technologies Administration)	A list of Health Services that residents of Israel are entitled to called the National List of Health Services (NLHS) which introduced in 1995. The list is updated annually and this is in line with the additional annual budget for technologies, specified by government for the year. In 1998 a process was established for the listing of medicines and a committee established called the Public National Advisory Committee (PNAC). The list specifies the benefits that residents are entitled to receive from the health plans (Greenberg et al., 2009).	The MTA provides an assessment that informs the PNAC decision for listing on the NLHS. The Ministry of Health makes the final approval of the list of new technologies approved. The list of technologies is only updated annually and this is a unique aspect of this fourth hurdle system (Greenberg et al., 2009, Rosen and Samuel, 2009). *Price: Ministry of Health established the maximum price for all pharmaceuticals approved for sale.*	Ministry of Health – Medical Technologies Administration	Ministry of Health – PNAC committee and Ministry of Health through act of parliament.	Government Department	-
Italy (Pricing and Reimbursement Committee)	The Italian Medicines Agency (AIFA) was established in July 2004 and is the main agency responsible to the Ministry of Health for national reimbursement decisions regarding medicines in the National Healthcare System (SSN). The healthcare system is predominantly funded by taxation and largely decentralised and consists of a national level, regional level and local level (AIFA, 2011).	The manufacturer must first apply to the AIFA by submitting a dossier for pricing and reimbursement. The Technical and Scientific Commission (CTS) deal with the applications for marketing authorisation and provides an assessment of the efficacy of new drugs. The Price and Reimbursement Committee (CPR) evaluate the dossier and negotiate the prices of new drugs and set the reimbursement class of the medicine. The regions can decide on the copayments for these medicines which lead to price differences to the patient across the country. In 2010 a	AIFA - CTS committee	AIFA – Price and Reimbursement committee	Not identified (Emailed Adrianna Gasparini at the AIFA. 14/09/2011)	Not identified

		new rule was introduced for hospital medicines that specified that within 30 days of the AIFA reimbursement decision the medicine should be included on the regions hospital formulary. The regions and provinces are able to challenge the decision on the grounds of the medicine meeting the criteria specified by the AIFA (Jommi, 2009, Gianfrate, 2010). *Price: Prices are negotiated and reimbursement decisions are made by the AIFA.*				
Hungary (Technology Appraisal Committee) Mixed tax and social insurance	The National Health Insurance Fund Administration (NHIFA) provides reimbursement decisions for new medicines and a Technology Appraisal Committee was established in 2004 to perform this task. The TAC is informed by the National Institute for Strategic Health Research (NISHR) of the Ministry of Health which coordinates the HTA body that appraises submissions called the Office for Health Technology Assessment (OHTA) (PPRI, 2007b).	The manufacturer submits to the NIHFA. The OHTA makes a critical appraisal of the submission and provides are report to the Technology Appraisal Committee (TAC). The Head of the Pharmaceutical Department of the NIHFA makes the reimbursement decision (PPRI, 2007b). *Price: The NHIFA decides reimbursement decision and also negotiates price.*	OHTA of the	NIHFA – TAC	Not identified. The NHIFA has a health insurance fund that is a separate fund within the state budget which is approved by parliament each year. (Sent an email to the NHIFA Gyula Kiraly for how the administration is funded.)	Not identified
Korea (HIRA)	The Ministry of Health and Welfare (MOHW) overseas the National Health System. The national health insurance system provides health care coverage to all citizens in the form of social insurance. The Health Insurance Review and Assessment Service (HIRA) conducts reviews and assessments for reimbursement and was established in July 2000 as an independent agency separated from	The manufacturer must submit to the HIRA and a report is provided. The Drug Reimbursement Committee (DREC) makes the recommendation and then price negotiations are made by the National Health Insurance Corporation. The final decision is made by the Ministry of Health and Welfare, (Bae and Lee, 2009). *Price: Price negotiations are made with*	HIRA	HIRA – DREC & Ministry of Health and Welfare	HIRA is funded by insurance contributions collected by the National Insurance Contribution (NHIC) 2011:WON 223million (HIRA, 2011a)	Not identified

	insurers, providers and other interested parties. Economic evaluation was introduced formally in 2006. The HTA assessment provided by HIRA is used by the National Insurance Corporation (NHIC) for negotiation of the price of reimbursed medicines (Bae, 2009)	*the National Health Insurance Corporation.*				
Mexico (General Health Council)	The General Health Council is the main government decision making body for the reimbursement of medicines. The Presidential Agreement of 2002 states that public institutions of the NHS should only use medicines from the basic formulary for primary care and the catalogue of inputs for secondary and tertiary care. The Council introduced a regulation in 2003 for the requirements including the use of pharmacoeconomic studies. There is a working group called the Interinstitutional Commission of the Basic Formulary of Inputs of the Health Sector that meets three times a year. Mixed system of financing with 50% covered by social insurance (General Health Council, 2011).	The manufacturer submits and the interinstitution subcommittee evaluates the submissions. The General Health Council provides the decision and provides a GB code for inclusion on the Basic Formulary or Catalogue of Inputs. The public institutions must use this as a basis for prescribing decisions but may produce their own formulary (Moise and Docteur, 2007). *Price: There is a voluntary maximum price but the social insurance institutions can negotiate on price.*	Interinstitution Sub Committee	General Health Council & Public institutions (Social insurers or social security agencies)	The Social Insurance Institutions provide the formulary for the final reimbursement decision (Moise and Docteur, 2007).	Not identified
Netherlands (CVZ)	Medicines in the outpatient setting are reimbursed by health insurers if they are included in the Drug Reimbursement System (GVS) which includes a reference price system. The Health Insurance Board (CVZ) is an independent non-governmental body that provides advice to the Minister of Health for the inclusion of medicines in the benefits package under the Health Insurance Act of	The manufacturer submits to the CVZ and an assessment will be undertaken by the Pharmaceutical Assistance Commission (CFH committee). The CVZ Board may convene an appraisal committee (ACP) for those medicines with added therapeutic value. The final advice is sent to the Minister who makes the final decision for inclusion in the Drug Reimbursement System (GVS), (Schäfer et al., 2010, CVZ, 2011,	CVZ – CFH committee	CVZ - Board & Ministry of Health.	The Dutch Ministry of Health through taxation (Personal Communication: Jacqueline Zwaap).	Yes – Annual Review 2010 – quantity of advice accounted for (CVZ, 2010).

	2006 (Zorgverzekeringswet, Zvw). CVZ was established in 1999 and is responsible for technologies within the basic health care package (CVZ, 2009).	CVZ, 2009) *Price: There is statutory price setting for interchangeable medicines and generics set by the Ministry of Health, Welfare and Sport.*				
New Zealand (PHARMAC)	A Pharmaceuticals Schedule operates in New Zealand which includes a list of all pharmaceuticals and related products. The Pharmaceutical Management Agency of New Zealand was established in 1993. In June 2001 it was given legal duty under the Crown Entities Act 2000 to perform its functions of managing the Pharmaceutical Schedule. PHARMAC is a government agency directly accountable to the Minister of Health and is part of the medicine system alongside Medsafe and the District Health Boards (DHBs). PHARMAC manages outpatient and inpatient medicines where national contracts have been negotiated (PHARMAC, 2011a).	The manufacturer submits to the PHARMAC. The Pharmacology and Therapeutics Advisory Committee (PTAC) reviews and provides a recommendation to the PHARMAC Board and price negotiations may take place. The PHARMAC Board then decide whether the medicine should be included in the schedule. (PHARMAC, 2011c) *Price: PHARMAC negotiates both price and reimbursement.*	PHARMAC - PTAC	PHARMAC Board	The Ministry of Health plan to pay $14m in 2011-2012 output agreement through general taxation (PHARMAC, 2011b).	Yes – Annual Report 2010 – considers access and expenditure on pharmaceuticals (PHARMAC, 2010b).
Norway (NoMA)	The residents of Norway are covered by a national social insurance scheme. The Norwegian Medicines Agency is responsible for the pricing and reimbursement of medicines and was established in 2001. The pricing and reimbursement process is regulated in Regulation No. 1559 1999. This specifies that a pharmacoeconomics evaluation should be provided for general reimbursement (Norwegian Medicines Agency, 2011).	The manufacturer initially submits to the Norwegian Medicines Agency for a blue prescription that covers the costs of essential medicines. The NoMA screens the application to make sure that it meets the requirements. A price application may be submitted simultaneously. The NoMA agency may request the Blue Prescription Board to consider the case for reimbursement and should be consulted if it is a major therapeutic innovation The Board provides an assessment within seven weeks of receiving the details of the manufacturer submission. The NoMA	NoMA	NoMA Blue Prescription Board & Ministry of Health	Not identified (Emailed Norwegian Medicines Agency no response to date)	Yes – Annual report 2010, focus on regulatory tasks (Statens legemiddelverk, 2010).

		can decide on the approval of the medicine in the list for provision by the National Insurance Administration. The NoMA cannot approve medicines with an annual cost increase of more than 5 million annually. The NoMA must submit a report to the Blue Prescription Committee/Board and the manufacturer is given the opportunity to comment. A copy of the committee assessment will be forwarded to the Ministry of Health Care Services (HOD) where advice maybe sought from the National Council for Health Care Priorities. The National Council for Health Care Priorities assesses whether the money spent on the medicine would be well spent with regards to other priorities. The Ministry can decide to reject the application following the further evaluation or it may favour approval and bring the case to parliament in the form of a parliamentary bill. (PPRI, 2008b) *Price: The NoMA is responsible for setting the maximum pharmacy purchase prices (PPP).*				
Poland (AOTM)	The Agency for Health Technology Assessment in Poland (AHTAPol) was established in 2006. In an Act of June 2009, the agency became a state entity with legal responsibility for making recommendations for the reimbursement list. The agency is responsible for listing, removing medicines from the list of guaranteed benefits and changes in the level and funding of the benefits. It has responsibility for many	The Ministry of Health refers the manufacturer submission to AHTAPol and the submission is analysed by the AHTAPol analytical team using the Polish Guidelines for the conduct of Health Technology Assessment. The Analytical Team will revise the submission and provide a report. The appraisal process is separate and performed by the Consultative Council that is chaired by the President of AHTAPol. The Consultative Council	AHTAPol analytic team	AHTAPol Consultative Council & Minister of Health	Public institution that is financed from the government budget through taxation and partly by manufacturers contributions: EUR2.45m per year. (Personal Communication:	Not identified

	technologies (AHTAPol, 2011).	takes into account the wider context specific judgements. The President of AHTAPol provides the final recommendation that is passed to the Ministry of Health. The Minister of Health decides the final decision for inclusion on the list, (Leopold and Vogler, 2009, AHTAPol, 2011). *Price: The price is agreed with the Ministry of Health*			Gabriela Ofierska-Sujkowska, Head of Reimbursement Recommendations, AHTAPol).	
Portugal (INFARMED)	The reimbursement system is set within the National Health Services (SNS), which is funded through general taxation. The National Authority of Medicines and Health Products (INFARMED) is a government agency that was established in 1993. There is a legal framework for the reimbursement of medicines and this is set out in Law No.118/92 June 25. INFARMED assesses medicines only, (PPRI, 2008a).	The manufacturer must agree a maximum price with the Directorate-General for Economic Activities (DGEA). The manufacturer then applies to the Ministry of Health and INFARMED for reimbursement. The Ministry of Health makes the final decision *(PPRI, 2008a).* *Price: The price is set by the Directorate General of Economic activities for a maximum price of new pharmaceuticals.*	INFARMED	INFARMED & Ministry of Health	Not identified (Emailed Laura at INFARMED.)	Not identified
Spain (Ministry of Health – Directorate General)	The National Health Service was established in Spain in 1986 under the General Health Law. The health system is decentralised and control given by 17 autonomous regions. The reimbursement and pricing decisions are made at the national level involving the Ministry of Health, Directorate General of Pharmacy and Health Products role established in 2003. The criteria considered by the Ministry of Health are contained in Art 89. Of Pharmaceutical Law – Public financing procedure, 2006, (Vogler et al., 2009b).	The Ministry of Health, Directorate General of Pharmacy and Health Products initiates the reimbursement process and the Spanish Medicine Agency for Health Products provides a report on the clinical utility of the medicine. The manufacturer must provide information to the Inter-ministerial Price Commission that agrees a maximum price. The Minister of Health makes the final decision and regions have responsibility for implementation of the decision, (Vogler et al., 2009b). *Price: The inter-ministerial price*	Ministry of Health and Spanish Agency for Medicines and Health Products	Ministry of Health, Directorate General of Pharmacy and Health Products	Government Department	-

		commission agrees a maximum price.				
Sweden (TLV)	The Dental and Pharmaceuticals Benefits Board (TLV) was established in 2008 to integrate medicines and dental care in one agency. The agency use to be known as the Pharmaceutical Benefits Board (LFN), which was established in 2002. The TLV agency is a central government agency whose legal remit is to determine whether a pharmaceutical product or dental care procedure shall be subsidised by the state reimbursement scheme. The TLV makes decisions for outpatient medicines and dental treatments. The Swedish public health system is funded by taxation (TLV, 2010a).	The manufacturer must submit an application for pricing and reimbursement. The TLV determines whether the medicine should be eligible for inclusion in the "high-cost threshold". There are many medicines included in the high-cost threshold and includes tax subsidised medicines where the state reimburses a proportion of the cost. The Pharmaceutical Benefits Board makes the final reimbursement decisions and these are mandatory. The County Councils implement the decisions for outpatient medicines (LFN, 2007). *Price: Responsible for implementing statutory pricing but does not negotiate on price.*	TLV	TLV	TLV is funded through central government budget decided by Swedish parliament through taxation. (Personal Communication: Martin Eriksson, TLV)	Yes – 2010, quantity and processing times (TLV, 2010b).
Switzerland (Federal Office for Public Health)	The Federal Office of Public Health (FOPH) is part of the Department of Home Affairs (FDHA). The FOPH is the integrated centre for excellence for health. It is responsible alongside the 26 cantons for public health and development of the national health policy. The FOPH is responsible under the ACT 117FC to regulate health and accident insurance. The FOPH provides the final recommendation for inclusion in the Pharmaceutical Specialities List (SL-list) for reimbursement. The FOPH is informed by the Federal Drug Commission that was established in 1995 and consists of scientific experts and stakeholders. It provides advice through consideration of evidence for inclusion in the	The manufacturer submits an application to the FOPH which is then considered by the Federal Drug Commission (FDC). The FOPH makes the final decision (Paris and Docteur, 2007). *Price: The FOPH agrees maximum price and reimbursement*	FDC (committee)	FOPH of Department of Health	Government Department	-

	speciality list (Federal Office of Public Health, 2011).					
UK: England and Wales (NICE)	The system is centred around NICE which was established in 1999 under direction of the Secretary of State. NICE reviews a number of technologies using different processes. Public system is predominantly funded through taxation (NICE, 2011).	NICE provides a recommendation. NICE recommendations require funding for the medicine 3 months after publication from taxation. They do not have responsibility for implementation, (Department of Health, 2011). *Price: Indirect price control through the Pharmaceutical Price Regulation Scheme (PPRS)*	NICE (special health authority) – ERG or Assessment Group	NICE (special health authority) – Technology Appraisal Committee	Department of Health through taxation (NICE, 2010a).	Yes previous annual report produced (NICE, 2010b).
UK: Scotland (SMC)	The provision of health care is devolved to health boards. The Scottish Medicines Consortium (SMC) was established in 2001 by the 15 Health Boards which today provides advice to the 14 health boards for funding of new medicines. Funding for public provision is funded through taxation in Scotland (SMC, 2011).	The SMC provides one stage advice to the health boards and Area Drug Therapeutic Committees with regards value for money. The health boards choose whether to include the medicine following advice from the SMC. Manufacturer is free to set price prior to the evaluation by the SMC, (SMC, 2011). *Price: Indirect price control through the Pharmaceutical Price Regulation Scheme (PPRS)*	SMC - NDC	SMC & Area Drug Therapeutic Committees	Funding from the Health Boards from the revenue allocated to them (Scottish Executive, 2003).	Yes previously- Last annual report produced in 2008 (quantity of guidance) (SMC, 2008).

Table A3.2 OECD countries' Policy Implementation Level

Policy Implementation Level of OECD formal HTA					
Country	**Establishment**	**Objective**	**Implementation**	**Accountability**	**References**
Australia	The Pharmaceutical Benefits Advisory Committee was established in 1953 in the National Health Act 1953. The Economic Sub-Committee (ESC) was established in 1994 to assess the validity of the manufacturer economic submissions. PBAC is an advisory committee that reports to the Ministry of Health. The PBAC costs around $10 million per year to operate, (Lopert, 2009).	The Pharmaceutical Benefits Scheme (PBS) aims to provide timely, reliable and affordable access to necessary medicines for Australians. The PBACs primary role is to recommend to the Minister for Health which drugs and medicinal preparations represent value for money and should be subsidised by the Australian Government under the PBS. The goal of Australian Government HTA processes is to maximise beneficial health outcomes to the Australian population within the overall funds available whilst being cognisant of the other important goals of the health system. PBAC provides recommendations for medicines and its remit was widened to include vaccines in 2006.	In Australia the Pharmaceutical Benefits Scheme (PBS) is part of the broader National Medicines Policy for which the government subsidises and is administered through Medicare Australia. The PBAC committee provides advisory recommendations to the Ministry of Health. There is a two-stage process where the PBAC makes a recommendation and then the Pharmaceutical Benefits Pricing Authority (PBPA) considers this for price negotiations.	Submissions are processed within 17 weeks and recommendations made. The recommendations by the PBAC are only advisory and the Minister for Health makes the final decision on listing.	(PBAC, 2008) (Lopert, 2009) (Department of Health and Ageing, 2011) (Australian Government, 2011b)
Austria	The regulation regarding pharmaceutical reimbursement is the responsibility of the Federal government specifically the Federal Ministry of Health, Family and Youth (BMFGJ). The health system us funded by social insurance based on the principles of statutory insurance, solidarity and self - governance, which includes 22 social security institutions. The Medicines Evaluation Committee (HEK) was established in 2005 and provides advice to the Federation	The main principles of the Austrian Health Care system are solidarity, affordability and universality. The system ensures high quality medical care for all citizens, independent of their social status or income. The mission of the HBV states that they aim "provides customer-oriented and conscientious protection against the risks of diseases, old age and unemployment."	The HVB and its 22 sickness funds provide implementation of the decisions in the social insurance system using the reimbursement code. A traffic light system operates in the Reimbursement Code, "green", "yellow" and "red zone". The reimbursement code is determined by the rules of procedure (351g ASVG 2004). The Reimbursement Code aims to provide physicians with a transparent and clear understandable set of medicines that are available for general reimbursement. The process maybe initiated by the Federation of by the	There is a legal framework governing the rules of procedure for inclusion in the code of reimbursement (351g of ASVG 2004). The HBV will provide a decision within 90 days of the original manufacturer submission.	(Federation of Social Security Institutions (HBV), 2011) (PPRI, 2007a) (Austrian Federation of Social Insurance Institutions, 2004)

	of Social Security Institutions (HBV). The Federation makes final reimbursement decisions. The BMFGJ takes the advice of the pricing committee (PK) for pricing decisions. The medicine maybe listed on the positive list for outpatient medicines called the reimbursement Code (EKO) or maybe included in the negative list.		manufacturer submitting an application for marketing authorisation. The Federation will review the application for completeness and the manufacturer will be required to provide the information within 14 days otherwise the application will be rejected. The Independent Pharmaceutical Commission (UHK) functions as an appeal court for when a manufacturer's medicine is not approved for reimbursement. The PK advises the BMFGJ on the price of the medicine, (PPRI, 2007a)		
Belgium	The Committee for Reimbursement of Medicines (CRM) was established in 2001 in a legal act (Royal Decree 21 December 2001). It is responsible for formulating proposals for the admission of pharmaceuticals for the list of reimbursable pharmaceuticals, advise the Minister on aspects of the policy on reimbursement of pharmaceutical products, formulate the insurance committee proposal interpretive rules for the reimbursement of pharmaceuticals. The CRM is located in the National Institute for Health and Disability Insurance. The NIHDI is a federal institution, which organises, manages and supervises the correct application of compulsory insurance in Belgium.	The NIHDI plays a key role in the Social Security System. It manages and organises the health care insurance for the reimbursement, payment of benefits and medical costs. Its objective is to provide reimbursement of medical costs in order to make high quality health care accessible to as many people as possible. The CRM has responsibility for providing advice to the Minister of Health and Social Affairs.	The NIHDI is responsible for the management and supervision of the compulsory health care and benefits (HCB) insurance. The health insurance funds are responsible for the reimbursement and payment of the benefits and medical costs. The CRM formulates advice to the Minister of Health and Social Affairs whose decision may differ because of budget or social considerations.	NIHDI falls under the responsibility of the Minister for Social Affairs. Listing decisions are made within 180 days of the application.	(NIHDI, 2011) (NIHDI, 2007) (Adriaens and Soete, 2010) (KCE, 2010)
Canada	CADTH was established in 1989 and the Common Drug Review (CDR) started accepting submissions in 2003 to standardise reviews across the country. CADTH is funded by the federal, provincial and	The objectives of the CDR process are to reduce duplication, to maximize the use of limited resources and expertise, and to enhance the consistency and quality of Drug reviews. The CDR accepts	The CADTH CDR recommendations are advisory and provided to each of the jurisdictions to make decisions on inclusion in their drug plans. CDR recommends whether a drug should be listed. Jurisdictions evaluate the impact of adding	CADTH is owned by, and reports directly to, the 13 Provincial/Territorial Deputy Ministers of Health and the Federal Deputy Minister of Health.	(CADTH, 2010a) (CADTH, 2011a)

	territorial governments as an independent not for profit agency. The Common Drug Review (CDR) undertakes reviews of Drug Submissions and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial (F/P/T) Drug Plans with the exception of Québec. The drug plans make their own decisions based on the recommendations and plans mandate, priorities and resources. The Common Drug Review (CDR) undertakes reviews of Drug Submissions and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial (F/P/T) Drug Plans with the exception of Québec.	submissions for new medicines with the exception of cancer medicines that are assessed by a different process. The Pan-Canadian Oncology Drug Review Process (pCODR) reviews all oncology medicines via a cross-jurisdictional process.	the drug to their formularies. Their considerations include: non-drug treatment options, policy, budget impact, and other economic considerations. Drug plans also assess drugs not covered by CDR (e.g. generics), monitor drug utilization, promote optimal prescribing, and manage the overall formulary.		
Denmark	The Danish Health Act of 2005 Sections 144(1-3) and 152 (2&4) decides whether to grant reimbursement for medicinal products. The Danish Medicines Agency is an agency under the Ministry of Interior and Health and provides final reimbursement decisions and is advised by the reimbursement committee which is an independent authority. The Reimbursement Committee (MTN) was established in 2003 by the Danish Minister for the Interior and Health to provide advice to the DMA.	The aim of the Danish Medicines Agency is to ensure the availability of effective and safe healthcare products – medicinal products, medical devices and new therapies and to promote the proper use of such products. According to section 144(1)-(3) and section 152(2) and (4) of the Danish Health Act, the Danish Medicines Agency decides whether the Regional Council is to grant general, including general conditional, reimbursement, for a medicinal product.	The recommendations provided by the Reimbursement Committee are advisory and the Danish Medicines Agency makes the final decision.	The DMA is an agency under and accountable to the Minister of Interior and Health. In almost all cases the decision on reimbursement status for a given pharmaceutical is made in fewer than 90 days from the application date in accordance with the Transparency Directive. The process time may pause when consultation occurs with the manufacturer to clarify aspects of the submission.	(Danish Medicines Agency, 2011) (Danish Medicines Agency, 2008)

Finland	Pharmaceutical manufacturers have the freedom to set price and a patient can receive reimbursement through the KELA, the social security institution (sometimes referred to as social insurance institution even though predominantly funded through taxation). This can take place once the Pharmaceutical Pricing Board has made a decision on the reimbursement status and price under the Health Insurance Act (1224/2004). The conditions set out in the payment of reimbursement under the health insurance act for a medicinal product is that the medicine must have a reimbursement status confirmed by the Pharmaceutical Pricing Board (PPB).	The chief objective of pharmaceutical service is to enable an efficient, safe, rational and cost-effective pharmacotherapy for all those in need of it. Inter-professional cooperation and agreeing on joint policies and goals regionally and locally are prerequisites for securing systematic and sustained operations. The utilisation of information systems available in social welfare and healthcare and their compatibility should be enhanced. The goal is to deliver all prescriptions electronically.	The PPB makes the final decision and patients can then receive reimbursement from the Social Insurance Institute, KELA for either basic reimbursement or special reimbursement. KELA aims to secure the income and promote the health of the entire nation, and to support the capacity of individual citizens to care for themselves.	The Pharmaceutical Pricing Board is the responsible authority for decisions on medicines prices and reimbursement. The authority is responsible to the Ministry of Social Affairs and Health who are responsible for the administrative development of the pharmaceutical service. The reimbursement and pricing decisions take up to 180 days.	(Ministry of Social Affairs and Health, 2011) (PPB, 2011) (KELA, 2011)
France	Haute Autorité de santé (HAS) was established by the health insurance Act of August 13 2004 by the Ministry of Health and Solidarity. HAS is an independent public scientific authority to assess medical technologies. Health funding is raised through social health insurance in France.	The aim of the agency is to improve the quality of care and guarantee equity within the healthcare system.	The reimbursement decisions in France are published in the Official Journal by the Ministry of Health in France and provided by the social insurance institutions through the mandatory social health insurance system. The National Union of Health Insurance Funds (UNCAM) co-ordinates the three national sickness funds (general scheme, agricultural scheme and social system of independent) and decides the rate of reimbursement following a listing decision by the HAS and CEPS committee. The HAS provides one of the two stages of advice regarding the case for reimbursement which includes consideration of clinical efficacy. Economic considerations made by the Economic Committee for Health Products (CEPS). the HAS opinion informs the pricing and	Legally required to provide advice to Ministry of Health in 90 days	(HAS, 2011b)

			volume agreements that are negotiated between the manufacturer and the Economic Committee for Health Products (CEPS) for outpatient medicines and medicines on top of DRG. Prices for those medicines for hospital use included in the DRG are negotiated directly with the individual hospitals.		
Germany	The Federal Joint Committee (G-BA) is a legal decision-making body in a self regulated statutory health insurance (SHI) system under the German Social Law (SGB V). It was established on 1st January 2004 as mandated by a federal health reform law (GKV Modernisation Act – GMG). The directives issued by the G-BA are legally binding for insured persons, providers and payers of health care (physicians, hospitals and sickness funds). A new body was created in 2004 called the Institute for Quality and Efficiency in Healthcare (IQWIG) a independent scientific body which is responsible for the assessment of new medicines at the request of the G-BA. The institute provides independent reports for drugs, surgical procedures, methods of diagnosis and treatment guidelines and disease management programme (DMP). The agency provides an assessment of the medical benefit. It is required from 2008 to produce a health economic assessment for the evaluation of costs and benefits of drugs. IQWIG provides advice to the Federal Joint Committee which makes the final	The objectives of the G-BA operate according to a legal basis through a code of procedure of the G-BA (Social Code (SGB V)). The services provided by the statutory health insurance must be "adequate, expedient and cost-effective" (Federal Joint Committee, 2011: How Innovations Enter Statutory). IQWIG is contracted by the G-BA to provide early benefits assessments and economic analysis and the agencies stated aims are to "examine objectively the advantage and disadvantages of medical services for patients"	The Federal Joint Committee provides the directives for those medicines that can be provided by the statutory health insurance fund (GKV) and reimbursed by the health insurance funds. The National Association of Statutory Health Insurance Funds performs a central role in the German healthcare system from 1 July 2008, being the central association of the health insurance funds at federal level in accordance with section 217a of Book V of the German Social Code (SGB V). The manufacturer sets price (can be prescribed) and then submits to the G-BA and the social insurance system covers fully the medicine. The G-BA will consider the early benefit assessment and employs IQWIG to provide the assessment. If the medicine is deemed to have no additional benefit the price of the medicine is set in the reference price. If the medicine has additional benefit the price is negotiated with the sickness funds at 6 months. No agreement on price results in an arbitration committee that will agree price. On dissatisfaction of the arbitration price, the manufacturer or social insurance funds can request IQWIG to provide an efficiency frontier analysis (2008). The reimbursement price is valid from one year onwards.	The Federal Joint Committee assesses within three months after a new pharmaceutical accessed the market whether any claimed additional benefit in relation to the appropriate comparator is proven. Prices remain free for up to a year within which time a price maybe negotiated or a cost benefit analysis requested from IQWIG.	(IQWIG, 2011) (Federal Joint Committee, 2011a) (Federal Joint Committee, 2010) (Leverkus, 2011)

	reimbursement decision for medicines. The Act for the Restructuring of the Pharmaceutical Market in Statutory Health Insurance (AMNOG) in 2011 has greatly changed the reimbursement system. G-BA aims to regulate SHI-wide issues of access, benefits and quality.		The system of clinical assessment is similar to the French agency and the economic assessment similar to other European agencies using a different form of evaluation "efficiency frontier"		
Ireland	There is no legal agreement applicable to reimbursement. There is an agreement between the Health Service Executive and Pharmaceutical industry. There is a General Medical Services (GMS) scheme and a Drugs Payment Scheme (DPS) provide reimbursement for those eligible in Ireland. The Health Service Executive is responsible for the operation and management of the public health services in Ireland on behalf of the Department of Health and Children. The HSE reports directly to the Minister for Health. The Corporate Pharmaceutical Unit of the HSE makes final recommendations on the reimbursement and pricing of medicines. The final decision is informed by recommendations from the National Centre for Pharmacoeconomics (NCPE) established in 1998.The NCPE was established in 1998 by the Department of Health and Children to undertake health economic evaluation and provide advisory recommendations to the CPU. The	The Health Service Executive (HSE) in the Corporate Pharmaceutical Unit in Ireland made an agreement with the pharmaceutical industry called the IHPA agreement in 2006. The objective was to ensure early access to, and security of supply of new medicines for Irish patients and ensure that the medicine that best meets the patients needs delivers best value for money, (IHPA,2006: IHPA agreement). The aim of the NCPE that provides recommendations to the HSE is to "promote expertise in Ireland for the advancement of the discipline of pharmacoeconomics through practice, research and education. Activities of the centre include economic evaluation of pharmaceutical products and the development of cost effective prescribing." (NCPE, 2011) It provides this through the evaluation of products and the development of cost-effective prescribing.	The CPU can request a full pharmacoeconomic submission from the manufacturer for high cost/budget impact medicines. The recommendations from the NCPE are passed to a committee in the CPU that makes the final decision on the reimbursement.	The reimbursement decisions are usually made within 90 days of the manufacturer submission (where there is no appeal against a not reimbursed decision).	(NCPE, 2011) (Tilson et al., 2010) (CPU, 2011)

	NCPE has been required to provide pharmacoeconomic assessment for selected new medicines since 2006.				
Israel	A list of Health Services that residents of Israel are entitled to called the National List of Health Services (NLHS) which introduced into law in 1995. The list is updated annually by the Ministry of Health and this is inline with the additional annual budget for technologies, specified by government for the year. In 1998 a process was established for the listing of medicines and a committee established called the Public National Advisory Committee (PNAC). The list specifies the benefits that residents are entitled to receive from the health plans.	The Israeli National Health Insurance (NHI) system introduced in 1995, was based on the policy goals of containment of drug expenditures; sustainability and equity of financing for pharmaceuticals; efficiency of expenditure in the pharmaceutical sector; and availability and accessibility of pharmaceuticals. The Healthy Israel 2020 strategy is being led by the Ministry of Health and aims to improve the health of and reduce disparities in access to health care and health outcomes among the population.	The National Health Insurance Law (NLHS) specifies a list of medicines to be provided by publically tax funded Health Maintenance Organisations (HMOs) in Israel. The membership of one of the four competing funds is mandatory and these provide the benefits approved by the Ministry of Health in the National List of Health Services (NLHS). The process is based on two stages: i) A HTA process considering the clinical, epidemiology, economic, legal and ethical aspects and a (ii) decision processes undertaken by the Public National Advisory Committee that operates within the government specified additional budget allocation. The MTA provides an assessment that informs the PNAC decision for listing on the NLHS. The Ministry of Health makes the final approval of the list of new technologies approved. The list of technologies is only updated annually and this is a unique aspect of this fourth hurdle system.	The list is only updated annually. The PNAC is accountable to the Ministry of Health. The Health Maintenance Organisations are required by law to add the new medicines that are added to the NLHS.	(Greenberg et al., 2009) (Shemer et al., 2009) (Rosen and Samuel, 2009)
Italy	The Italian Medicines Agency (AIFA) was established in July 2004 and is the main agency responsible to the Ministry of Health for national reimbursement decisions regarding medicines in the National Healthcare System (SSN). The manufacturer must first apply to the AIFA by submitting a dossier for pricing and reimbursement. The Technical and Scientific Commission (CTS) deal with the applications for marketing	The objective of the AIFA is to promote good health through medicines, set fair pharmaceutical policies and assure their consistent application nationwide, manage the value and cost of medicines, promote pharmaceutical Research and Development and demonstrate leadership at home and internationally.	The medicines in the PFN are implemented at the regional level. The regions can decide on the copayments for these medicines which can lead to price differences to the patient across the country. In 2010 a new rule was introduced for hospital medicines that specified that within 30 days of the AIFA reimbursement decision the medicine should be included on the regions hospital formulary. The regions and provinces are able to challenge the decision on the grounds of the medicine meeting the criteria specified by	The listings are included in the official journal of Italy. The pricing and reimbursement decision should take no longer than 180 days from the time of the initial submission.	(AIFA, 2011) (Lo Scalzo et al., 2009)

	authorisation and provides an assessment of the efficacy of new drugs. The Price and Reimbursement Committee (CPR) evaluate the dossier and negotiate the prices of new drugs and set the reimbursement class of the medicine:		the AIFA.		
Hungary	The National Health Insurance Fund (NIHFA) provides reimbursement decisions for new medicines and a Technology Appraisal Committee was established in 2004 to perform this task. The TAC is informed by the National Institute for Strategic Health Research (NISHR) which coordinates the HTA body that appraises submissions called the Office for Health Technology Assessment (OHTA).	The aim of the NHIFA with regards to pharmaceuticals is "to provide access to new value added therapies by continuously recycling resources from off-patented products to innovative products with proven therapeutic effectiveness." The basic principles of the financing of pharmaceuticals in Hungary includes, professional foundation within evidence based decision-making, consideration of budget framework, transparency, predictability, publicity with regards to access to data for stakeholders, transparency, enforcement of equality of access, needs based and cost-efficiency. The OHTA aims to determine guidelines of analysing technologies through a consideration of the clinical evidence, efficacy and cost-effectiveness in comparison to alternative uses of resources. This facilitates the appropriate use of cost-effective health care technologies.	The manufacturer submits to the NIHFA. The OHTA at the NISHR makes a critical appraisal of the manufacturer submission that informs the decision made by the Technology Appraisal Committee (TAC). The Head of the Pharmaceutical Department at the NIHFA makes the decision. An appeal must be submitted within 15 days of the decision otherwise this becomes the final decision. Prices and reimbursement levels are published in the Official Journal of the Republic of Hungary before marketing can take place.	The reimbursement decision is provided within 90 days of the application by the manufacturer.	(PPRI, 2007b) (Office of Health Technology Assessment, 2011)
Korea	The Ministry of Health and Welfare (MOHW) overseas the National Health System. The national health insurance system provides health care coverage to all citizens in the form of social insurance. The	HIRA is dedicated to maintaining and improving national health by fulfilling its commitment to health care review and quality assessment. HIRA aims to be an organisation that is recognised and respected by all physicians,	The National Health Insurance Corporation (NHIC) implements the decisions and pays the health care institutions for the medicines provided in the positive list. The manufacturer must submit Pharmacoeconomic data to the HIRA and	HIRA is a statutory public corporation under the direction of the Ministry of Health and Welfare.	(HIRA, 2011b) (Yang, 2009) (Bae and Lee, 2009)

	Health Insurance Review and Assessment Service (HIRA) conducts reviews and assessments for reimbursement and was established in July 2000 as an independent agency separated from insurers, providers and other interested parties. Economic evaluation was introduced formally in 2006. The HTA assessment provided by HIRA is used by the National Insurance Corporation (NHIC) for negotiation of the price of reimbursed medicines.	patients, parties and people in the country. It is established under the National Health Insurance Act for improving the national health care ad developing social security though fair and efficient heath care review and evaluation.	this is critiqued by members of staff. A HTA report is provided to the Drug Reimbursement Committee (DREC). The DREC makes recommendations for the second stage of the process, which involves price negotiations. The National Health Insurance Corporation using the information from the DREC report undertakes the price negotiation stage. The NHIC provides a maximum price for the medicine. The Ministry of Health and Welfare makes the final decision for reimbursement listing.		(Song, 2009)
Mexico	The General Health Council is the main government decision making body for the reimbursement of medicines. The Presidential Agreement of 2002 states that public institutions of the NHS should only use medicines form the basic formulary for primary care and the catalogue of inputs for secondary and tertiary care. The Council introduced a regulation in 2003 for the requirements including the use of pharmacoeconomic studies. There is a working group called the Interinstitutional Commission of the Basic Formulary of Inputs of the Health Sector that meets three times a year. Mixed system of financing with 50% covered by social insurance. Centro Nacional de Excelencia Tecnológica en Salud (CENETEC) the HTA agency of Mexico may also provide advice to the GHS. CENETEC was established in 2004.	The General Health Councils main objective in Mexico is to provide co-ordination for all institutions and entities comprised in the NHS in line with Article 4 of the Mexican Constitution which states that men and women are equal under law and every person has a right to receive medical treatment when deemed as necessary, (Vázquez, 2005)	There is the Basic formulary that is designed for primary care and the Catalogue of inputs that is designed for secondary and tertiary care. The Interinsitution sub committees review and evaluate the submissions and the General Health Council make the decision on inclusion on the Basic Formulary or Catalogue of Inputs. The institutions must use the Basic Formulary as a basis for there prescribing decisions. However, they may choose not to use some medicines and may produce their own formulary. As there are a number of different public institutions delivering care in Mexico such as Instituto Mexicano del Seguro Social (IMSS), Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado (ISSSTE), Seguro Popular (SP), IMSS Oportunidades, Petróleos Mexicanos (Pemex), Secretaría de Marina (Semar). These institutions make the final decision on access to the medicines.	The General Health Council is a constitutional body that provides national guidance on health policy in Mexico. The listing recommendations should be made within 4 months of the initial manufacturer submission.	(General Health Council, 2011) (Vázquez, 2005)

Netherlands	Medicines in the outpatient setting are reimbursed by health insurers if they are included in the Drug Reimbursement System (GVS) which includes a reference price system. The Health Insurance Board (CVZ) is an independent non-governmental body that provides advice to the Minister of Health for the inclusion of medicines in the benefits package under the Health Insurance Act of 2006 (Zorgverzekeringswet, Zvw). CVZ was established in 1999.The Pharmaceutical Assistance Commission (CFH) provides the assessment of the medicine. The ACP provides the appraisal of the medicine. There is a separate decision-making process for inpatient and outpatient medicines.	The Health Care Insurance Board (CVZ) tasks include providing advice and implementing the Dutch statutory health insurance. CVZ has a major role in the social insurance system of maintaining the quality, accessibility and affordability of health care in the Netherlands. CVZ's advice is based not only or care-related considerations, but also considerations relating to finance and society. CVZs missions are to "safeguards and develops the public conditions for the health care insurance system, so that Dutch citizens can obtain their right to care." There are four stated package criteria of necessity, effectiveness, cost-effectiveness and feasibility.	The Dutch Health Care Insurance Board provides the assessment, appraisal and are involved in the implementation. The CVZ provides the risk adjusted contributions to the health insures for provision of those medicines included in the basic health insurance package. There are two processes for deciding which outpatient and inpatient medicines should be included. There are two related consecutive processes, assessment process and the CFH/CVD process management. The manufacturer submits to the CFH. The manufacturer submission is evaluated and reports prepared by consultants and CVD. This is then sent to the meeting by the CFH committee (a pharmacotherapeutic report and a pharmacoeconomic analysis). CFH discusses the report and manufacturers submission. After the CFH draft report the stakeholders are given the opportunity to comment. The CFH may require additional data. The comments from the stakeholders are discussed and a final report prepared. The CFH provides the report to the Health Board (CVZ) and this is considered. The Board may consider an ACP which takes into account other societal factors or may consider a public consultation (if procedure has not been followed appropriately). The final advice is sent to the Minister who makes the final decision. The decision is sent in a letter to the manufacturer.	CVZ is an independent organisation responsible for carrying out the task of government. The tasks are conducted under the guidance of the Ministry of Health, Welfare and Sport and within the AWBZ framework (Exceptional Medical Expenses Act). The Minister will make a decision within 90 days of receiving the application from the manufacturer.	(CVZ, 2011) (Schäfer et al., 2010) (CVZ, 2009)
New Zealand	A Pharmaceuticals Schedule operates in New Zealand which includes a list of all pharmaceuticals and related products. The Pharmaceutical Management Agency of New Zealand was established in 1993. In	PHARMAC's statutory objective is to "secure, for eligible people in need of pharmaceuticals, the best health outcomes that are reasonably achievable from pharmaceutical treatment and from within the amount of funding provided."	The District Health Boards of New Zealand are responsible for implementing the decisions made by the PHARMAC agency. The manufacturer submits to PHARMAC using the guidance on funding applications to the agency. The Pharmacology and Therapeutics Advisory Committee (PTAC)	The PHARMAC is accountable to the Minister of Health. The Minister of Health can issue strategic directions to PHARMAC if required.	(PHARMAC, 2010a) (PHARMAC, 2007) (PHARMAC, 2011c)

	June 2001 it was given legal duty under the Crown Entities Act 2000 to perform its functions of managing the Pharmaceutical Schedule. PHARMAC is a government agency directly accountable to the Minister of Health and is part of the medicine system alongside Medsafe and the District Health Boards (DHBs). PHARMAC manages outpatient and inpatient medicines where national contracts have been negotiated. The Pharmaceutical schedule sets out the criteria for access to the pharmaceuticals in the community. It also includes hospital medicines where national contracts have been negotiated. Medicines are funded from the Community Pharmaceutical budget which is fixed each year by the Minister of Health in consultation with PHARMAC and the DHB's.		review and collate additional information on the medicine. It may also ask PHARMAC to undertake additional analysis if this has not been provided by the manufacturer. The PTAC provides a recommendation for prioritisation of the medicine by the PHARMAC board. At this stage price negotiations may take place with the manufacturer. The recommendations are then set out for consultation with interested parties. Once the consultation is received the PHARMAC board with decided whether to approve the medicine based on the nine criteria. The PHARMAC is not bound by the process and may vary this when it is deemed appropriate. The recommendations by the PTAC are advisory and the recommendations by the PHARMAC board are mandatory with respect to funding. Applications can also be made for Exceptional Circumstances (EC) to fund medicines that are not funded in the community or hospitals. There are three types: 1. Community EC – This is for rare clinical situations 2. Hospital EC – This is to enable a quicker discharge from hospital 3. Cancer EC – This is for medicines not funded in the cancer medicine basket.		
Norway	The Norwegian Medicines Agency (NoMA) was established on the 1st of January 2001. The agency directs supervision of production, clinical trials and marketing of pharmaceuticals. It authorises and monitors the correct and	The NoMA is responsible for supervising the production, trials and marketing of medicines. It approves medicines and monitors their use, and ensures cost-efficient, effective and well-documented use of medicines. The inspectorate also	The mandatory National Insurance Scheme which operates through the government provides coverage for those in employment and taxation provides funding for others provided by the reimbursement list in Norway. The manufacturer initially submits to the Norwegian Medicines	The NoMA allocated time for dealing with the pricing and reimbursement decision is 180 days.	(Norwegian Medicines Agency, 2011) (PPRI, 2008b) (University of

	economical use of pharmaceuticals. It is responsible for reimbursement and pricing of medicines for the public list.	supervises the supply-chain. NOMA also regulates the prices and trade conditions for pharmacies. The agency considers the reimbursement of medicines following Section 14 of the Norwegian Law Gazette. The Norwegian health systems fundamental aim is to give the citizens equal access to health services, irrespective of their location, gender, age, financial status and to prioritise those with greatest need (Mørland et al., 2010). Price control through international reference pricing of prescription drugs and price revisions has been a strategy for pharmaceutical cost containment in Norway during the period 1994 to 2004 (Håkonsen et al., 2009).	Agency for a blue prescription that covers the costs of essential medicines. Individual reimbursement may be made from a doctor or patient to the NoMA. The manufacturer may present the application either prior or after gaining marketing authorisation for the medicine. The NoMA screens the application to make sure that it meets the requirements. A price application may be submitted simultaneously. The NoMA agency may request the Blue Prescription Board to consider the case for reimbursement. The Board should be consulted if this is a major therapeutic innovation The Board provides an assessment within seven weeks of receiving the details of the manufacturer submission. The NoMA can decide on the approval of the medicine in the list for provision by the National Insurance Administration. The NoMA cannot approve medicines with an annual cost increase of more than 5 million annually. The NoMA must submit a report to the Blue Prescription Committee/Board and the manufacturer is given the opportunity to comment. A copy of the committee assessment will be forwarded to the Ministry of Health Care Services (HOD) where advice maybe sought from the National Council for Health Care Priorities. The National Council for Health Care Priorities assesses whether the money spent on the medicine would be well spent with regards to other priorities. The Ministry can decide to reject the application following the further evaluation or it may favour approval and bring the case to parliament in the form of a parliamentary bill.		Oslo, 2011)

Poland	The Agency for Health Technology Assessment in Poland (AHTAPol) was established in 2006. In an Act of June 2009, the agency became a state entity with legal responsibility. The agency became responsible for listing, removing medicines from the list of guaranteed benefits and changes in the level and funding of the benefits. The Consultative Council (CC) acts as an advisory board and considers the evaluation report prepared by the AHTAPol analytic team, experts and representatives of the National Health Fund (NHF) on recommendations for new medicines. The President of the AHTAPol makes the final recommendation to the Minister of Health. The Minister of Health makes the final decision for listing of the medicine.	The objective of the AHTAPol is to provide recommendations for the classification of health care services as guaranteed benefit. The Polish Constitution requires all citizens of the Republic of Poland to be entitled to equal access to health services from public providers of health services and these should be free of charge and provided by public funds.	The Polish health system is based on a social insurance system by a National Health Fund (NFZ) through 16 sickness funds. The manufacturer provides a submission to the Ministry of Health that provides details of the decision problem, clinical effectiveness, cost-effectiveness and impact on the health system. The Ministry of Health refers this to AHTAPol and the submission is analysed by the AHTAPol analytical team using the Polish Guidelines for the conduct of Health Technology Assessment. The Analytical Team will revise the submission and provide a report. The appraisal process is separate and performed by the Consultative Council that is chaired by the President of AHTAPol. The Consultative Council takes into account the wider context specific judgements. The President of AHTAPol provides the final recommendation that is passed to the Ministry of Health. The Minister of Health decides the final decision for inclusion on the list.	The HTA process is stipulated by law to take only 45-60 days to final recommendation.	(AHTAPol, 2011) (Leopold and Vogler, 2009)
Portugal	The reimbursement system is set within the National Health Services (SNS), which is funded through general taxation. The National Authority of Medicines and Health Products (INFARMED) is a government agency that was established in 1993. There is a legal framework for the reimbursement of medicines and this is set out in Law No.118/92 June 25. INFARMED concerns all elements of drug regulation with the exception of medicine pricing, evaluating, authorising, regulating and control	INFARMED's main aim is to ensure the quality, safety and efficacy of medicines and the quality, safety of health products in order to avoid the risks of their use while ensuring adequate standards of public health and consumer's protection. The Portuguese Constitution (Seventh Revision, 2005) states that "everyone has the right to health...by means of a universal and general health service which with regard to the economic and social situation of citizens who use it, shall tend to be free of charge.'	The manufacturer must submit to the Directorate-General for Economic Activities (DGEA) following marketing authorisation to obtain a maximum price for the medicine. The DGEA is a government organisation that has responsibility for its administrative tasks (self governance). Pricing is undertaken by DGEA and reimbursement recommendations are made by INFARMED, although these two processes are closely linked for outpatient medicines. The manufacturer agrees a maximum price and then applies to the Ministry of Health/INFARMED for reimbursement. The application is screed	INFARMED is required to process an application within 90 days for medicines, 75 days for generics. The deadline is suspended when the applicant is notified that they are required to submit additional information. INFARMED is accountable to the Ministry of Health.	(INFARMED, 2011) (Vogler and Leopold, 2009) (PPRI, 2008a)

	of human medicine products, including medicinal devices and cosmetics. Medicine pricing is performed by the Directorate-General for Economic Activities (DGEA) prior to an application for reimbursement.		by INFARMED and if necessary clarification is gained from the manufacturer. The pharma-therapeutic submission is analysed by external pharmacologists to determine the added therapeutic value in comparison with existing alternatives. Economists then review the pharmacoeconomic evaluation. If there is no therapeutic advantage the economic evaluation is based on an evaluation of the prices. If the medicine demonstrates an added therapeutic value, a economic evaluation is provided that has followed the INFARMED guideline. The INFARMED board makes a recommendation on whether to grant reimbursement. The Ministry of Health makes the final recommendation for inclusion on the list.		
Spain	The National Health Service was established in Spain in 1986 under the General Health Law. The health system is decentralised and control given by 17 autonomous regions. The reimbursement and pricing decisions are made at the national level involving the Ministry of Health, Directorate General of Pharmacy and Health Products role established in 2003. The criteria considered by the Ministry of Health are contained in Art 89. Of Pharmaceutical Law – Public financing procedure, 2006. The Spanish Agency for Medicines and Health Products was established in 1998 and the Inter-ministerial Commission for Pharmaceutical Prices in 2003.	The Spanish Constitution (1978) states that public authorities should maintain a public social security system for all citizens guaranteeing adequate social assistance and benefits in situations of need, recognising the right to protection of Health, through preventative services and the provision of benefits and services. The law states that public authorities should co-operate with the common aims of providing citizens with the right to health protection, common goal of ensuring equity, quality and social participation (Law 16/2003 May 28). The Spanish Agency for Medicines and Health Products is a specialised technical agency performing evaluation, registration, licensing, inspecting, monitoring and control of medicinal products for human and	The Ministry of Health initiates the procedure once they have received an application from the manufacturer on the technical and economic characteristics of the medicine. The Spanish Agency for Medicines and health Products provides a report on the clinical utility of the medicine. The manufacturer must also provide all necessary information to the Inter-ministerial Price commission that has representatives from the autonomous regions. The Commission agrees a maximum price with the manufacturer. The Minister of Health makes the final listing decision (positive list or negative list.) The regions have responsibility for implication of these decisions at this level.	The Directorate General of Pharmacy and Health Products, Ministry of Health is responsible for co-ordinating the reimbursement decision. The Minister of Health makes the final reimbursement decision.	(Directorate General of Pharmacy and Health Products, 2011) (Spanish Medicine and Health Products Agency, 2011) (Vogler et al., 2009a)

		veterinary health products, cosmetics and personal care products, and conducting economic analysis for the assessment of these products, subject to the executive powers of the regions. Pharmaceutical coverage is characterised as a high coverage and rapidly accessible country. In 2010 two new laws were issued to reduce expenditure to ensure NHS sustainability which included measures to reduce prices and reference price modifications (Ferre, 2011).			
Sweden	The Dental and Pharmaceuticals Benefits Board was established in 2008 to integrate medicines and dental care in one agency. The agency use to be known as the Pharmaceutical Benefits Board (LFN), which was established in 2002. The TLV agency is a central government agency whose legal remit is to determine whether a pharmaceutical product or dental care procedure shall be subsidised by the state. The TLV makes decisions for outpatient medicines and dental treatments.	The mission of the TLV is to examine which medicines, medical devices and dental care treatments will be subsidised by society. The agency makes decisions on the reimbursement and price for substitutable medicines. The main consideration is with attaining value for money whilst considering other criteria The Swedish government subsidises medicines for various reasons but particularly to ensure universal access to high quality, effective medicines.	The manufacturer must submit an application for pricing and reimbursement. The TLV determines whether the medicine should be eligible for inclusion in the "high-cost threshold". There are many medicines included in the high-cost threshold and includes tax subsidised medicines where the state reimburses a proportion of the cost. The Pharmaceutical Benefits Board makes the final reimbursement decisions and these are mandatory. The decisions made by the Board are on the basis of Praxis. Praxis is the process by which a theory, lesson or skill is enacted, realised or practices. Each decision made by the TLV allows further interpretation of the legislation and evolution through experience. The County Councils implement the decisions for outpatient medicines.	The TLV aims to provide notification of the price and reimbursement of a medicine within 180 days of the receipt of the application. The TLV generally aims to complete the process within 120 days. The TLV is accountable to the Ministry of Health and Social Affairs.	(TLV, 2011) (TLV, 2010a) (LFN, 2007) (LFN, 2003)
Switzerland	The Federal Office of Public Health (FOPH) is part of the Department of Home Affairs (FDHA). The FOPH is the integrated centre for	The aim of the FOPH is to promote people's health skills and enable them to take responsibility for their own health and health behaviour.	In Switzerland, all of the population must purchase health insurance which provides reimbursement for medicines. The insurers will pay for medicines that are	The FOPH is accountable to the Federal Department for Home Affairs (FDHA). The reimbursement application	(Federal Office of Public Health, 2011)

	excellence for health. It is responsible alongside the 26 cantons for public health and development of the national health policy. The FOPH is responsible under the ACT 117FC to regulate health and accident insurance. The FOPH provides the final recommendation for inclusion in the Pharmaceutical Specialities List (SL-list) for reimbursement. The FOPH is informed by the Federal Drug Commission that was established in 1995 and consists of scientific experts and stakeholders. It provides advice through consideration of evidence for inclusion in the speciality list.	The FOPH also aims to shape the national structural framework in such a way that health promotion, prevention, health protection, care and palliation of illness and accidents can be implemented in an integrated way that provides the greatest possible health gains to everyone. The aims of the health insurance law (KVG) are to achieve high quality at the lowest possible cost to ensure access to medical care.	included in the basic list of medicines reimbursed. The manufacturer submits an application to the Federal Office of Public Health (FOPH/BAG) which is then considered by the Federal Drug Commission. The Federal Drug Commission which is an expert body reporting initial recommendations to the FOPH. The FOPH provides the final decision for reimbursement and pricing applications for inclusion in the Pharmaceutical Specialities List (SL list). Citizens of Switzerland can access these medicines through their basic health insurance which can be used when the medicines are dispensed through community pharmacies, hospital pharmacies or dispensing doctors.	to final decision usually takes around 4 to 5 months.	(Paris and Docteur, 2007)
United Kingdom – England	The National Institute for Health and Clinical Excellence (NICE) provides guidance, sets standards and manages a national database to improve people's health and prevent and treat ill health. NICE was setup on the 1st of April 1999 to ensure everyone has equal access to medical treatments and high quality care from the NHS regardless of where they live in England and Wales. The Centre for Health Technology Evaluation develops guidance for the use of new and existing medicines, treatment and procedures within the NHS.	NICE was set up on 1 April 1999 to ensure everyone has equal access to medical treatments and high quality care from the NHS, regardless of where they live in England and Wales. NICE's technology appraisals programme makes recommendations about the use of medicines in the NHS, based on how well a medicine works, and whether it offers value for money compared to existing treatments (cost-effectiveness). The NHS is legally obliged to found and resource treatments recommended by NICE's technology appraisals. The Chairman of NICE Sir Michael Rawlins states that "NICE is a national organisation for providing guidance on promoting good health and preventing ill health".	The NICE recommendations apply to England and Wales and are enforceable within three months of the publication of the appraisal. The NHS providers are required by direction of the Secretary of State to provide funding for medicines recommended under the Single Technology Appraisal (STA) and Multiple Technology Appraisal (MTA) processes. NICE is not directly responsible for the implementation of the recommendations and this is undertaken through the NHS providers and funders. The NHS bodies need to assess how much the medicine guidance will cost to implement and must plan for provide these by identifying and releasing funding. There are two forms of technology appraisal for medicines: a Multiple Technology Appraisal (MTA) that covers more than one technology for more than one indications and the Single Technology Appraisal (STA) that covers one	The MTA process aims to complete in 54 weeks and the STA process aims to complete with 37 weeks. NICE is a Special Health Authority. They are an arms length body of the NHS. The Board and Senior Management Team set the strategic direction and ensure financial stewardship and corporate governance.	(NICE, 2011) (NICE, 2009b) (NICE, 2009a) (NICE, 2008)

			technology for one indication. STA process: The Department of Health refers a list of appraisal topics and consultees and commentators are identified. Consultees can submit evidence during the appraisal, comment on the appraisal documents and appeal against the appraisal committee's final recommendations. Commentators are invited by NICE to take part in the appraisal process and comment on various documents produced during the process. The scope is prepared by the Department of Health and consultees and commentators are requested to comment on the draft scope. The manufacturer is invited to provide an evidence submission and consultees can also submit a statement on the potential clinical and cost effectiveness of the treatment. NICE commissions and independent academic centre to technically review the evidence submission and prepare an Evidence Review Group (ERG) report. An evaluation report is prepared for the appraisal committee that includes the ERG report, written submissions, patient expert personal statements, clinical specialist personal statements and comments on the ERG report. The independent appraisal committee considers the evaluation report and evidence from nominated clinical experts, patients and carers. The committee discussions are held in public. The appraisal committee makes a provisional recommendation. An Appraisal Consultation Document (ACD) is produced if the recommendation is more restrictive than the licensed indication of the medicine. The consultees have four weeks		

			to comment. The appraisal committee then considers the comments on the ACD and the final recommendation is made in the Final Appraisal Determination (FAD). Consultees can appeal against the final recommendations in the FAD. If there are no appeals and the appeal is not upheld the final mandatory recommendations are made by NICE. The MTA process is similar to the STA process up to the point of evidence submission. NICE commissions an independent academic centre (Assessment Group) to review the published evidence on the technology and prepare an assessment report. The Evaluation report includes the assessment report, written submissions, patient expert statements, clinical specialists and comments received on the assessment report. The appraisal committee holds its deliberation in public. The committee makes the provisional recommendation in an ACD. The appraisal committee considers the comments on the ACD and a Final Appraisal Determination (FAD) is produced. Consultees can appeal against the final recommendations.		
United Kingdom - Scotland	The Scottish Medicines Consortium (SMC) was established in 2001 by the 15 Health Boards. Funding for public provision is funded through taxation in Scotland.	The aim of the agency is to accept those newly licensed drugs which clearly represent good value for money and reduce postcode prescribing.	Provides one stage advice to the health boards and Area Drug Therapeutic Committees with regards value for money. The health boards choose whether to include the medicine following advice from the SMC. Manufacturer is free to set price prior to the evaluation by the SMC.	NHS Scotland and the Ministry of Health.	(SMC, 2011)

Box A3.1: Chapter 3 appendix references

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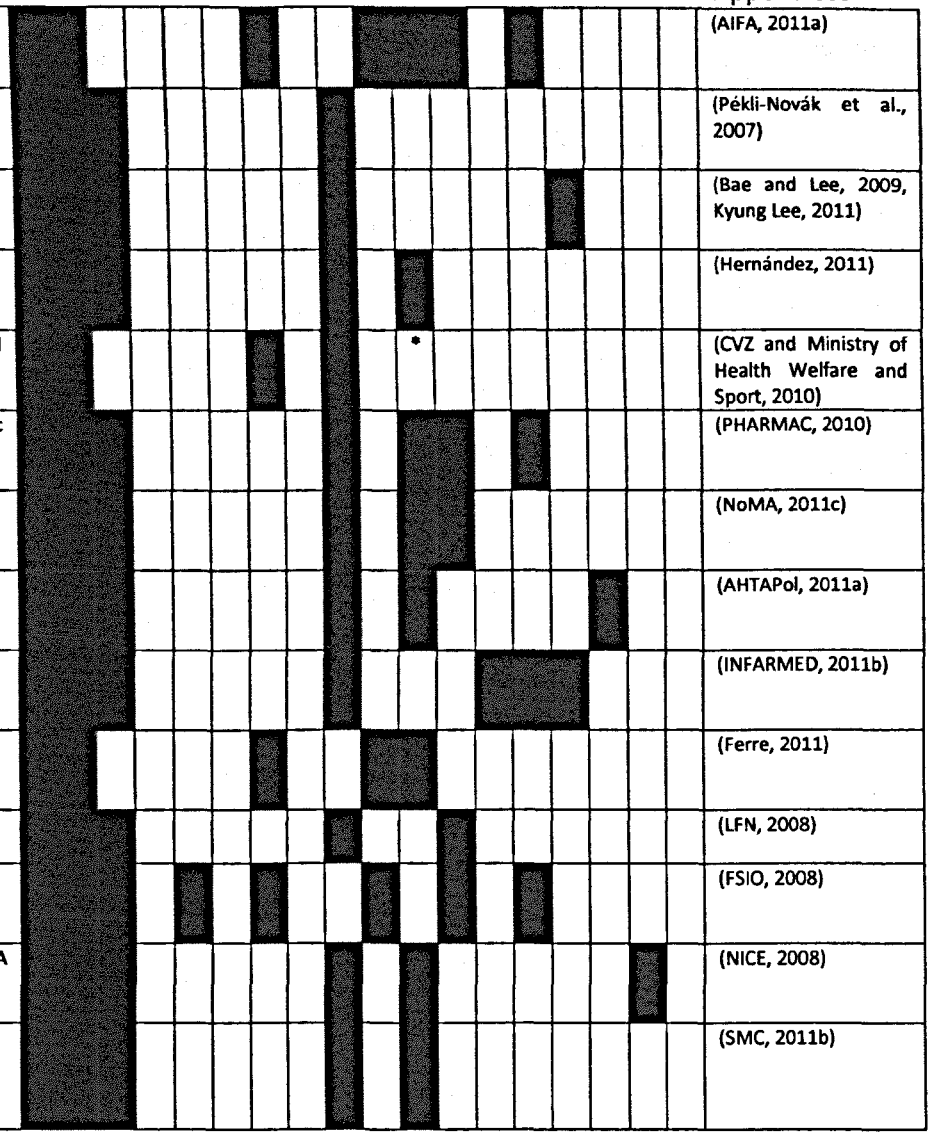
Chapter 4 appendix

Table A4.1: Technology Decision Level (source: reproduced from Hutton et al. 2006)

	Assessment (1)	Decision (2)	Outputs and Implementation (3)
Constitution and governance	Consultation and involvement of stakeholders	Who makes the decision	Appeal and dissent
Methods, processes	Methodology	Decision-making process	Implementation and communication
Use of evidence	Evidence-base for assessment	Evidence base and additional influences on decision	Monitoring and reappraisal
Transparency, accountability	Presentation and communication of assessment results	Content and documentation of the decision	Evidence of impact of the decision

Table A4.2: Information required in Manufacturer submission

Country, (Institutions), Committee or Assessment team	Types of medicines assessed	Manufacturer required submission	Third party independent assessment	Information required in manufacturer submission																		References
				Description of medicines	Clinical efficacy and safety	Clinical effectiveness	Applicability	Appropriateness	Usability	Added therapeutic	ASMR and SMR	Cost-effectiveness	Cost-effectiveness	Budget Impact	Forecast of number of	Proposed maximum price	Prices in other	Completed assessments	Organisational	Equity and equality	Any other relevant	
Australia (PBAC)	All new medicines including vaccines (IP & OP)	Yes	No	■	■	■						■		■							■	(PBAC, 2008)
Austria (HVB) Pharmaceutical Evaluation Board (HEK)	New medicines for outpatient use (OP) [PPRI report]	Yes	No	■	■					■		■										(Austrian Federation of Social Insurance Institutions, 2004)
Belgium (NIHDI CRM) NIHDI staff	New medicines (IP & OP) [PPRI Report]	Yes	No	■	■	■	■		■	■		■		■								(KCE, 2008, Adriaens and Soete, 2010)
Canada (CADTH CDR) - Clinical Review Team	New medicines excluding submissions for oncology medicines (IP & OP)*	Yes	Yes clinical review	■	■	■						■		■								(CADTH, 2010)
Denmark (DMA) – DMA staff	New medicines (OP list) [PPRI Report]	Yes	No	■	■					■			■	■								(Danish Medicines Agency, 2008)
Finland (PPB) – Expert Committee	New medicines (OP list) [PPRI Report]	Yes	No	■	■					■		■			■		■					(PPB, 2011)
France (HAS) – HAS staff	All new medicines (IP & OP) including vaccines	Yes	No	■	■						■											(Rochaix and Xerri, 2009)
Germany (G-BA)	New medicines (IP & OP), excludes lifestyle medicines not available on prescription only.	Yes	Yes economic analysis	■	■					■				■								(Federal Joint Committee, 2011a)
Ireland (Corporate Pharmaceutical Unit) and NCPE	New prescription only medicines selected on basis of budget impact (IP & OP)	Yes	No	■	■	■						■		■				■				(NCPE, 2009)
Israel (Ministry of Health) Medical Technologies Administration	New medicines submitted for inclusion in the Benefits Basket (IP & OP)	Yes	No	■	■	■						■		■								(Ministry of Health, 2010)

Italy (Pricing and Reimbursement Committee CPR)	All new medicines (IP & OP) [PPRI Report]	Yes	No		(AIFA, 2011a)
Hungary (Technology Appraisal Committee) Office for Health Technology Assessment (OHTA)	New medicines (IP & OP) [PPRI Report]	Yes	No		(Pékli-Novák et al., 2007)
Korea (HIRA) - HIRA staff	New medicines (IP & OP)	Yes	No		(Bae and Lee, 2009, Kyung Lee, 2011)
Mexico (General Health Council) Interinstitutional sub committee	New medicines (IP – Catalogue of inputs, OP – Basic formulary)	Yes	No		(Hernández, 2011)
Netherlands (CVZ) - Pharmaceutical Assistance Commission (CFH)	New medicines (IP CVZ process and OP CVZ process)	Yes	Yes for added therapeutic value report		(CVZ and Ministry of Health Welfare and Sport, 2010)
New Zealand (PHARMAC) – Pharmacology and Therapeutics Advisory Committee (PTAC)	New medicines (OP & Some IP medicines) plus separate Pharmaceutical Cancer Treatments (PCTs)	Yes	Yes if economic analysis absent		(PHARMAC, 2010)
Norway (NoMA) – NoMA staff	All new medicines (OP, not IP – decided by hospital formularies) [PPRI Report]	Yes	No		(NoMA, 2011c)
Poland (AHTAPol) – AHTAPol Analytic team	All new medicines (OP, IP medicines includes but decision made within hospitals) [PPRI Report]	Yes	No		(AHTAPol, 2011a)
Portugal (INFARMED) External economists and Pharmacologists	New medicines (OP & IP)	Yes	No		(INFARMED, 2011b)
Spain (Ministry of Health) – Directorate General for Pharmacy and Health Products	New medicines (OP & IP)	Yes	No		(Ferre, 2011)
Sweden (TLV) – TLV staff	New medicines (OP – only covered by Pharmaceutical Benefits Scheme) [PPRI Report]	Yes	No		(LFN, 2008)
Switzerland (Federal Office for Public Health) FOPH staff	New medicines (OP & IP)	Yes	No		(FSIO, 2008)
England (NICE) – NICE staff Evidence Review Group or assessment group	New prescription only medicines selected for appraisal by the Secretary of State (excludes vaccines) (IP & OP)	Yes	Yes for MTA process		(NICE, 2008)
Scotland (SMC) – New Drugs Committee (NDC)	New prescription only medicines (excluding for diagnosis, vaccines, equivalent to generic at same cost, no patients eligible for treatment in Scotland, if NICE MTA imminent) (IP & OP)	Yes	No		(SMC, 2011b)

*Joint Oncology Drug Review (JODR) based in Ontario reviews oncology medicines separately. *Budget impact should be supplied if exempt, SMC template: http://www.scottishmedicines.org.uk/Submission_Process/Submission_Guidance_and_Templates_for_Industry/Templates-Guidance-for-Submission/Templates-Guidance-for-Submission

Table A4.3: Guidelines for Health Economic analysis

Reimbursement System	Use of Pharmacoeconomics	Type of economic analysis							Perspective	Comparator	Costs	Discount Rate Benefits (%)	Discount Rate Costs (%)	Sensitivity analysis	Reference
		Cost-benefit	Cost-utility	Cost-effectiveness	Cost-minimisation	Cost-consequence	Cost-value analysis	Efficiency Frontier							
Australia (PBAC)	Mandatory for new medicines		P						Societal	Standard treatment	Direct and indirect	5	5	Deterministic SA	(PBAC, 2008)
Austria (HEK)	Mandatory for new medicines with added therapeutic value or no alternative								Justified	Standard treatment	All direct and indirect	5	5	Deterministic /probabilistic SA	(IPR, 2006)
Belgium (CRM)	Mandatory for new medicines with added therapeutic value								HC	Relevant alternative	Direct	1.5	3	Probabilistic SA	(KCE, 2008)
Canada (CADTH CDR)	Mandatory for new medicines		P						HC & SS	Usual care	Direct costs + SS	5	5	Deterministic /Probabilistic SA	(CADTH, 2006)
Denmark (DMA)	Optional								Societal	Not reported	Direct + indirect	d	d	Not reported	(Alban et al., 1997)
Finland (PPB)	Mandatory for new medicines								Societal	Commonly used	Direct + indirect	3	3	SA – type not specified	(Ministry of Social Affairs and Health, 2009)
France (HAS)	Not required for HAS submission for new medicines														
Germany (G-BA)	Only required if arbitration cannot obtain an agreement on price							P	HC (SHI)	All relevant alternatives	Direct costs	3	3	Deterministic/ Probabilistic SA	(IQWIG, 2009)
Ireland (CPU/NCPE)	Mandatory requirement for high budget impact medicines		P						HC +SS	Routine care	Direct costs	4	4	Deterministic/ Probabilistic SA	(HIQA, 2010)
Israel (MTA)	Mandatory requirement for new medicines		P						HC	Standard care	Direct costs	3	3	SA – type not specified	(Ministry of Health, 2010)

Italy (AIFA)	Optional recommended for medicines with added therapeutic value		Societal	Most widespread care	Direct + indirect	3	3	Deterministic /Probabilistic SA	(Capri et al., 2001)
Hungary (TAC)	Mandatory for new medicines		Justified	Standard therapy	Perspectiv e depend	5	5	Deterministic SA	(Szende et al., 2002)
Korea (HIRA)	Mandatory for new medicines		Societal	Most prevalent alternative	Direct + indirect	5	5	Deterministic /Probabilistic SA	(HIRA, 2006)
Mexico (GHC)	Mandatory for new medicines		HC	Routine care	Direct costs	5	5	Deterministic /Probabilistic SA	(General Health Council, 2008)
Netherlands (CVZ)	Mandatory for medicines meeting criteria +		Societal	Treatment in practice	All Direct and Indirect	1.5	4	Deterministic /Probabilistic SA	(CVZ, 2006)
New Zealand (PHARMAC)	Optional for manufacturer but is a requirement and PHARMAC will provide		HC	Treatment replaced	Direct costs	3.5	3.5	Deterministic /Probabilistic SA†	(PHARMAC, 2007)
Norway (NoMA)	Mandatory pharmacoeconomics submission for new medicines except✚		Societal	Most prevalent treatment	Direct + indirect	2.5-5	2.5-5	Deterministic SA	(NoMA, 2005)
Poland (AHTAPol)	Mandatory requirement for new medicines		Societal	Relevant treatment replaced	Direct + indirect	3.5	5	Deterministic /Probabilistic SA	(AHTAPol, 2009)
Portugal (INFARMED)	Mandatory for new medicines		Societal	Common practice treatment	Direct + productivi ty	5	5	Deterministic /Probabilistic SA	(INFARMED, 1998)
Spain (Ministry of Health)	Not required		Societal	Standard current practice	Direct + indirect	3	3	Deterministic /Probabilistic SA	(López-Bastida et al., 2010)
Sweden (TLV)	Mandatory for new medicines		Societal	Most appropriate alternative	Direct + indirect	3	3	SA stated – type not specified	(LFN, 2003)
Switzerland (FOPH)	Optional								
England (NICE)	Mandatory required for new medicines		HC+SS	Routinely used best practice	Direct + indirect	3.5	3.5	Deterministic and/Probabili stic SA	(NICE, 2008)

Scotland (SMC)	Mandatory required for new medicines		P				HC+SS	Treatment replaced	Direct costs	3.5	3.5	Deterministic SA	(SMC, 2011b)

Table A4.4: Communication of assessment of evidence

Country and agency/institution	Details of communication of assessment	Details of appraisal	Website address
Australia (PBAC)	Details of the decision outcomes are provided in documents alongside the recommendation but no separate assessment document. The decision outcome document is called the Public Summary Document (PBAC, 2011).	Yes	http://www.health.gov.au/internet/main/publishing.nsf/Content/public-summary-documents-by-meeting
Austria (HEK)	The reasons for the decisions are provided when these deviate from the manufacturers proposed use (Austrian Social Security, 2011).	Yes	N/A
Belgium (CRM)	The evaluation report contains details of the assessment including therapeutic value and economic analysis (Class 1 added therapeutic value) is provided on the website alongside the Ministerial decision (NIHDI, 2011).	Yes	http://www.inami.fgov.be/inami_prd/ssp/cns2/pages/SpecialityCns.asp
Canada (CADTH, CDR)	CDR provides a summary of the assessment that guides the decision outcome on the website of the CDR called the CEDAC Final Recommendation (CADTH, 2011b).	Yes	http://cadth.ca/en/products/cdr
Denmark (DMA)	Details of the appraisal are provided on the website in the minutes but not in the form of a specific report of the decision and these documents are called Minutes of the Reimbursement Committee (Danish Medicines Agency, 2011).	Yes	http://laegemiddelstyrelsen.dk/en/topics/statistics,-prices-and-reimbursement/reimbursement-of-medicines/the-reimbursement-committee/minutes
Finland (PPB)	The assessment report is not provided on the website and there are no details of the deliberations (Ministry of Social Affairs and Health, 2011b).	No	N/A
France (HAS)	Details of the assessment are provided by HAS alongside the appraisal of the evidence detailing the decision on the SMR and ASMR called the Summary Opinion (HAS, 2011a).	Yes	http://www.has-sante.fr/portail/jcms/c_5268/medicaments?cid=c_5268
Germany (G-BA)	The Federal Joint Committee includes a tracking system which includes summary documentation, supporting reasons for the decision and the decision text. The details of	Yes	http://www.g-ba.de/informationen/beschluesse/zum-unterausschuss/2/sortiert-nach/beschluss.DATUM/absteigend/ab/0/#1340/

	the manufacturer dossier are included but excluding any commercially confidential information (Federal Joint Committee, 2011b).		
Ireland (Corporate unit and NCPE)	A summary of the deliberations and items from the assessment are included in a report that is published on the NCPE website. This is called the Economic Evaluation (NCPE, 2011b).	Yes	http://www.ncpe.ie/category.php?cid=33
Israel (Medical Technologies Administration)	Details of the assessments and appraisal are not published only the decision and no details of the deliberations (Greenberg et al., 2009).	No	N/A
Italy (Pricing and Reimbursement Committee)	The assessment report for reimbursement is not published on the website or the deliberations (AIFA, 2011a).	No	N/A
Hungary (Technology Appraisal Committee)	The assessment report is not published on the website or the deliberations	No	N/A
Korea (HIRA)	The manufacturer submission nor the HTA is published on the website but details of the HTA report are shared with the manufacturer throughout the process.(Yang, 2009).	No	N/A
Mexico (General Health Council)	The assessment report is not published and details of the listing recommendation are only provided (General Health Council, 2011b).	No	N/A
Netherlands (CVZ)	The advice is published on the website including the Commission for Pharmaceutical Assistance (CFH) report of the added therapeutic value but no manufacturer submission is published (CVZ, 2011b).	Yes	http://www.cvz.nl/publicaties/cfhrapporten
New Zealand (PHARMAC)	The decisions are produced in a schedule. The Technology Assessment Reports are not all published because of the commercial sensitivity of some of the data. The agency provides some TARs. The Pharmacology and Therapeutics Advisory Committee publishes the minutes which include discussion of some of the details of the assessment in the discussion sections (PHARMAC, 2011c).	Yes	http://www.pharmac.govt.nz/healthpros/EconomicAnalysis/CUAs
Norway (NoMA)	The minutes of the blue prescription	Yes	http://www.slv.no/templates/InterPage 16445.aspx?filterBy=CopyToMedecs

	committee are provided on the website with discussions of details of the assessment (NoMA, 2011c).		
Poland (AOTM)	The website contains a document summarising the considerations of the Consultative Council (CC) called the Position of the Consultative Council. This includes details of the assessment and recommendations (AHTAPol, 2011c).	Yes	http://www.aotm.gov.pl/index.php?id=112
Portugal (INFARMED)	The assessment is not published on the website. The listing recommendations for the considerations are only published (Maria, 2010).	No	N/A
Spain (Ministry of Health)	The manufacturer submission or assessment is not published on the website of the Ministry of Health	No	N/A
Sweden (TLV)	The assessment and deliberations are provided with the listing recommendation on the agency website and this is called the decision document (TLV, 2011a).	No	http://www.tlv.se/beslut/beslut-lakemedel/generell-subvention/?page=3
Switzerland (Federal Office for Public Health)	The assessment is not provided on the website nor is the manufacturer submission.	Yes	N/A
England and Wales (NICE)	Comprehensive details of the manufacturer submission are provided for STA, executive summary for MTA. Assessment report and Evidence Review Group reports provided for the website which is published, other stakeholder submission. These are date stamped and the process history is provided on the website (NICE, 2011e).	Yes	http://www.nice.org.uk/guidance/ta/published/index.jsp
Scotland (SMC)	The details of the assessment are provided in the advice document that is presented on the website. This is called the SMC advice document (SMC, 2011e).	Yes	http://www.scottishmedicines.org.uk/SMC_Advice/Advice_Directory/SMC_Advice_Directory

Table A4.5: Composition of appraisal committees

Country and agency/institution	Appraisal Committee name	Number of members	Medical Practitioners (specialists,	Pharmacologist	Pharmacists	Patient representatives/Public	Health Economists/Economist	Medical Association	Other Government Ministry	Social health Insurance	Pharmaceutical industry	Federal Representatives	Ministry of Health	Public members	Legal representative	Other commercial organisations	Regions Health care planners	Reimbursement	HTA expertise	References
Australia (PBAC)	Pharmaceutical Benefits Advisory Committee*	18	■	■	■	■														(PBAC, 2008)
Austria (HEK)	Medicines Evaluation Committee (HEK)	20	■	■	■			■		■		■								(Austrian Federation of Social Insurance Institutions, 2004)
Belgium (CRM)	Drug Reimbursement Committee (CRM)	30	■	■	■				†		†									(Adriaens and Soete, 2010)
Canada (CADTH, CDR)	Canadian Expert Drug Advisory Committee (CEDAC)	13	■	■	■	■								■						(CADTH, 2011a)
Denmark (DMA)	Reimbursement Committee	7	■														■			(DMA, 2011b)
Finland (PPB)	Pharmaceutical Pricing Board (PPB)	7	■	■	■		■			■					■					(Ministry of Social Affairs and Health, 2011a)
France (HAS)	Transparency Committee (TC) ¥	20	■	■	■															(HAS, 2011b)
Germany (G-BA)	Federal Joint Committee (G-BA)	14	■			†				■										(Federal Joint Committee, 2010)
Ireland (Corporate Pharmaceutical Unit & NCPE)	Products Committee/NCPE ∞	-	■		■		■													(NCPE, 2011a)
Israel (Medical Technologies Administration)	Public National Advisory Committee (PNAC)	20	■				■		■				■	■						(Greenberg et al., 2009)
Italy (Pricing and Reimbursement Committee)	Pricing and Reimbursement Committee (CPR) §	12	■		■		■		■											(AIFA, 2011b)
Hungary (Technology Appraisal Committee)	Technology Appraisal Committee (TAC)	11	■		■			■	■	■								†		(Gulácsi et al., 2009)
Mexico (General Health Council)	Council	21	■					■	■	■			■							(General Health Council, 2011a)

Netherlands (CVZ)	Appraisal Committee (ACP) ᵍ	8		(CVZ and Ministry of Health Welfare and Sport, 2010)
New Zealand (PHARMAC)	Pharmaceutical Management Agency (PHARMAC) Board ∏	5		(PHARMAC, 2011b)
Norway (NoMA)	Blue Prescription Board	7		(NoMA, 2011b)
Poland (AHTAPol)	Consultative Council (CC)	12		(AHTAPol, 2011b)
Portugal (INFARMED)	INFARMED Board	5		(INFARMED, 2011a)
Spain (Ministry of Health)	Ministry of Health	-		(Vogler et al., 2009)
Korea (HIRA)	Drug Reimbursement Committee (DREC)	18		(Bae and Lee, 2009, Yang, 2009)
Sweden (TLV)	Dental and Pharmaceutical Board (TLV)	6		(TLV, 2011b)
Switzerland (Federal Office for Public Health)	Federal Drug Commission (FDC)	20		(Paris and Docteur, 2007)
Scotland (SMC)	Scottish Medicines Consortium (SMC) Board ≈	38		(SMC, 2011c)
England and Wales (NICE)	Technology Appraisal Committee (TAC)	33		(NICE, 2011a)

* There is also the Economics Sub-Committee (ESC) that advises on the economic analyses and technical aspects of these analyses which includes health economists, clinical specialists, epidemiologists, general practitioners, public health academics, Health Scientists, Pharmacologist and one industry representative

† These are consultative members but are not voting members.

¥ The Economics Committee for Health Products (CEPS) assesses the price covered by the compulsory health insurance following the TC committee's appraisal. The CEPS consists of 26 members consisting of representatives from Social Security, Health, Competition, Consumption and Fraud, Competitiveness industry and services, National Health Insurance, National Fund of Agricultural and Mutual Assistance Association, Union representatives, Health Care Delivery and Research.

ᵒᵒ The National Centre for Pharmacoeconomics provides an appraisal and recommendation and includes 10 members. The members include pharmacologists, pharmacists, epidemiologists, mathematicians, statisticians and health economists.

§ The Scientific Technical Commission (STC) provides advice on the added therapeutic value and is composed of 17 members including medical practitioners and pharmacologists.

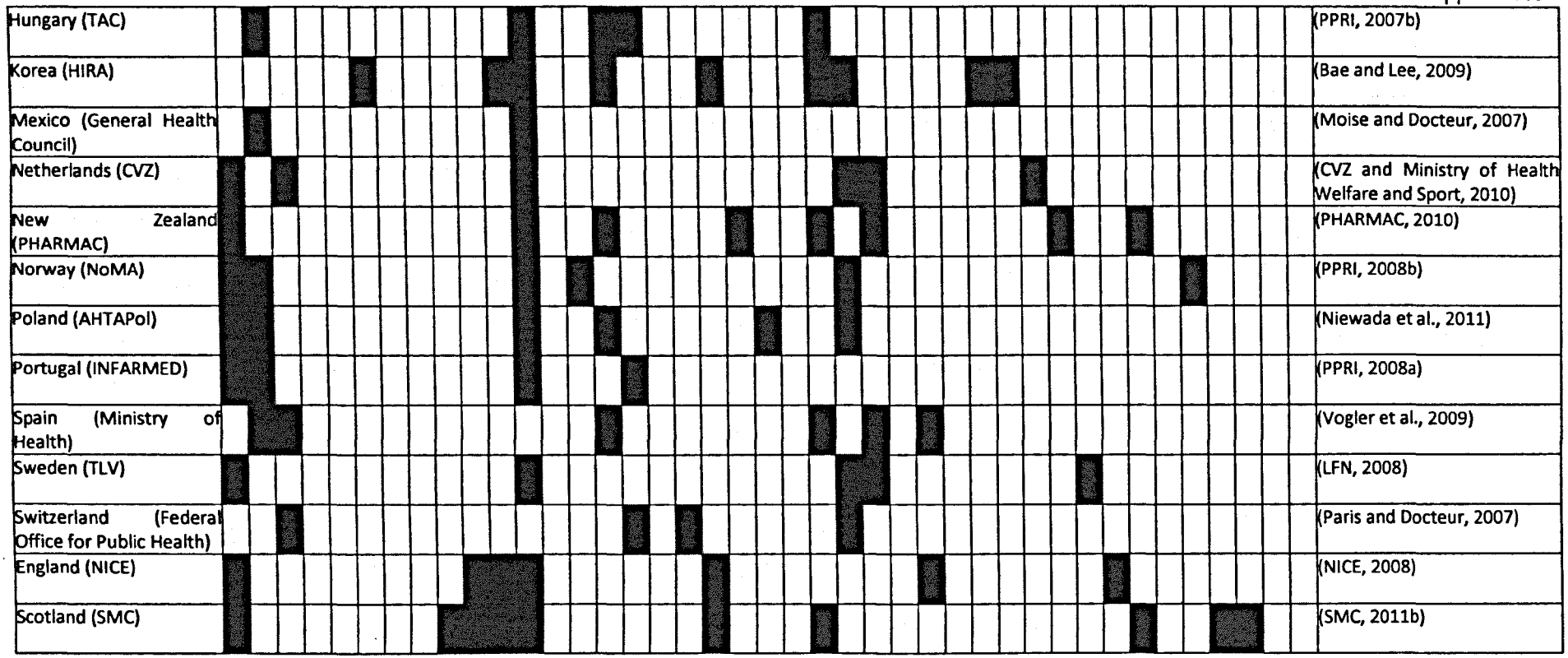
ᵍ The CFH advises the CVZ Board that consists of 3 board members and 6 expert members with knowledge of social security issues. The CFH committee is responsible for the assessment of medicines and consists of 22 members including medical practitioners, pharmacologists, pharmacists, health economists and the Ministry of Health. The CVZ Board may seek advice from the new Appraisal Committee (ACP) which was setup in April 2008 to considers the appraisal of a medicine from a societal perspective. The ACP committee consists of nine members with knowledge in the field of social security, healthcare insurance, scientific, practice and the patient perspective.

∏ The Pharmacology and Therapeutics Advisory Committee (PTAC) is a clinical advisory committee that has a role to provide objective clinical advice to the PHARMAC Board. The committee consists of 12 Medical Practitioners that are nominated by the professional medical bodies.

≈ The New Drugs Committee consists of 21 members and provides advice to the SMC Board on the technical aspects of the assessment. The NDC includes clinicians, pharmacists, health economists, a statistician and two industry representatives.

Table A4.6: Stated factors by institution

Country	Clinical Evidence Factors											Economic Evidence Factors								Non – Evidence Factors																						References
	Clinical -effectiveness	Clinical -efficacy	Added therapeutic value	Improvement in Medical Benefit	Therapeutic value	Clinical usefulness/value	Pharmacological evaluation	Comparative health gain	Substantial improvement in	HRQL inadequately captured.	Uncertainty surrounding the	Cost-effectiveness	Cost-effectiveness (efficiency	Cost-value analysis	Budget impact for the public	Price of the medicine	Comparison of prices and	R&D Cost Criterion	Degree of certainty surrounding	Patient affordability in absence of	Social, organisational	Equity considerations	Alternative medicines present	Severity of medical condition	Need	Nature of disease	Innovative nature of medicine	Life saving technology	International countries medicine	International treatment guidelines	Feasibility	Government priority for Health	Human Value principle of equality	End of life Supplementary	Other relevant special criteria	Patient Perspective	Prolonging treatment or risk of	Differential benefits in different	Bridging to another definitive	Number of patients likely to	Likely development of resistance	
Australia	■							■			■	■			■					■		■	■	■														■			■	(PBAC, 2008)
Austria			■				■					■																														(Austrian Federation of Social Insurance Institutions, 2004)
Belgium (CRM) – Class 1 medicines			■									■			■	■									■																	(Adriaens and Soete, 2010)
Canada (CADTH CDR)	■	■										■																								■						(CADTH, 2010)
Denmark (DMA) – added therapeutic value			■									■				■																										(Danish Medicines Agency, 2008)
Finland (PPB) – Special reimbursement			■									■			■									■	■	■																(PPB, 2011)
France (HAS)				■	■																																					(Grandfils, 2008)
Germany (G-BA)			■										■		■																											(Federal Joint Committee, 2011a)
Ireland (CPU & NCPE)	■										■	■			■								■				■															(NCPE, 2010)
Israel (MTA)									■			■			■								■					■												■		(Ministry of Health, 2010)
Italy (CPR)		■	■									■			■		■		■				■																			(AIFA, 2007)



Hungary (TAC)	(PPRI, 2007b)
Korea (HIRA)	(Bae and Lee, 2009)
Mexico (General Health Council)	(Moise and Docteur, 2007)
Netherlands (CVZ)	(CVZ and Ministry of Health Welfare and Sport, 2010)
New Zealand (PHARMAC)	(PHARMAC, 2010)
Norway (NoMA)	(PPRI, 2008b)
Poland (AHTAPol)	(Niewada et al., 2011)
Portugal (INFARMED)	(PPRI, 2008a)
Spain (Ministry of Health)	(Vogler et al., 2009)
Sweden (TLV)	(LFN, 2008)
Switzerland (Federal Office for Public Health)	(Paris and Docteur, 2007)
England (NICE)	(NICE, 2008)
Scotland (SMC)	(SMC, 2011b)

Table A4.7: Clinical-effectiveness criteria

	Australia	Canada	Ireland	New Zealand	Mexico	Norway	Portugal	Poland	Sweden	England	Scotland
Clinical-effectiveness definition	The comparative clinical effectiveness should be presented as both effectiveness (Australian practice) and toxicity with respect to the magnitude of the clinical effect and clinical importance in comparison with the relevant comparator in Australia.	The clinical effectiveness of the drug should be compared with alternatives in real clinical practice in Canada (when available).	HTA Economic Guidelines: "In the context of drugs, efficacy has been defined as 'clinical outcomes derived from patients' use of a pharmaceutical product in controlled settings, typically randomised control Phase I-III trials'. Expanding this definition to health technologies in general, the efficacy of a health technology relates to its performance under ideal circumstances. In contrast, effectiveness refers to the performance of a technology under normal circumstances, such as in routine clinical practice."	The term is defined as "Benefit of treatment in 'real world' setting."	It is preferable to use measures of effectiveness of health products (E.g. improvements in health achieved in the real field) instead of efficacy measures (E.g. improvements in health achieved in the context of a strictly clinical trial controlled) (if available)	The medicinal product has a scientifically well-documented and clinically relevant effect in a defined, appropriate patient population	Clinical effect should be assessed in terms of effectiveness whenever possible. If this information is not available efficacy can be used. The economic guideline categorises this as: "Effectiveness is a measurement of the beneficial effect of a technology or strategy assessed in normal clinical practice. It is sometimes very difficult to reconcile the methodological precision of a clinical trial with the environment of real clinical practice. In the real world there are many health care providers with different prescribing profiles, writing prescriptions for heterogeneous groups of patients, who are normally not so well informed and more prone to co-morbidity	The guideline specifies that: "Effectiveness data are from pragmatic clinical trials. They can also be obtained from observational studies and databases (including patient registers) collecting information on the use of a given technology. The data should also be collected in the form of a systematic review." The comparators used in the comparison should reflect Polish practice.	The clinical effects of the medicine should be demonstrated. The best evidence includes directly comparative studies with the most relevant comparison alternative.	The NICE glossary defines clinical effectiveness as: "How beneficial a test or treatment is under usual or everyday conditions, compared with doing nothing or opting for another type of care."	The SMC glossary defines clinical effectiveness as "The evaluation of benefit or risk, in a standard clinical setting, using outcomes of importance to the patient."

							and/or the use of drugs that were not studied in the original clinical trials."				
Clinical effectiveness appraised	This is appraised by a systematic search of the evidence and a qualitative interpretation of the magnitude and effect. A medicine may be more or at least as effective for consideration. A medicines that is less effective and more toxic maybe considered for listing. The data is then used in the cost-effectiveness modelling.	A descriptive summary is provided in the decision documentation of the effectiveness when this is available. The data is used in the cost-effectiveness modelling.	A descriptive summary provided and the data on effectiveness is used in the cost-effectiveness modelling.	A descriptive summary of the clinical-effectiveness is documented in the proposal for funding.	There is no categorisation scale for measuring effectiveness.	The categorisation was not identified for the appraisal.	The descriptive assessment of effectiveness or efficacy is used in the economic modelling.	A descriptive summary of the clinical effectiveness is considered.	A descriptive summary of the clinical effectiveness is provided in the decision document.	The clinical effectiveness is provided in the clinical evidence section of the guidance.	A clinical efficacy and clinical effectiveness section is provided in the SMC guidance.
Reference:	(PBAC, 2008)	(CADTH, 2011c)	(HIQA, 2010)	(PHARMAC, 2010)	(General Health Council, 2008)	(NoMA, 2011a)	(INFARMED, 1998)	(AHTAPol, 2009)	(LFN, 2008)	(NICE, 2011d)	(SMC, 2011a)

Table A4.8 Added therapeutic value criteria

	Austria	Belgium	Denmark	Finland	France	Germany	Italy	Netherlands	Spain	Switzerland
Added Benefit/ Added therapeutic value definition	The medical therapeutic value with respect to the efficacy and perception of innovation as defined with respect to specific groups of patients in relation to the therapeutic alternatives.	The therapeutic value of the medicine is the composite evaluation of efficacy (trial results of therapeutic effect), effectiveness (if it is effective in real life practice), adverse side effects, applicability (different subgroups of the population) and ease of use (by care givers or avoiding mistakes and errors) Defined in the Royal Decree 21 December 2001.	The therapeutic effect (value added and adverse effects) are considered in a well defined indication.	The therapeutic value of the medicine should be assessed in comparison to other similar alternatives provided by studies in the marketing authorisation and new studies of the clinical efficacy of the medicine.	The Medical Benefit is assessed based on the severity of the disorder, the clinical effectiveness of the medicine and impact on public health. Improvement in Medical Benefit (ASMR). The ASMR is a score of the added value of the medicine compared to the medicine used in practice.	An additional therapeutic benefit as any patient related outcome such as improvement of health condition, shortening of the duration of disease, improved survival and quality of life (either qualitative or quantitative).	The extent of the therapeutic innovation is considered with respect to availability of existing treatments and extent of therapeutic benefit. The added therapeutic value is considered with respect to the effectiveness, efficacy, pharmacological innovation and technological innovation.	The factors included to assess the therapeutic value are the efficacy, effectiveness, side effects, applicability, convenience, experience and quality of life.	Therapeutic value obtained but no definition found.	The therapeutic value is assessed by considering the efficacy and appropriateness
Level of assessment	The therapeutic benefit is classified under the following categories: 1.Substantial therapeutic benefit in the majority of patients 2.Substantial therapeutic benefit for a subgroup 3. Added therapeutic benefit for the majority of patients 4. Added therapeutic benefit for a subgroup of patients 5. Similar therapeutic benefit for patients 6. No added therapeutic benefit.	Class 1: Medicines with significant therapeutic value Class 2: Medicines with modest or no therapeutic value. Class 3: Generic medicines.	There are no categories of therapeutic value defined by the Danish Medicines Agency.	There is no categorisation of the therapeutic value of the medicine by the PPB.	The SMR is defined as: 1. Major 2. Important 3. Moderate 4. Low 5. Insufficient The ASMR has five levels: I) Major Improvement; (II) Important; (III) Moderate; (IV) Minor and (V) No improvement.	1 - Major improvement in benefit: A significant additional benefit, primarily a cure for the disease, a significant survival time, a long-term freedom/avoidance of serious side effects. 2 - Significant improvement in benefit: A significant additional benefit, moderate life extension, substantial slow down in symptoms, avoidance of serious side effects. 3 - A small additional benefit is when one of the functional benefits shows a moderate reduction in non-fatal symptoms or side effects. 4 - An additional benefit exists but is not quantifiable because there no scientific evidence base is possible 5 - There is no demonstration of	The medicines are considered in comparison to the relevant comparison and ranked: A. No adequate treatment B. Medicines developed for which subgroups are resistant or non-respond. C. Medicine for treatment where recognised treatments already exist. Score C are considered under: C1. Medicines more effective or safer medicine or medicines with a better pharmacokinetic profile compared to existing medicines. C2. Medicines representing a simple pharmacological innovation, medicines with new mechanism of action with a therapeutic	1. Medicines with a therapeutic loss in comparison with other included treatment options; 2. Medicines which have equivalent therapeutic value compared to those of others in the package 3. Medicines with a therapeutic value in comparison to other medicines already in the insurance package.	No evidence of assessment of levels of effectiveness.	The therapeutic value of the medicine should be classified by the Federal Drug Commission on the following levels of innovation: 1. Therapeutic breakthrough 2. Therapeutic progress 3. Savings compared to other medicines 4. No therapeutic progress and no savings 5. Inappropriate for social insurance

						value added benefit. 6 - The benefits of the drug to be evaluated is less than the benefit of the appropriate comparison treatment.	role similar to existing medicines C3. Medicines representing a simple technological innovation e.g. a new chemical substance or medicine with a therapeutic role similar to existing medicines. Medicines are considered with respect to the extent of the therapeutic effect: A. Greater benefits on clinical end-points (mortality, morbidity) or a validated surrogate endpoint B. partial benefit on the disease or limited evidence of greater benefit C. Minor or temporary benefit on some aspects of disease (partial symptom) relief.			
Implications for reimbursement and pricing	Demonstrate added therapeutic value for inclusion in the yellow or green box of the Reimbursement Code. Maximum pricing in relation to EU average price.	Class 2 medicines are set in comparison with international prices and comparator medicines. Class 1 can receive a price premium above the comparator medicines by supply of a pharmacoeconomics analysis. Maximum prices are set depending on class, Class 1: premium price, Class 2: no superior price, Class 3: Lower price.	The price of the medicine must be reasonable in relation to the added therapeutic value. Free pricing operates in Denmark.	The added therapeutic value and costs are taken into account when pricing and reimbursement decisions are made.	The ASMR levels 1-3 relate to a premium price and are categorised as innovative whereas the other groups are categorised similar price or lower by the CEPS institution.	If additional benefit assessed this will be quantified and the price negotiated with the federal association of health insurance funds. If there is no documented additional benefit the medicines will be allocated to the pharmaco-therapeutic comparable drugs in the reference price system.	The clinical therapeutic value determines the negotiation process for pricing in combination with a pharmacoeconomics analysis	If medicines have similar benefits to existing medicines are categorised in 1A of the medicines list. Those medicines with an added therapeutic benefit are categorised in list 1B and require an economic evaluation.	Therapeutic value is taken into account when deciding to list a medicine or not list (negative list).	The medicine must be effective to be included on the reimbursement list.
Reference	(Austrian Federation of Social Insurance Institutions, 2004)	(Adriaens and Soete, 2010)	(Danish Medicines Agency, 2008)	(PPB, 2011)	(Meyer, 2011, Rochaix and Xerri, 2009)	(Federal Joint Committee, 2011a)	(AIFA, 2007)	(CVZ and Ministry of Health Welfare and Sport, 2010)	(Vogler et al., 2009)	(Paris and Docteur, 2007)

Table A4.9: Thresholds across countries

	Explicit threshold range	Implicit threshold range – past decisions	Implicit threshold – WTP	No threshold range identified	References
England and Wales - NICE					(NICE, 2008)
Scotland – SMC					(SMC, 2011b)
The Netherland – CVZ					(CVZ, 2011a, RVZ, 2006)
Australia - PBAC					(Lopert, 2009, Henry et al., 2005)
Canada – CADTH CDR					(Menon and Stafinski, 2009, Rocchi et al., 2008)
Ireland – NCPE & HSE					(Tilson et al., 2010)
Korea – HIRA					(Shiroiwa et al., 2010)
Sweden - TLV					(Persson et al., 2010)
New Zealand - PHARMAC					(Metcalfe and Grocott, 2010, Simoens, 2009)
Austria – HEK					(KCE, 2010)
Belgium – CRM					(KCE, 2008)
Denmark – DMA					(Sorenson, 2009b)
Finland – PPB					(Personal Communication, 2011: Prof Blom)
Hungary – TAC					(Sorenson, 2009a)
Italy – AIFA					(Ettelt et al., 2007)
Israel – MTA					(Greenberg et al., 2009)
Norway - NoMA					(Personal Communication, 2011: Kristun Svanqvist)
Mexico - GHC					No details identified or response.
Poland - AHTAPol					(Sorenson, 2009a)
Portugal - INFARMED					No details identified or response.

Table A4.10: Thresholds and other factors

	Threshold explicit/implicit Cost per QALY			Other Economics		Clinical evidence factors					Non-evidence based considerations															References
	Explicit (range)	Implicit: past decisions	Implicit: WTP	Budget impact	Patient affordability in absence of	Clinical effectiveness/Clinical usefulness	Comparative Health gain	Substantial improvement in extension of life	Differential benefit in different groups	HRQL inadequately captured by QALYs	Bridging to another definitive therapy	Likely development of resistance	Equity considerations	Severity of medical condition	Need	Human value principle of equality	End of life	Innovative nature of medicine	Uncertainty surrounding the evidence	Alternative medicines present	International countries reimbursement	Feasibility	Government priority for health funding	Other special criteria	Patient Perspective	
England and Wales – NICE	£20k – 30k range					+				+							+	+	+							(NICE, 2008)
Scotland – SMC	£20k – 30k range					+		+	+	+	+								+	+				+		(SMC, 2011b)
The Netherland – CVZ	€10k – 80k by severity																									(CVZ, 2011a, RVZ, 2006)
Australia - PBAC		AUS $52.4k Range																								(Henry et al., 2005, Lopert, 2009)
Canada – CADTH CDR						+																			+	(Menon and Stafinski, 2009, Rocchi et al., 2008)
Ireland – NCPE & HSE		€45k		+		+												+	+	+						(Tilson et al., 2010)
New Zealand – PHARMAC		(~NZ40k -200k																								(Metcalfe and Grocott, 2010, Simoens, 2009)
Korea – HIRA			KWN69 m Range	+		+								+					+		+					(Shiroiwa et al., 2010)
Sweden - TLV																										(Persson et al., 2010)

Table A4.11: Decision outcome and status

Final Decision Institution (Final Decisions)	Advisory Recommendation	List type	List Name	Listing Restrictions	Outcome Based Conditional Reimbursement (CED/CTC)	Copayment	References
Australia (PBAC)	Advisory recommendation (Ministry of Health)	Positive list	Schedule of Pharmaceutical Benefits (SPB)	Restricted benefit, authority required	Defer listing pending the provision of certain information on the medicine.	Concessional: Before safety net $5.60 (After safety net: $336 prescription charge = $0) General patients: Before safety net: $34.20 (After safety net: $1317.20 prescription charge = $5.60)	(PBAC, 2008)
Austria (HVB) (Legal List)	Final Decision	Positive list & Negative list	Reimbursement Code (EKO)	Red box – initially referenced priced & Yellow box (disease or age group) require approval by head physician. Light Yellow box (disease or age group) freely prescribed by doctors. General and Individual reimbursement scheme.	No scheme of conditional listing identified.	Flat rate prescription is paid for all medicines	(Austrian Federation of Social Insurance Institutions, 2004, PPRI, 2007a)
Belgium (CRM) (Legal List)	Final Decision	Positive list	Positive list by chapter	Restricted reimbursement: Chapters II – reimbursement for all common indications and prescribers keeps this on file and Chapter IV – reimbursement subject	Coverage with evidence development - The manufacturer must clarify factors through additional data in the list of factors at 18 and 36 months.	5 categories of reimbursement cost sharing A(100%), B(85%, max EU7.20), C(50%, max EU8.90), Cs(40%), Cx(20%).	(Adriaens and Soete, 2010, Gerkens and Merkur, 2010, KCE, 2010)

				to particular reimbursement conditions and requires prior approval by health insurance.			
Canada (CADTH, CDR)	Advisory recommendation (Drug plan)	Positive list	Individual Drug plan formularies	List with criteria to a specific patient population	Defer pending clarification of information	Copayments and deductibles set at a health plan level.	(CADTH, 2010)
Denmark (DMA)	Final Decision	Positive list	General Reimbursement List	General conditional reimbursement (patient groups or disease specific), Individual reimbursement	No scheme of conditional reimbursement identified.	Copayment depending on previous one year expenditure on medicines.	(Danish Medicines Agency, 2008, DMA, 2011a)
Finland (PPB) Law: Health Insurance Act 1224/2004 (Ref: Website)	Final Decision (Government Department)	Positive list	Positive list	Restricted reimbursement, either restricted basic or restricted special.	No conditional listing requirements identified,	Three categories of copayment (100,72,42%)	(Kivioja, 2008, Ministry of Social Affairs and Health, 2005, PPB, 2011)
France (HAS)	Advisory recommendation (Ministry of Health)	Positive list	List of Pharmaceuticals Reimbursed by Social Insurance and List of Pharmaceuticals Reimbursed by Hospitals	Generally no restrictions	Additional observational studies that cover the patient population where uncertainty present.	Copayment of 100%,65%,35%, 15% depending on severity and medical benefit	(Meyer, 2011, Rochaix and Xerri, 2009)
Germany (G-BA) (Legal list Fifth Social Code, § 92)	Final Decision	Negative list	Benefits catalogue Pharmaceutical Directive Drug Policy SGB V	Prescribing restrictions can be set by the Federal Joint Committee (FJC) (patient group to be prescribed).	No scheme of conditional reimbursement identified.	Basic copayment.	(Federal Joint Committee, 2011a, Federal Joint Committee, 2011c, Leverkus, 2011)
Hungary (NHIFA Technology Appraisal Committee) (Legal list Decree of the Ministry of Health 32/2004)	Final Decision	Positive list & Negative list	NHIFA Positive and Negative List	No restrictions stated	No conditional reimbursement. Performance linked reimbursement schemes operate alongside price volume agreements.	Indication based reimbursement rates 100%, 90%, 70% & 50%.	(PPRI, 2007b, Dankó, 2010)
Ireland (Corporate unit and NCPE)	Final Decision	Positive list	Community Drugs Scheme	Restrictions to patient group (NCPE)	No scheme of conditional reimbursement	Copayment depends on scheme from 100%	(Tilson et al., 2010)

					identified.	reimbursed to maximum payment.	
Israel (Medical Technologies Administration)	Final Decision (Government Department)	Positive list	National List of Health Services (NLHS)	No restrictions identified.	No conditional listing requirements identified	Dependent on health plan. Three health plans charge 15% of price minimum 13 NIS. The Clalit health plan charges a set 12 NIS. Medications added before 1998 are charged 10% of maximum price minimum of 12 NIS. There is a chronically ill ceiling of 250 NIS. (HiT, 2009)	(Greenberg et al., 2009)
Italy (AIFA Board) Law no. 326 of November 24, 2003	Final Decision	Positive list	National Pharmaceutical Formulary Group A	AIFA Notes – guidelines for restrictions on patient population or characteristics of the disease	No conditional reimbursement through coverage with evidence development. Conditional treatment continuation operates (Carlson 2010). Performance linked reimbursement introduced since 2006.	Fixed prescription charge called the 'ticket' is present in some regions. Exemptions for 100% reimbursement apply.	(Folino-Gallo et al., 2008, Gori et al., 2010, Jommi, 2009)
Korea (HIRA) Established under article 55 of National Insurance Act	Advisory recommendation (Ministry of Health)	Positive list	Positive List System (PLS)	No restrictions identified.	A limited application of coverage with evidence development for off label medicines but no formal institutionalisation of CED.	Copayment for proportion of cost paid by patient in inpatient (10-20%) of cost, tertiary care and general hospital 50% treatment cost, hospital 40%, Clinic 30% and pharmacy	(Bae and Lee, 2009, Jang, 2010, Kyung Lee, 2011, Moo Lee, 2011)

						30%. A threshold limit of 3 million WON) where no further payment required.	
Mexico (General Health Council), Agreement	Final Decision	Positive list	Basic Formulary and Catalogue of Inputs provides basis for local formularies	No restrictions stated	No details of outcome based conditional reimbursement identified.	Copayment dependent on social insurance institution.	(Moise and Docteur, 2007)
Netherlands (CVZ)	Advisory recommendation (Ministry of Health)	Positive list	Drug Reimbursement System 1B and 2	List 2: a particular condition, within a specific age group, by specialist doctor or special permission required.	Coverage with evidence development for inpatient medicines.	100% covered for added therapeutic value medicines. Those medicines that are equivalent have a maximum reimbursement where some medicines may require an excess between the price and maximum reimbursable.	(CVZ and Ministry of Health Welfare and Sport, 2010, van Halteren, 2011)
New Zealand (PHARMAC)	Final Decision	Positive list	Pharmaceutical Schedule	Restrictions and Special Authority (prescriber has to request subsidy from authority for a named person).	No scheme of conditional outcomes based reimbursement identified.	A complex system depending on patient enrolment to a primary health organisation and eligibility depends on situation and base copayment can range from $3 to $15 per prescription	(PHARMAC, 2010, PHARMAC, 2011a, PTAC, 2010)
Norway (NoMA) Legal Regulations FOR 2007-06-28 nr 814 (Ref: Website)	Final Decision	Positive list	Blue Prescription list	Restrictions to indication or patient group and individual reimbursement can be made.	No scheme of conditional outcomes based reimbursement identified.	38% of the prescription but no more than 520 million per prescription and individuals exempt	(Lovdata, 2009, Ministry of Health and Care Services, 2004, PPRI, 2008b)

						from charge. Certain medicines are covered for 100% such as communicable diseases.	
Poland (AOTM) (Journals of Laws 2008 No.164 item 1027) (Ref: Website, HAI, 2010, Matusewicz, 2009)	Advisory recommendation (Ministry of Health)	Positive list	Reimbursement list	Conditions for provision.	Coverage with evidence development - Temporary financing provided data gathered by AHTAPol recommendation.	The copayment depends on the condition and socioeconomic situation. There are four categories, 100% reimbursed for some treatments and vulnerable groups, lump sum of PLN 3.20, 70% reimbursed for non-life threatening disease and 50% for common ailments. (HAI, 2010)	(Lipska, 2010, Matusewicz and Lipska, 2009, Personal Communication: Ofierska-Sujkowska, 2011)
Portugal (INFARMED) Legal Decree-Law No 129/2005 August and Decree No. 1474/2004, 21 December (outpatient) Decree-Law No.228/2008 25 November (inpatient)	Advisory recommendation (Ministry of Health)	Positive list	Prontuario list	Restrictions for therapeutic indications	No conditional coverage schemes. Other non-outcomes based schemes in operation.	Four types of copayment, Category A 100%,95%, Category B 69%, Category C: 37% and Category D 15%	(PPRI, 2008a, Vogler and Leopold, 2009)
Spain (Ministry of Health – Directorate General) Law: :aw 26/2006 Guarantee and Rational Use of Medicines and Health Products)	Final Decision (Government Department)	Positive list & Negative list	Positive list & Negative list	No restriction evident	No conditional listing requirements identified at a national level.	Cost sharing for patient under 65 is 40% and free for over 65 years. Those medicines treating chronic diseases or life	(Noticias Juridicas, 2011, Vogler et al., 2009, Vallejo, 2009)

						threatening 10% contribution.	
Sweden (TLV) (Legal 2002:160 on Pharmaceutical Benefits)	Final Decision	Positive list	General Subsidy Decisions	Restrictions limited to area or special patient group	Coverage with evidence development where reimbursement is limited in time to make it possible for new data to be provided for example on long term effects or follow up data to check that the medicine is being used according to the restriction.	There is a cost ceiling where the patient never pays more than SEK 1,800 in a twelve month period. 100% up to 900 SEK, 900-1700 SEK, 50% of the cost 900-1300, 1700-3300 SEL 25% of 1300-1700, 3300-4300 10% of cost 1700-1800 SEK. More than 4300 SEK 0%.	(LFN, 2007, LFN, 2008, TLV, 2011d)
Switzerland (Federal Office for Public Health) Law of Heath Insurance 1996	Final Decision (Government Department)	Positive list	Pharmaceutical Specialities List (SL List)	Limitations to a particular quantity or patient medical indication	No conditional listing requirements identified	Deductable can range from CHF 300 to CHF 2,500. 10% of the cost of the medicine for outpatient after deductable. Inpatient medicines are covered. 20% for those where interchangeable generic is available up to 933 CHF.	(Federal Office of Public Health, 2011, Paris and Docteur, 2007)
United Kingdom England and Wales (NICE) (Ref: NICE Website)	Final Decision	Negative list	NICE Recommendations	Optimised or only in research (OIR)	Coverage with evidence development for those where recommended only in research.. Conditional patient access agreements for payment of medicines.	A flat prescription fee is paid for all medicines at £7.40 per prescription.	(NICE, 2009b, NICE, 2009a, NICE, 2011f, NICE, 2011c)

United Kingdom Scotland (SMC) (Ref: Website)	Advisory recommendation (Health Board	Positive and Negative list	Health Board Formulary	Accepted for restricted use, patient indication, group or authority to prescribe.	No conditional listing	No prescription charge (abolished in March 2011)	(Health Policy and Strategy Directorate, 2010, SMC, 2011e, SMC, 2011d)

Table A4.12: Opportunity to appeal

Country and agency/institution	Ad	Appeal/Dissent mechanism	Entitled to Appeal/Dissent	Grounds	Independent Appeal Committee	Independent Appeal Committee Members	References
Australia (PBAC)		Resubmission to PBAC	Manufacturer	Resubmission includes new data or modifies previous submission.	No	No	(PBAC, 2008)
Austria (HEK/HBV)		Appeal Committee	Manufacturer	Negative decision	Independent Drug Commission (UHK)	Public meetings 8 independent expert members – The commission can veto but not overall a decision by the HVB	(PPRI, 2007a)
Belgium (CRM)		Council of State Administrative Court	Manufacturer	Procedural only	No	No	(KCE, 2010)
Canada (CADTH, CDR)		Request for Reconsideration by CEDAC	Stakeholders (Manufacturer and Drug Plans)	Procedural and recommendation is not supported by evidence	No	No	(CADTH, 2010)
Denmark (DMA)		Danish Ministry of Interior and Health	Manufacturer	Procedural only and cannot reassess evidence	No	No	(Danish Medicines Agency, 2008)
Finland (PPB)		Supreme Administrative Court	Manufacturer	Negative decision	No	No	(Kivioja, 2008)
France (HAS)		Reconsideration hearing by HAS by committee and Supreme Administrative Court	Manufacturer	Negative advice	No	No	(Rochaix and Xerri, 2009)
Germany (G-BA)		Verbal hearing for benefit assessment. Appeal the arbitration for cost-effectiveness at price setting	Manufacturer & Sickness funds	Price and therapeutic value	No	No	(Leverkus, 2011)
Hungary		Appeal Committee	Not identified	Not recommended	Appeal	Director General	(PPRI, 2007b)

(Technology Appraisal Committee)				decision	Committee	makes the decision. Members from government departments, Pharmacy, National insurance (7 members)	
Ireland (Corporate unit and NCPE)		Appeal Expert Committee	Manufacturer	Negative decision	Expert Committee	Details of the committee could not be identified from documentation.	(Tilson et al., 2010)
Israel (Medical Technologies Administration)		No procedure identified	No procedure identified	No procedure identified	No	No	(Greenberg et al., 2009)
Italy (Pricing and Reimbursement Committee)		No procedure identified	No procedure identified	No procedure identified	No	No	(AIFA, 2010)
Korea (HIRA)		Resubmission to HIRA	Manufacturer	Resubmission no appeal against DREC decision only final decision to Court	No	No	(Kim & Chang, 2011)
Mexico (General Health Council)		Resubmission to the GHS	Manufacturer	Resubmission to the GHS after four months	No	No	(Moise and Docteur, 2007)
Netherlands (CVZ)		Participation procedure and Administrative Court	Stakeholders	Participation procedure and administrative court on procedural grounds	No	No	(Overheid, 2011)
New Zealand (PHARMAC)		Reapplication or Court of New Zealand	Manufacturer	New data available or address issues previously raised. Court of New Zealand can consider where Public law breached.	No	No	(PHARMAC, 2006)
Norway (NoMA)		Ministry of Health and Care Services	Manufacturer	Not recommended decision	No	No	(Lovdata, 2009)
Poland (AOTM)		No procedure identified	No procedure identified	No procedure identified	No	No	No details of procedure

							identified.
Portugal (INFARMED)		Supreme Administrative Court	Manufacturer	Negative decision	No	No	(PPRI, 2008a)
Spain (Ministry of Health – Directorate General)		Not identified	Not identified	Not identified	No	No	(Vogler et al., 2009)
Sweden (TLV)		General Administrative Court	Manufacturer	Reasons and proposed changes	No	No	(LFN, 2007)
Switzerland (Federal Office for Public Health)		Reconsideration request or Appeal Committee	Manufacturer	Negative decision	Appeal Commission	Details of the appeal committee not available in English language documentation.	(Federal Office of Public Health, 2011)
England and Wales (NICE)		Appeal Committee	Stakeholders (consultees –national body representing patients, body representing health professional and manufacturer)	3 procedural grounds	Appeal Panel	Non-executive directors of NICE, NHS representatives, representatives with experience of the relevant industry and lay members.	(NICE, 2011b)
Scotland (SMC)		Resubmission and Appeal Committee	Manufacturer	Review existing data and analyses	Independent Review Panel (IRP) & SMC arbitrator	3 members of SMC and 4 members of the Scottish Area Drug and Therapeutic Committees	(SMC, 2011d)

Table A4.13: Reappraisal requirements

Country and agency/institution	Reappraisal requirements	Time after initial decision process specifies reappraisal	Coverage with evidence development
Australia (PBAC)	Resubmission by manufacturer– new evidence available (PBAC, 2008).	-	-
Austria (HEK/HVB)	Reassessment by HVB if it believes no longer meets the criteria (medico-therapeutic or health economic criteria and the manufacturer required to provide a case). This may result in delisting (PPRI, 2007a).	-	-
Belgium (CRM)	There are two reasons for reappraisal, that the initial appraisal was based on a number of hypothetical factors and new evidence was required. Those medicines that had concerns with uncertainty of evidence in class 1 medicines where the manufacturer claims added therapeutic value and is conducted between 18 and 36 months. The assessment report will contain new evidence and any real life cost-effectiveness evidence. The Minister may request a multiple appraisal. This can result in delisting (KCE, 2010).	18 -36 months	CED, (KCE, 2010)
Canada (CADTH, CDR)	Resubmission by the manufacturer during the embargo period of a reduced price and in the circumstance where new clinical evidence or cost information becomes available that significantly effects the cost-effectiveness of the medicine (CADTH, 2010).	-	-
Denmark (DMA)	Medicines are prioritised according to criteria to decide which medicines should reassessed which includes, significance of the medicine to the primary sector, public health aspects, new evidence, high costs or high consumption (Danish Medicines Agency, 2008).	-	-
Finland (PPB)	The decisions provided by the PPB are for a fixed period of 3 years for new medicines. At 36 months a renewed confirmation is required and this should document any changes that have taken place with respect to experience of use, clinical studies and treatment prices. The manufacturer may propose an increase in the price but these needs to be accompanied by evidence (Ministry of Social Affairs and Health, 2005).	36 months	-
France (HAS)	The HAS can self refer medicines in the presence of new evidence but reviews all medicines at 5 years post-listing. This may result in delisting of the medicine at 5 years and the manufacturer can submit new evidence at any point for reassessment of the medicine (Rochaix and Xerri, 2009).	60 months	CED, (Rochaix and Xerri, 2009)
Germany (G-BA)	After one year of the final G-BA decision, the manufacturer can request a new benefit assessment if there is new scientific knowledge. It is also possible that the G-BA decides that there is new scientific evidence that makes it necessary to perform a new assessment (Federal Joint Committee, 2011c).	-	-
Hungary (Technology Appraisal Committee)	Resubmission through the regular procedure (PPRI, 2007b).	-	-
Ireland (Corporate unit and NCPE)	Resubmission by the manufacturer if new evidence becomes available that affects the pharmacoeconomics (Tilson et al., 2010).	-	-

Israel (Medical Technologies Administration)	Resubmission by the manufacturer in the next cycle (one year) when new evidence becomes available for adding to the list. The technologies already on the list have never been delisted and obsolete or ineffective treatments remain (Greenberg et al., 2009).	-	-
Italy (Pricing and Reimbursement Committee)	On expiration of the terms the manufacturer or the agency can request reconsideration and negotiation. A variation on the reimbursement category can be applied for if new evidence is found. Conditional price reimbursement with respect to payment by outcome has been introduced since 2006 (Jommi, 2009).	24 months	-
Korea (HIRA)	Resubmission - The manufacturer can request a re-evaluation of the medicine. Existing medicines are reviewed overtime to ensure that they meet the criteria for the PLS. The medicines are reassessed by therapeutic class and this is based on the growth in use of the medicines and the budget impact of the medicines. Those medicines that are not considered cost-effective are delisted (Bae and Lee, 2009).	-	-
Mexico (General Health Council)	The basic inputs list is regularly reviewed to modify for inclusion and exclusion of medicines. A medicine maybe de-listed for a number of reasons 1.) It is not longer prescribed; 2.) Medicine will not be used; 3) Awareness of another product of greater efficacy or lower toxicity (Moise and Docteur, 2007).	-	-
Netherlands (CVZ)	There are two different processes where outpatient medicines can be reassessed by application by the manufacturer 6 months after the Ministers previous decision (CVZ and Ministry of Health Welfare and Sport, 2010). The inpatient medicines are assessed for real-life cost-effectiveness four years after the decision (van Halteren, 2011).	48months*	CED, (van Halteren, 2011)*
New Zealand (PHARMAC)	Resubmission by the manufacturer following reasons, 1. New information or data becomes available, 2. The manufacturer wishes to respond to previous issues. The PHARMAC can decide to delist the medicine (PHARMAC, 2010).	-	-
Norway (NoMA)	The NoMA may consider whether the criteria are met for individual medicines in the list. The manufacturer has the opportunity to submit new information to demonstrate the medicine still meets the criteria. The NoMA may include new conditions for these to be met or may delist the medicine if the criteria are no longer met (Lovdata, 2009, Ministry of Health and Care Services, 2004).	-	-
Poland (AOTM)	The Ministry of Health may review the medicine at 2 years. There is no explicit provision for the procedure on the expiry of the decision. The Ministry of Health may commission AHTAPol to reassess the medicine or may decide to prolong the terms of the decision (Personal Communication: Ofierska-Sujkowska, 2011).	24 months	-
Portugal (INFARMED)	The medicines are reviewed at 3 years to ensure that they meet the criteria set by law. The manufacturer is notified and given the opportunity to adjust price. The medicines may be delisted and the reason made publically available. The decision may be made due to excessive cost, therapeutic efficacy doubtful, comparative effectiveness lower than medicines reimbursed for same indication (PPRI, 2008a).	36 months	-
Spain (Ministry of Health – Directorate General)	Re-assessment may occur after one year of the reimbursement and price decision. There may have been new medicines added to the list, which are at a lower price. The Directorate	12 months	-

	General for Pharmacy and Health Products may decide to de-list the medicine (Noticias Juridicas, 2011, Vallejo, 2009).		
Sweden (TLV)	Medicines that have been given conditional reimbursement are reappraised. The TLV may decide to remove the medicine as either part of the reimbursement review (2002) by therapeutic group or by the ad hoc consideration of individual medicines. The manufacturer is contacted with regards to individual cases that are reviewed for reimbursement (LFN, 2008, TLV, 2011c).	-	CED, (LFN, 2008)
Switzerland (Federal Office for Public Health)	Medicines are reviewed at 36 months after they have been included in the SL list. The medicine will be appraised to consider whether it still remains value for money. The documents must be submitted by the manufacturer 30 months prior to the review of the medicine. If the review shows the price is too high in comparison to the appropriate alternatives the FOPH can request a price reduction. Alternatively, if the medicine is found to be significantly cheaper in comparison to other countries, a price increase may occur. The FOPH also reviews the medicines listed for 15 years or after the expiration of the patent. The conditions of effectiveness, appropriateness and efficiency will be assessed to ensure these are still met (Federal Office of Public Health, 2011, Paris and Docteur, 2007) .	36 months	-
Scotland (SMC)	Resubmission in the light of new evidence or a new analysis but no periodic review (SMC, 2011d).	-	-
England and Wales (NICE)	A review date is listed on the guidance for when the review process will commence and will depend on the guidance, available evidence and knowledge on the topic. Evidence is collected to inform the review process and the views of stakeholders are sought to identify additional evidence. If a large amount of new evidence is available the guidance will be reviewed, in contrast if there is little new evidence the review will be delayed (NICE, 2011b).	-	CED, (NICE, 2011f)

Table A4.14 Technology Decision Level: Assessment of medicines

Country	Type of stakeholder involvement	Methods of evidence synthesis for assessment	Consultation on assessment of evidence	Communication of assessment (e.g. manufacturers submission)
Australia	Manufacturer provides an assessment of the medicine meeting the criteria set out in a guideline for manufacturers. Two sub-committees assess the manufacturer submission: the Drug Utilisation Sub Committee (DUSC) and the Economic Sub-committee (ESC). The DUSC considers the pattern of drug uses and assesses the financial forecasts for future in use in major submissions. The ESC reviews the health economic analysis and assesses the quality, internal and external validity. The members include clinicians, clinical epidemiologists, health economists, biostatisticians and clinical pharmacologists (Australian Government, 2011).	Evidence of clinical effectiveness and cost-effectiveness is required for all manufacturer major submissions to the PBAC. These need to be relevant to the Australian context. Head to head trials are the most appropriate form of clinical evidence. If direct head to head evidence is unavailable then an indirect comparison maybe appropriate or non-randomised studies could be used. Cost-utility analysis is required. Supplementary analysis may take into account the broader impacts on costs and outcomes (For example: production changes and impacts on carers). The assessment should include the following: 1. Description of new medicine 2. Clinical Effectiveness 3. Cost-effectiveness 4. Budget impact 5. Any other relevant information (PBAC, 2008)	The manufacturer has the opportunity to consult on the evidence on two occasions. The first occasion is prior to the technical committee where a detailed commentary of the manufacturer submission is provided. The manufacturer can then provide comments that are then passed to the technical details. The second opportunity to comment follows after the technical committees have assessed the evidence. (Lopert, 2009).	The manufacturer's submission is not provided on the website. Specific details are provided in the decision documentation (PBAC, 2011).
Austria	1. The manufacturer provides the application. 2. The HEK provides an appraisal and recommendation to the Federation (HBV) (PPRI, 2007a)	The manufacturer must include details of the pharmacology, medico-therapeutic advantage and health economic considerations. The comparison must consider the most frequent indication, appropriate dosage and the main groups of patients affected. 1. Pharmacological evaluation. The classification and evaluation of the medicine from a pharmacological viewpoint in the context of available therapeutic alternatives 2. Medical therapeutic evaluation - The therapeutic	The manufacturer can respond to clarification for comment on the submission and requests for further data. External experts are considered in the process of assessment nominated by the manufacturer (Austrian Federation of Social Insurance Institutions, 2004).	The manufacturer submission is not provided on the website. The reasons for decisions of the HEK are provided in the minutes when these deviate from the manufacturers proposed use (Austrian Social Security, 2011a).

		benefit in comparison with the other therapeutic alternative and a review of the validity of the data submitted. The added therapeutic advantage should be assessed. The internal and external validity of the evidence should be considered in the application. A hierarchy of evidence is described, 1. Prospective RCTs, 2. Systematic Review of a large number of RCTs, 3. RCTs with smaller number of enrolled patients, 4. Non-RCT observational evidence 5. Professional committee opinion 6. Individual expert opinion (Austrian Federation of Social Insurance Institutions, 2004). 3. A Health Economic Evaluation – This is based on the medical therapeutic evaluation. The perspective should be from the Social Insurance Programme. There are no official Guidelines for the conduct of economic evaluation but a consensus document is used (IPR, 2006).		
Belgium	The committee can appeal to internal and external experts that are either medical doctors or pharmacists. The experts provide a scientific judgement of the added therapeutic value of the medicine (KCE, 2010).	The assessment of medicines is based on the therapeutic class, which can be categorised into Class I, Class II and Class III. Class I are specialities with increased therapeutic value, Class 2 are medicines with no increase in therapeutic value and Class III are generics. The following aspects should be assessed in the manufacturer submission: efficacy, safety, effectiveness, applicability, usability, level of evidence, price, budget impact and cost-effectiveness. The cost-effectiveness analysis should follow recent guidelines that are published in Value in Health (KCE, 2008, Adriaens and Soete, 2010)	An appraisal report is sent to the CRM and they can either approve or modify the report. If the appraisal outcome differs from the manufacturers original request this is then sent to the manufacturer for comment. The manufacturer then has 10 days within which they can respond to the provisional appraisal (KCE, 2010).	The evaluation report and comments from the manufacturer can be obtained from the NIHDI website that includes the therapeutic value, other aspects of the appraisal and the ministerial decision (NIHDI, 2011).
Canada	The manufacturer provides the initial submission and this is reviewed by a team consisting of clinical reviewers, clinical experts, information specialists, methodologists, administrative support and peer reviewers. This is input into the CDR clinical review section and also considered in the CEDAC	The CDR review seeks to answer the following critical questions: 1. How does it compare with alternatives? 2. Which patients will it benefit? 3. Will it deliver value for money? The manufacturer should achieve this by presenting evidence on the safety, efficacy and effectiveness of the new medicine. A systematic review of the evidence should be performed. RCTs, observational studies and expert opinion are all acceptable forms of evidence. The CDR requires the manufacturer to provide a	There are two opportunities for comment: The review provided by the CDR review team is provided to the manufacturer for comment. The recommendation will be sent with the justification to the manufacturer in an embargo period prior to the announcement of the decision. The manufacturer may request a re-consideration or a resubmission at a	The summary of the recommendation and outcomes are published on the CADTH website (CADTH, 2011c).

	deliberations. The CDR produces an independent clinical review which uses aspects of the manufacturer review (CADTH, 2010).	pharmacoeconomic submission and the electronic model used. The economic evaluation of health technologies (2006) states that a Cost-effectiveness or Cost-utility analysis should be provided if: 1. The medicine is the first available to the treat the disease or a new class of therapeutic effect; 2. Has demonstrated differences in efficacy and safety in head to head trials, manufacturer argues with evidence that there are differences between the relevant medicines in outcomes (CADTH, 2006). Those medicines demonstrating other outcomes (non-clinical outcomes or surrogate outcomes) only require cost-consequence. All other medicines require details of price and cost. There is a reference case for the base case economic evaluation.. Budget impact analysis is required for each of the jurisdictions in which the medicines proposed use (CADTH, 2010).	reduced price. Patient groups are also invited to submit a patient group submission (2010 onwards) (CADTH, 2011e).	
Denmark	The manufacturer provides a submission for consideration by the reimbursement committee and the DMA. The manufacturer is free to set the price of the medicine (Danish Medicines Agency, 2008).	The application provided by the manufacturer must include the following (Danish Medicines Agency, 2008): 1. Marketing authorisation 2. Information about the expected expenditure of the medicine 3. Pharmacological and clinical document 4. Clinical assessment report 5. Comparable clinical efficacy and safety 6. Appropriate scientific studies A health economic analysis is optional. And a guideline is provided on the agency website. Price should be set proportionate to the therapeutic value. Health economic analysis should be valued against existing treatments or if the price is higher than other reimbursed medicines (Alban et al., 1997).	The reimbursement committee provides a written recommendation to the Danish Medicines Agency. This includes a reasoned assessment provided for the opinion of the reimbursement committee. If the medicine is not granted general reimbursement it will be considered for conditional reimbursement. If the medicine is not granted either general or conditional reimbursement, the recommendation will be presented to the manufacturer for consultation before making its final decision. A copy of the medical assessment, price survey and appraisal of the health economic analysis is provided (Danish Medicines Agency, 2008).	The manufacturer's submission is not provided on the website but details of the appraisal decisions are provided (Danish Medicines Agency, 2011).
Finland	There is an expert group consisting of seven members	The manufacturer application for basic reimbursement and price should include the following elements (PPB,	An appeal can be made at the end of the process. No formal consultation	The manufacturer submission is not provided on the website.

	that provides advice to the Pharmaceutical Pricing Board for the decision on whether the medicine should have special reimbursement status or before expanding reimbursement to a new indication. An expert group consisting of a maximum of seven members operates as part of the Pharmaceuticals Pricing Board. This expert group represents medical, pharmacological, health economics and social insurance expertise. The board decides on the reimbursement and reasonable wholesale price of medicinal products (Ministry of Social Affairs and Health, 2011b).	2011): 1. A proposal for reimbursement and a reasonable wholesale price 2. The medicinal products therapeutic value and clinical assessment. 3. Treatment costs 4. Health economic evaluation demonstrating the cost-effectiveness of a new active substance medicine or selected by the PPB. 5. Future sales forecast 6. Prices in other European Economic Area Countries (EEA). A guideline for the development of economic evaluation was introduced on the 1st of May 2011. Cost-utility analyses are preferred except in the case of equivalence where cost minimisations may be used. There are no statements of a cost-effectiveness threshold used in decision-making (Ministry of Social Affairs and Health, 2009).	process was identified from the literature or the Ministry of Social Affairs and Health website.	Notification of price and reimbursement are provided on the website but no details of assessment and appraisal were identified (Ministry of Social Affairs and Health, 2011c).
France	The assessment involves HAS staff and the committee of clinical experts. The pricing decision is linked to the ASMR assessment and this is provided by the CEPS following the SMR and ASMR assessment provided by the Transparency Committee (Meyer, 2011).	HAS considers all pharmaceuticals once marketing authorisation has been granted. The manufacturer is required to present relevant data on clinical efficacy, comparative safety and relative effectiveness. 1. Clinical effectiveness: HAS requires the manufacturer to submit all relevant studies for the clinical efficacy of the medicine but there are no requirements for these to be identified by a systematic review of the evidence. In the absence of head to head trials a network meta-analysis is permitted. The HAS commission a separate literature review of the evidence. The manufacturer provides a claimed score for the Service Médical Rendu (SMR) and L'amélioration du Service Medical (ASMR). The transparency committee is given information from a literature review and the manufacturer's submission (Rochaix and Xerri, 2009).	There are no formal process for patient group involvement in HAS decisions. The decisions are provided by clinical experts. (Falissard et al., 2010).	The manufacturer submits a dossier to the HAS but this is not published on the website. A fee of 2,875 EURO is required for the processing of the submission, HAS provides a 'opinion' document published on their website which contains an assessment of evidence, details of the appraisal and recommendation (HAS, 2011a).
Germany	The Federal Joint Committee	A new early assessment has been introduced from 1st of	The pharmaceutical company has the	The manufacturer dossier is

	(FJC) requires the manufacturer to submit on the new medicine The Federal Joint Committee can commission the Institute for Quality and Efficiency in Health Care or third parties with assessing the benefits provided in the manufacturer submission (Federal Joint Committee, 2011a).	January 2011. An application for early assessment should include: 1. Approved use 2. Medical benefits (MTC and ITC are appropriate in the absence of head to head evidence to demonstrate benefit). 3. Additional medical benefit for appropriate comparator treatment 4. Number of patients and patient groups for which significant additional therapeutic benefit 5. Cost for the statutory health insurance The extent of the therapeutic benefit should be assessed on a scale of 1-6: 1 - Major improvement in benefit: A significant additional benefit, primarily a cure for the disease, a significant survival time, a long-term freedom/avoidance of serious side effects. 2 - Significant improvement in benefit: A significant additional benefit, moderate life extension, substantial slow down in symptoms, avoidance of serious side effects. 3 - A small additional benefit is when one of the functional benefits shows a moderate reduction in non-fatal symptoms or side effects. 4 - An additional benefit exists but is not quantifiable because there no scientific evidence base is possible 5 - There is no demonstration of value added benefit. 6 - The benefits of the drug to be evaluated is less than the benefit of the appropriate comparison treatment. (Federal Joint Committee, 2011b) The efficiency frontier is the approach adopted for economic analysis when this is required by the Federal Joint Committee (IQWIG, 2009).	opportunity to have consultation prior to submitting to the FJC and this may be with regard to appropriate studies (prior to conducting the phase III trial) or selection of the appropriate comparator. The findings of the benefit assessment will be published in Internet and pharmaceutical companies, associations and experts are given the opportunity to make written and verbal hearings on the findings. Experts of medical science and practice, governing bodies of medical associations, patient representatives as well as umbrella organizations of manufacturers of medical products and devices in this way given the opportunity to respond (Federal Joint Committee, 2011a).	published simultaneously with the benefit assessment on the website of the Federal Joint Committee (Federal Joint Committee, 2011d).
Ireland	The NCPE provides a rapid review of the medicine and will provide an appraisal of the manufacturers pharmacoeconomic analysis if this is required (referred by the products committee). The NCPE provides a critical appraisal of	The rapid review template states that the following information should be provided for assessment (NCPE, 2009): 1. Reimbursement scheme 2. Target indication and licensed group 3. Clinical evidence (relevant trials and characteristics) 4. Adverse events	At the initial stages of the decision-making process the manufacturer is invited to attend a meeting about the process and development of the scope for the assessment of the medicine (NCPE, 2011b).	The manufacturer submission is not provided on the website but a summary of the deliberations can be found on the NCPE website (NCPE, 2011d).

	the health economic evaluation using the Drummond 10 point checklist (NCPE, 2011b).	5. Price 6. Budget impact and Cost per patient 7. Completed assessments and decision by other jurisdictions The pharmacoeconomics assessment must include cost-effectiveness analysis (cost per life year or cost-utility) and this may be required for high budget impact medicines The guidelines state that probabilistic sensitivity analysis is mandatory to assess the uncertainty surrounding the evidence. Indirect comparisons may be required if no head to head comparisons are available. An assessment of the budget impact is required in the evaluation (HIQA, 2010).		
Israel	The manufacturer provides a submission using the guidelines provided by the Ministry of Health. The manufacturer's submission is assessed by the Medical Technologies Administration (MTA) to report on the clinical, epidemiology and economic considerations. This is then passed to the Medical Technologies Forum that grades the technologies on a scale of 1-10 using the stated criteria set out in the deliberations section of this framework. The MTF consists of experts in HTA (Greenberg et al., 2009).	The manufacturer submission should include the following information (Ministry of Health, 2010): 1. Indication and potential use of the technology 2. Proof of its safety, efficacy and effectiveness. 3. Advantage over a technology already in the NHLS 4. Budget impact analysis 5. As of 2007 a health economic evaluation.	There is no stated process for consultation following the MTA assessment of the evidence. The final recommendation on new medicines is made by the PNAC which has representation from the Ministry of Health, Health Maintenance Organisations and members of the public (Greenberg et al., 2009).	The decisions of the PNAC are published on the Ministry of Health website but details of the manufacturer submission are not provided (Greenberg et al., 2009).
Italy	The AIFA has a sub-committee that is responsible for the assessment of therapeutic innovation. The Technical Scientific Committee (TSC) assesses the national and European marketing authorisation applications, delivers a consultative opinion on these and provides	The manufacturer is required to submit details of the clinical studies and pharmacoeconomic studies for those medicines that are believed to be a therapeutic innovation. The manufacturer should provide details of (Folino-Gallo et al., 2008): 1. Therapeutic value/Therapeutic Innovation 2. Pharmacovigilance data 3. Price in other EU countries 4. Price of similar products within the same pharmacotherapeutic group	The manufacturer can participate in the hearing performed for the price negotiations based on the findings of the CTS committee (AIFA, 2011a).	The list of medicines reimbursed is provided on the website. The manufacturer submission is not published by the AIFA (AIFA, 2011b).

	classification for reimbursement (AIFA, 2011b).	5. Internal market forecast 6. Number of potential patients Guidelines are available in Italy for the conduct of pharmacoeconomic studies (Capri et al., 2001). The AFIA CTS committee will assess the medicine for the therapeutic importance taking into account the following: 1. Severity of disease: A :Treatment for serious diseases B: Treatment to eliminate the risk of serious diseases C: Treatment for non-serious diseases 2. Availability of existing medicines: A: Medicine is for the treatment where there is currently no adequate treatment B: Medicine is designed for the treatment of diseases in subgroup of patients C: Medicine is for the treatment of diseases where no recognised treatment exists 3. Main outcome criteria: A: Major benefits on clinical endpoints B: Partial benefit for the disease C: Minor or temporary benefit for the disease. Pharmacoeconomic studies are not a mandatory requirement. (AIFA, 2007)		
Hungary	The NHIFA includes the Technology Appraisal Committee that makes the final decision on the reimbursement of the medicine. This is informed by the critical appraisal provided by the OHTA (Office of Health Technology Assessment, 2011).	The manufacturer can submit under either a normal procedure or a simplified procedure. The normal procedure is for new active substances and this requires a Health Technology Assessment. The simplified procedure is for the reimbursement of bioequivalent generics. The manufacturer submission should include details of (Pékli-Novák et al., 2007): 1. Clinical efficacy 2. Clinical effectiveness 3. Cost-effectiveness of the new medicine There is a guideline for the conduct of pharmacoeconomic studies. There is a preference for cost-effectiveness analysis, cost-utility analysis and cost-minimisation analysis. Cost benefit analysis should not be submitted (Szende et al., 2002).	There does not appear to be any formal consultation stages in the process. Apart from the opportunity to appeal at the end of the decision-making process.	The manufacturer's submissions could not be identified on the website.
Korea	The manufacturer makes a submission to HIRA and HIRA	The application by the manufacturer should include the following (Kyung Lee, 2011, Bae and Lee, 2009):	The manufacturer is given the opportunity to respond to questions	Neither the manufacturer submission nor the HTA

	staff assesses this (Kyung Lee, 2011).	1. A copy of the marketing authorisation 2. Therapeutic Benefit 3. Clinical data 4. Evidence of comparative effectiveness. Head to head RCT data is strongly preferred and this should be obtained by a systematic search of the available evidence. 5. Pharmacoeconomic analysis (KREP) guideline introduced in 2005. 6. Reimbursement status in other countries. The recommendations for pharmacoeconomic analysis include that it should be performed from a societal perspective. Productivity costs should be assessed in a sensitivity analysis. Probabilistic analysis is encouraged (HIRA, 2006).	regarding the submission and with respect to the final HTA report produced by HIRA staff. The DREC committee may hold public hearings where the manufacturer can attend and be involved in the discussions. This has more commonly occurred when a number of medicines are being re-appraised (Yang, 2009, Bae and Lee, 2009)	informing the process is published on the website. However, the detailed HTA information is shared with the manufacturer throughout the process (Yang, 2009).
Mexico	The manufacturer submits to the General Health Council (GHS). The sub-committees of the Interinstitutional commission meet once a month and reviews the applications for inclusion. The Technical Secretary of the Commission chairs the sub-committee (Moise and Docteur, 2007).	The following information should be submitted: a. Generic name; b. current health record; c. same trade name if any; d. Dosage form; e. Presentation; f. Quantitative formula or the active ingredients and additives; g. cite recent scientific validity of each of the components of formula relating to pharmacokinetics, pharmacodynamics, clinical and therapeutic sustained controlled studies are useful for evidence-based medical practice; h. Schedule to the proposed generic description of the input requested update; i. Shelf life and storage conditions; j. Pharmacoeconomic studies that range from cost-minimization analysis cost-effectiveness, cost-utility, cost-benefit to unit prices (Hernández, 2011). The manufacturer submission must contain a pharmacoeconomic assessment. A guide to Economic evaluation was published in 2008 and is available on the GHC website. The guidelines specific that cost-effectiveness or cost-utility analysis may be presented depending on the clinical problem. The results from a societal perspective can be presented separately if they are substantially different (such as lost productivity cost s and transportation costs for patients). Budget impact analysis is required. Probabilistic sensitivity analysis is recommended. A standard structure is provided in the	If the medicine is accepted for inclusion on the GHS informs the manufacturer. The decision is then placed on the GHS website where other stakeholders can then challenge the decision (General Health Council, 2011b).	The manufacturer's submission is not provided on the website. The GHS only provides details of the listing (General Health Council, 2011b).

		guideline for the reporting of the pharmacoeconomic analysis (General Health Council, 2008).		
Netherlands	The manufacturer submits to the CVD and a committee called the Pharmaceutical Assistance Commission (CFH) oversees the assessment report. There are two processes, one for outpatient medicines and one for inpatient medicines (van Halteren, 2011).	Outpatient Medicines: If exempt from provision of a economic analysis the following should be provided (CVZ and Ministry of Health Welfare and Sport, 2010): 1. Indications 2. Number of patients medicines treats 3. The price of the medicine 4. The budget impact of the medicine 5. The availability of other treatments 6. A motivation for not conducting an economic analysis 7. Orphan status 8. Cost-minimisation for medicines with similar therapeutic value. The assessment for outpatient medicines is summarised below for those requiring an economic analysis. The manufacturer submission should include the following. 1. Literature search (systematic) regarding the search strategy, terms, criteria and the date of search. This should identify all relevant studies, including reviews, meta-analysis and relevant guidelines. 2. An assessment of therapeutic value by comparator and outcome measure 3. SPC for licensed indication 4. EPAR 5. Cost-consequence analysis 6. Pharmacoeconomic analysis (a guideline is provided on the website which was introduced in 1999). This should be structured in accordance with the guideline and the model should be attached. There are certain types of medicines that can be exempt from a pharmacoeconomic analysis: 1.) Medicines for an Orphan indication 2.) Medicines with a cost of less than £500,000 per year 3.) Therapeutically equivalent and with no	After the first meeting of the CFH to consider the draft reports, the stakeholders are given the opportunity to comment. Stakeholders may include clinicians, patients and insurers. A response time of 5 days to the consultation is provided. If the CFH decides additional data is required then this will be requested in writing to the manufacturer (the process time is suspended at this point). If the manufacturer does not submit the required data in 3 months the report will be automatically submitted to the Health Board (CVZ) unchanged (CVZ and Ministry of Health Welfare and Sport, 2010).	CVZ advice and CFH report including annexes are published on the website of the CVD among publications of CFH reports (CVZ, 2011b).

		additional costs. Inpatient Medicines: The assessment for inpatient medicines includes therapeutic value and budget impact. There is a plan for the collection of real life data (coverage with evidence development) to conduct a real life cost-effectiveness at four years (van Halteren, 2011).		
New Zealand	The Pharmacology and Therapeutics Advisory Committee (PTAC) provides advice in relation to the community and hospital pharmaceuticals. PTAC comprises medical experts that have broad experiences of the medicines and indications. PTAC is the primary clinical advisory body and there may be other specialist sub-committees for certain clinical fields (oncology). PTAC critically reviews and appraises using the same criteria specified by PHARMAC. The group recommends priority ratings in the advisory notes to the PHARMAC (usually high, medium and low). The committee will also describe the criteria and the weight attached to each. A high priority cost-effective medicine is likely to be progressed faster than a low priority and not cost-effective medicine (PHARMAC, 2010).	The manufacturer should provide the following in a submission to PHARMAC (PHARMAC, 2010): 1. Pharmacological information (e.g. forms, strength, indication and dose etc) 2. Added therapeutic value (e.g. main therapeutic claims and advantages / disadvantages in comparison to other medicines) A systematic search should be performed and there is an evidence hierarchy grades 1 -4 3. Price information (e.g. proposed price and international prices) 4. Epidemiological information 5. Market information (expected sales) 6. Detailed information on costs and benefits of the medicine 7. Information regarding packaging and pack size PHARMAC will review and undertake either a cost-utility analysis (CUA) or a Budget Impact Analysis (BIA – conducted over a five year period). The manufacturer should provide a CUA when submitting and should follow the guideline presented in the Prescription for Pharmacoeconomic Analysis (PFPA), published in 2007 (PHARMAC, 2007). A PHARMAC analyst reviews the pharmacoeconomic analysis and will amend if required. Manufacturers are advised to provide a CD with a copy of the model. If the model is amended the PTAC will be supplied with note clearly explaining the differences between the two models. There is an iterative process with regards to the complexity of the economic evaluation for each unique decision. The timeframes, impact on pharmaceutical budget, reliability of results, reporting,	Prior to the PTAC committee, medical groups and other interested parties may be invited to comment on the pharmaceutical as part of the assessment. This allows parties to outline specific issues relating to the medicine (PHARMAC, 2010).	The details of the funding applications are provided on the PHARMAC website. The agency does not publish most of the Technology Assessment Reports because of commercial sensitivity. It does provide some TARs that were used to inform the decisions on funding of medicines (PHARMAC, 2011e). Details of the online schedule for the medicines funded are also available on the website. The Pharmacology and Therapeutics Advisory Committee publishes the minutes which include discussion of some of the details of the assessment.

		impact of the CUA on the decision and availability of health economic resources determine this. Probabilistic Sensitivity analysis should be undertaken when more detailed analyses are required (PHARMAC, 2010). The PHARMAC states that a good assessment by the manufacturer will include: 1. Critical appraisal of the key clinical evidence 2. Information relating to all 9 of the PHARMAC decision criteria 3. Market and epidemiological information 4. Cost-effectiveness in the preferred form of a cost-utility analysis and budget impact analysis. 5. Disclosure of information on ongoing trials and patents.		
Norway	The manufacturer submits to NoMA and this can be approved by the NoMA depending on the budget and nature of the medicine. If this needs to be referred the Blue medicines Board a report will be prepared. The NoMA will create a background report that assesses the manufacturer submission. This will include data about the disease, possible alternative treatments, the new drug's possible place in the treatment image, drug efficacy. The NoMA will also analyze and provide comments on the application and the health economic analysis (PPRI, 2008b).	The manufacturer should submit the following information to NoMA (NoMA, 2011a): 1. The indication and any restrictions proposed from the marketing authorisation 2. EU approval and SPC 3. Description of the illness and epidemiology 4. Treatment regime 5. Overview of existing treatment programme and total number of patients for proposed indication 6. Position of medicine in the treatment programme 7. Current and predicted sales 8. Description of clinical benefit 9. Pharmacoeconomic analyses which should follow the NoMA guideline published in 2002. A probabilistic sensitivity analysis is not a requirement but is stated as an advantage. 10. Budget consequences – the added expense should be included for the National Insurance Administration for a five year period. 11. A reference list of published and unpublished studies supporting the application. Pharmacoeconomics is a requirement for the submission to the NoMA (NoMA, 2005). A cost-utility analysis should	The NoMA gives interested parties the opportunity to comment before a final decision is made. The NoMA will outline the criteria for the decision. The manufacturer will be given four weeks to respond if the medicine does not meet the criteria because of the price. The manufacturer can provide feedback and any proposed changes. A final notice will be given if the medicine does not meet the criteria within which interested parties have four weeks to comment (Ministry of Health and Care Services, 2004).	The manufacturer's submission is not provided on the website. The decisions of the NoMA and minutes of the Blue prescription committee are provided on the website (NoMA, 2011c).

		be supplemented with a cost-value analysis. A cost-value analysis uses a set of alternative value for health conditions of various types (adjustment between health and disabled individuals, (Nord et al., 1999)).		
Poland	The manufacturer submits to the Ministry of Health. The Analytical Team of the AHTAPol assesses the manufacturer submission and may revise this before this is provided to the Consultative Committee (AHTAPol, 2011a).	The assessment is performed by a review of the manufacturer submission and this includes the following elements: 1. The decision problem 2. Clinical analysis – The efficacy and safety in a specific population in comparison to the appropriate comparators. A systematic review should be performed including details of the search strategy, information selection, quality assessment (hierarchy of evidence provided in the guideline). Meta-analysis and indirect comparison can be performed in the case of lack of direct head to head comparisons. 3. Economic analysis – This may either use a model structure that is relevant to the Polish context, an evaluation identified in a systematic review or a novo economic evaluation performed for the Polish context. 4. Analysis of impact on the health system – This includes an assessment of the budget impact, assessment of the organisational consequences for the health care system and an assessment of the possible ethical and social implications of the new technology. A Guideline for Health Technology Assessment (2009) is provided on the AHTAPol website (AHTAPol, 2009).	The manufacturer is given the opportunity to provide comment when the Analytical Team have prepared their report. The Consultative council takes the opinions of Medical Schools and the National Health Fund into account. There does not appear to be a formal process for taking other stakeholders views into account such as patients (Lipska, 2010).	The manufacturer submissions are not provided on the agency website but manufacturer commentaries are provided on the website. The website contains a document summarising the considerations of the Consultative Council (CC). This includes details of the assessment and recommendations (AHTAPol, 2011c).
Portugal	The manufacturer submits to INFARMED and external pharmacologists assess the added therapeutic value of the medicine. Economists assess the economic evaluation provided in accordance with the Portuguese guidelines for the conduct of economic	The manufacturer application should contain the following details (INFARMED, 2011c): 1. The marketing authorisation 2. The maximum price approval document provided by the Directorate-General of Economic Activities. The proposed reimbursement price maybe equal or below the price that was agreed by the DGAE. 3. SPC	The manufacturer is given the opportunity for clarification of the pharmaco-therapeutic analysis and pharmaco-economic analysis (PPRI, 2008a).	The manufacturer submission is not published on the website. The listing recommendations of the INFARMED and the official Gazette annually (Maria, 2010).

	evaluation. The manufacturer has the opportunity to provide additional information and clarify elements of the assessment (PPRI, 2008a).	4. The price and reimbursement status in member states of the EU 5. Declaration of the manufacturer for inclusion in the reimbursement list 6. Evidence of the added therapeutic advantage of the medicine 7. The Pharmacoeconomic evaluation that demonstrates an economic advantage by the criteria set within the law. The Pharmacoeconomic evaluation should follow the Portuguese guideline 1998 (INFARMED, 1998). The guideline specifies that any recognised scientific economic technique can be used including cost-benefit analysis. A cost-utility analysis is the preferable type of analysis. Probabilistic sensitivity analysis maybe used. A template is provided for the reporting of the economic analysis. 8. Packaging size 9. Status of registration in EU countries The application includes two analysis (PPRI, 2008a): 1. A pharmaco-therapeutic analysis 2. A pharmaco-economic analysis		
Spain	The stakeholders involved are the Ministry of Health, Directorate General for Pharmacy and Health Products and the Spanish Agency for Medicines and Health Products (Vogler et al., 2009).	The manufacturer is required to submit details of the technical and economic characteristics of the medicine, (Ferre, 2011): 1. Therapeutic utility report (place in therapy, alternatives, alternatives, applicability) 2. Pharmacoeconomics assessment (Price of the medicine, cost comparison, budget impact) Pharmacoeconomic studies are not mandatory but are sometimes submitted by the manufacturer for the pricing process. There is a Guideline for Economic Evaluation originally published in 1995, (López-Bastida et al., 2010)	No formal consultation process with other stakeholders could be identified in the reimbursement process.	The manufacturer submission is not published on the Ministry of Health website.
Sweden	The manufacturer submits to the TLV. The TLV allocates an executive officer, health economist and a legal expert. The application is screened for completeness and then sent to	An application should include the following information (LFN, 2008): 1. Information on patient groups 2. Information on which other relevant products are already included in the pharmaceutical benefits for the indication	The stakeholders have a formal role in the decision process. The TLV in Sweden consults with the manufacturer at various stages. The TLV will clarify the submission with the manufacturer and obtain any further	The manufacturer's submission is not provided on the website. The details of the assessment and deliberations may be provided with the listing recommendations (TLV, 2011a).

	the Pharmaceutical Benefits Group for County Councils (representing 18 county councils). The county councils have four weeks to prepare a case. The TLV may meet up with the manufacturer to gain clarification with regards to the application (LFN, 2003).	3. Estimated number of patients treated by the medicine 4. Average cost of treatment per day 5. Description of all relevant clinical studies 6. Clinical effects and effects relevant to the health economics. The best available evidence will be that which directly compares studies with the most relevant comparator. Indirect comparison from a systematic review may be used if this is not possible. 7. Health Economics in accordance to the guideline for Economic Evaluation 2003 should be conducted. The perspective should be societal, cost-effectiveness analysis using QALYs as a measure of effect, EQ5D is recommended and cost-benefit analysis using willingness to pay can be used when QALYs are not feasible (LFN, 2003).	information. The TLV may arrange a meeting with the manufacturer to do this if necessary. The documents that include the assessment and proposed decision are sent to the manufacturer for the opportunity to correct any factual errors and to comment on the justifications provided for the proposed decision. The Pharmaceutical Benefits Group for the County Councils are given the opportunity to provide comments and put forward any issues with the documentation and proposed decision. Patient groups are represented in the process by two members of the Executive Board that provide the decision having involvement with patient organisations in the past (LFN, 2008).	
Switzerland	The medicines regulatory agency, Swiss Agency for Therapeutic Products (SATP) informs the clinical efficacy assessment and the Federal Drug Commission assesses the submission presented by the manufacturer (Paris and Docteur, 2007).	The application for a new active substance should include the following (FSIO, 2008): 1. A summary of the justification of the application broken down by effectiveness, appropriateness and efficiency. 2. Comparative effectiveness – does the medicine fulfil the criteria for an innovation reward in comparison with the available alternatives. 3. Number of patients treated by the medicine 4. The expiration date of the patent 5. A foreign price comparison for the approved indications 6. The three most important clinical studies usually published in the "Lancet" or "The New England Journal of Medicine". 7. Pharmacoeconomic studies if these are available. 8. Epidemiology data.	There is no formal consultation with other stakeholders on the evidence presented. One member of the insured are on the Federal Drug Commission committee but there does not appear to be any other means by which patients can comment on the documents. There is no formal process for stakeholders to comment on the assessment and appraisal provided by the Federal Drug Commission and BAG/FOPH (Paris and Docteur, 2007).	The manufacturer submission is not provided on the website nor could the appraisal documentation provided by Federal Drugs Commission be identified.
United Kingdom -	e manufacturer, independent assessment centre (ERG or	The manufacturer is required to provide evidence of clinical-effectiveness and cost-effectiveness and can be	There are several stages at which consultees and commentators can	The NICE website contains an audit of the process with time

England	assessment group), wide variety of stakeholders and patient representatives. NICE define the process in three stages which include scoping, assessment and appraisal (NICE, 2008).	found in the Guide to methods of technology appraisal (2008) (NICE, 2008). The assessment process is a systematic evaluation of the relevant evidence available on a technology. In general medicines can be considered clinically effective if, in normal clinical practice, they confer an overall health benefit taking account of any harmful effects when compared with relevant alternative treatments. Technologies can be considered to be cost-effective if their health benefits are greater than the opportunity costs measured in terms of the health benefits are greater than the opportunity costs measured in terms of the health benefits associated with programmes that may be displaced to fund the new technology. The main submission should include at a minimum the following 1. The aims of treatment and current approved indications for the technology 2. An overview of the current treatment pathway, including how the technology is expected to fit into the treatment pathway 3. An assessment of the clinical-effectiveness, containing a critical appraisal, interpretation and synthesis of the clinical effectiveness evidence 4. A tabulation of the values and sources of the key parameters to be used in the assessment of cost effectiveness 5. An assessment of the cost-effectiveness containing a reference-case analysis of the cost-effectiveness based on the synthesis of clinical-effectiveness evidence. A justification for any cost-effectiveness analysis not fulfilling the reference case requirement is essential. 6. An assessment of the resource impact containing estimates of the impact of the technology on the NHS, including uptake/treatment rates, population health gain, resource implication and financial costs. Details with the requirements for clinical-effectiveness and cost-effectiveness:	comment on the assessment of the medicine. A consultee includes national groups representing patients and carers, bodies representing health professionals, manufacturer (s) or sponsor (s) of the technology in development, the Department of Health, the Welsh Assembly Government, Specialised commissioning groups. Primary care trusts and local health boards. Commentator organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre, research groups working in the area and other groups (NHS confederation, BNF etc). The consultees and commentators may provide comments on the draft scope. The consultees and commentators may provide a submission in a structured report. The committee can hear evidence from nominated clinical experts, patients and carers. The consultees and commentators have four weeks to comment on the Appraisal Consultation Document (ACD). Consultees can also appeal against the final recommendations in the FAD (NICE, 2009b, NICE, 2009a).	stamped documents. The manufacturer submission is included, ERG report or Assessment Report, Clarification documents that are provided by the manufacturer of the independent assessment group and any stakeholder submissions or documents. The details of all the medicines assessment and appraisals are published on the website (NICE, 2011e).

		1. Evidence of relative treatment effects – There is no hierarchy of evidence. NICE has a strong preference for evidence from 'head-to-head' RCTs that direct compare the technology with the appropriate comparator in the relevant groups. Non-RCT evidence that is both experimental and observational maybe used when RCTs are not available or to substitute this information. A systematic consideration of the evidence should be included. 2. Evidence for cost-effectiveness – A systematic review of economic evaluations should be performed and a new analysis of the cost-effectiveness of the medicine. Evidence from other study designs other than RCTs may be necessary. 3. Acceptability, appropriateness and preference 4. Feasibility and impact 5. Equity and equality		
United Kingdom - Scotland	The manufacturer, SMC board, New Drugs Committee and Patient groups all input into the decision-making process. There is no third party review of the evidence or generation of an independent model (SMC, 2011e).	The SMC considers all newly licensed medicines, new formulations of existing medicines and new indications for established products (SMC excludes assessment of vaccines, branded generics, non-prescription-only medicines (POMs), blood products, plasma substitutes and diagnostic medicines) once marketing authorisation has been granted. The manufacturer is required to submit evidence on clinical efficacy, comparative effectiveness, clinical effectiveness, cost-effectiveness and budget impact (SMC, 2011c): 1. Clinical effectiveness: The SMC requires the manufacturer to provide evidence assembled systematically for the indication(s) of the medicine including details of RCTs (active controlled most relevant), meta-analyses, and most relevant effects of a medicine. The manufacturer provides evidence of clinical efficacy and is required to consider the medicine in terms of the applicability to clinical practice in Scotland, guidelines and relevant protocols for	Patient Interest Groups are able to collect comments from a number of patients and carers and provide these in the form of a submission of evidence to the SMC. There is a submission guide and submission template provided on the SMC website (SMC, 2011f). The health boards and a number of experts are formally involved in the process of decision-making.	The manufacturer submits a New Product Assessment Form (NPAF) but no fee is required for the processing of the submission. The NPAF is not published on the SMC website. An advice document is published on the SMC website (SMC, 2011h).

		the most relevant active comparator medicines. In the absence of head to head evidence a network meta-analysis is required by the SMC. The network meta-analyses should be described with reference to a systematic review for studies included and the search strategy for trials included and clinical/statistical heterogeneity between data sources. 2. Cost-effectiveness: The responsibility for demonstrating the cost-effectiveness and any further analysis relevant to Scottish practice rests with the manufacturer and failure to submit cost-effectiveness automatically results in a not recommended decision. A reference case is not provided but the SMC specifies that cost-utility analysis is the preferred form of economic evaluation and health effects should be expressed in Quality-Adjusted Life Years (QALYs). Modelling is the main framework used to synthesise data of clinical and cost-effectiveness, in the absence of real-life effectiveness data. Manufacturers are required to provide sensitivity analysis in the form of single and multi-way analysis to allow the committee to explore the uncertainty in the estimates.		

Table A4.15: Technology assessment level: Deliberation of factors for decision

Country	Institutions involved	Type of stakeholders involved in appraisal	Stated factors for the appraisal of medicines	Communication of summary of appraisal and decision
Australia	The PBAC provides an advisory recommendation which the Minister of Health with take into account alongside the price negotiations with the PBPA (PBAC, 2008).	The PBAC committee members are appointed by the Minister for Health, include medical practitioners (specialists, general practitioners and clinical pharmacologists), pharmacists, consumers and health economists (PBAC, 2008).	There is no stated cost-effectiveness threshold in Australia. There are many factors taken into account and the guidance for submission categorises these as qualitative and quantitative factors. The factors are not weighed equally and different factors may be more or less important depending on the situation (PBAC, 2008). Quantitative factors: 1. Comparative cost-effectiveness 2. Comparative health gain 3. Patient affordability in the absence of PBS 4. Budget impact for PBS and government Qualitative factors: 1. Uncertainty surrounding the evidence 2. Equity considerations 3. Presence of effective alternatives 4. Severity of the medical condition treated 5. Ability to target patients most likely to benefit 6. Likely development of resistance	The PBS outcomes are presented in a summary document (around 4 pages) on the Department of Health and Ageing website. This details the main deliberations and a summary of the evidence considered by the manufacturer (PBAC, 2011).
Austria	The HEK provides the reimbursement recommendation though a majority vote of the members providing that half of the members are present. The HBV (Federation) provides the reimbursement decision and the Pricing Committee (PK) advises the Ministry of Health, Family and Youth (BMFGJ) on the pricing of the medicine. The Federation only has to provide the reasons for rejecting the medicine and	The Medicines Evaluation Committee (HEK) is an advisory body to the Federation of Social Security Institutions (HBV) for inclusion of the medicines in the code of reimbursement (EKO). The members of the HEK and manufacturers holding the marketing authorisation must not discuss any aspects of the review. The committee consists of 20 members and the agendas of the meetings are published on the HBV website. The HEK consists of 20 members including ten members from the Social Insurance System including specialists from the	The HEK consider the following factors when considering an application (Austrian Federation of Social Insurance Institutions, 2004): 1. Pharmacological evaluation 2. Medico-therapeutic assessment – the added therapeutic value of the medicine. The therapeutic benefit is classified under the following categories: 1. Substantial therapeutic benefit in the majority of patients 2. Substantial therapeutic benefit for a subgroup 3. Added therapeutic benefit for the majority of patients 4. Added therapeutic benefit for a subgroup of patients 5. Similar therapeutic benefit for patients 6. No added therapeutic benefit. 3. The Health Economic evaluation. There is no explicitly	The details of those medicines included in the reimbursement code can be found on the following website (Austrian Social Security, 2011b).

	must provide reasons in reference to points for which the manufacturer has had the opportunity to comment (PPRI, 2007a).	Federation, three independent Scientific representatives (pharmacologists and physicians from university institutions), two representatives from the Federal Labour Board, two representatives from the Austrian Medical Association, one representative of the Austrian Chamber of Pharmacists. Each member of the committee has one deputy. The Federation appoints the members and their deputies for a period of 5 years (Austrian Federation of Social Insurance Institutions, 2004).	reported cost-effectiveness threshold.	
Belgium	The NIHDI CRM provides advice to the Minister of Health. The Ministry of Economy provides information on the maximum price (Adriaens and Soete, 2010).	The CRM voting members consist of: seven members with an academic term in Belgian universities; eight members appointed by the insurers; four members appointed by the professional associations representing the medical profession; three members appointed by professional associations representing the pharmacists – These all have voting rights. The members that are consultative with no voting rights are two members appointed by professional associations representing the pharmaceutical industry; one member nominated by the Minister responsible for Social Affairs in its attributions; one member nominated by the Minister responsible for Public Health in its attributions; one member nominated by the Minister in Economic Affairs in its	Class 1 medicines are those with added therapeutic value, Class 2 are those with comparable therapeutic value and Class 3 are generic medicines The decision to reimburse those medicines in class 1 depends on the following criteria: 1. The therapeutic value, taking into account efficacy, effectiveness and the user-friendliness of the product 2. The market price of the drug 3. The clinical effectiveness and likely impact taking into account of the therapeutic and social needs 4. The budget impact for national health insurance 5. The cost-effectiveness of the product from a perspective of national health insurance. Class 2 and 3 drugs do not have to be assessed with regards to cost-effectiveness and further class 3 do not have to have an assessment of therapeutic value (Adriaens and Soete, 2010).	The Ministers decisions are published on the NIHDI website alongside the evaluation reports (NIHDI, 2011).

		attributions; one member representing the Department of the medical examination of the NIHDI(Adriaens and Soete, 2010).		
Canada	The PBAC makes recommendations to each of the provinces that make the final decision on the reimbursement and pricing given their local priorities (CADTH, 2011a).	The Canadian Expert Drug Advisory Committee (CEDAC) is an appointed, national, independent body of physicians, pharmacists and other health care professionals and public members (CADTH, 2011b).	The CEDAC will consider in its deliberations the following factors (CADTH, 2010): 1. Clinical studies, which assess safety and/or efficacy of the Drug in appropriate populations (Note: When available, effectiveness data will be compared with current accepted therapy) 2. Therapeutic advantages and disadvantages relative to current accepted therapy 3. Cost-effectiveness relative to current accepted therapy 4. Patient perspectives obtained through Patient Group Input.	The final recommendation and reasons for the recommendation are released publicly on the CADTH website (CADTH, 2011c).
Denmark	The Danish Medicines Agency (DMA) makes the final decision on general reimbursement and the individual reimbursement status of medicines. The Reimbursement committee provides advisory recommendations to the DMA. The DMA's final decisions may be appealed to the Ministry of Interior and Health (Danish Medicines Agency, 2008).	The Reimbursement Committee consists of a maximum of 7 people, of whom 2 must be general practitioners. Members are appointed by the Minister of the Interior and Health after recommendation by the Danish Medicines Agency. One member is appointed by the Minister of the Interior and Health after recommendation by the Regions' Board for Salaries and Rates (Regionernes Lønnings- og Takstnævn). The committee's members are appointed for 4 years at a time and collectively possess a broad professional expertise (DMA, 2011c). The DMA takes the advice from the professional medical recommendation from the reimbursement committee (MTN), other scientific societies,	The decision to provide the medicine under general reimbursement considers the following criteria (Danish Medicines Agency, 2008): 1. Medicines therapeutic effect (Hierarchy of evidence considered) 2. Value added proportionate to the price. 3. Pharmacological documentation 4. Side effects 5. Price survey 6. Optional health economic evaluation to determine that a premium price is reasonable in relation to the therapeutic effect.	The recommendations are provided on the website. The details of any reappraisal are also provided on the website. The minutes of each of the reimbursement committees meetings are provided on the website (DMA, 2011b).

		Pharmaceutical industry and patient organisations.		
Finland	The PPB works in conjunction with the Social Health Insurance institution and the Ministry of Social Affairs and Health. PPB will request an opinion from Kela and from its own clinical expert group. Kela plays a role in evaluating the pharmacoeconomic reports on new medicines. Having received the expert opinions, PPB makes an independent decision (Ministry of Social Affairs and Health, 2011a).	The Pharmaceuticals Pricing Board consists of seven members and their deputies nominated by the Ministry of Social Affairs and Health for three years at a time. The board members have to be university graduates with at least a Masters Degree. At least one of the members has to represent medical, one pharmaceutical, one legal and one economic expertise. Two members of the Pharmaceuticals Pricing Board are from the Ministry of Social Affairs and Health, one from the Ministry of Finance, two from the Social Insurance Institution (Kela), one from the National Agency for Medicines and one from the National Research and Development Centre for Welfare and Health (STAKES (Ministry of Social Affairs and Health, 2011b)).	There are different criteria dependent on the type of reimbursement, basic or special. On the basis of severity certain diseases are reimbursed in a list produced in 2005. Basic reimbursement focuses: Added therapeutic value of the medicine Special reimbursement focuses (PPB, 2011): 1. Need – the necessity og a medical product and nature of disease 2. Added therapeutic value 3. Cost-effectiveness 4. Economic considerations (cost of treatment and budget impact).	The reimbursement decisions and reasonable wholesale prices are provided on the Ministry of Social Affairs and Health website (Ministry of Social Affairs and Health, 2011c).
France	The HAS committee is called the Transparency committee and considers the dossier from the manufacturer and a review of the literature. A recommendation is produced along with a judgement of the ASMR and SMR are provided for the second stage where price is negotiated by the CEPS. The final reimbursement	Transparency committee includes physicians, pharmacist, specialist in methodology and epidemiology. There is no third party synthesis of evidence (HAS, 2011b).	The committee judges the SMR and ASMR for the medicines. This is performed by a majority vote for the two criteria. SMR: The score takes into account the severity of the condition and other data specific to the drug such as the effectiveness and adverse reactions, place in the therapeutic strategy, existence of other therapeutic alternatives and importance for public health. The SMR determines the level of cost-sharing paid by members of the health insurance system and whether the medicine justifies reimbursement. The SMR takes four categories; Major, Moderate, Low and insufficient (does not justify reimbursement). ASMR: The Improvement in Medical Benefit is first provided	The decisions are provided on the HAS website (HAS, 2011a).

	recommendation and price is made by CEPS in the Ministry of Health (Rochaix and Xerri, 2009).		in the manufacturer submission as a claimed score for the medicine. The ASMR is a score of the relative-effectiveness of the medicine compared to the medicine used in practice. There are five different levels of ASMR from Major Improvement (I), Important (II), Moderate (III), Minor (IV) and no improvement (V). The ASMR determines the pricing that is negotiated between the manufacturer and CEPS. A separate ASMR may be rewarded to a medicine that has different benefits in different indications or patient subgroups. The ASMR determines the price negotiated by the CEPS. CEPS negotiates price for outpatient medicines and those medicines that are used in hospital but not included in the DRG (those included in the DRG are negotiated with individual hospitals). Those rated on the ASMR of I, II or III are allowed to set a price higher than the comparator, IV depends on the context and V must be cost-saving in relation to the relevant comparator (s). The CEPS also sets price volume agreements with the manufacturer where in the event that sales exceed the forecasts for the four years the company is required to provide a claw back for the additional costs (Grandfils, 2008).	
Germany	The Federal Joint Committee decides whether a medicine should undergo an early benefit assessment. The IQWIG may be delegated to review the manufacturer's submission and the G-BA will make an early assessment of the benefit of the medicine. IQWIG may be asked to provide a cost-effectiveness analysis by the manufacturer following arbitration for the price of the medicine (Federal Joint Committee, 2011d).	The G-BA makes the final decision. The committee includes three impartial members (including a chairman), five representatives of payers (statutory health insurance) and five representatives of providers (doctors, dentists and hospitals). A patient representative has the right to observe deliberations but does not have the right to vote (Federal Joint Committee, 2010).	At early assessment the added therapeutic value is assessed (benefit). This will follow a 6 point assessment (Federal Joint Committee, 2011b): 1 - Major improvement in benefit: A significant additional benefit, primarily a cure for the disease, a significant survival time, a long-term freedom/avoidance of serious side effects. 2 - Significant improvement in benefit: A significant additional benefit, moderate life extension, substantial slow down in symptoms, avoidance of serious side effects. 3 - A small additional benefit is when one of the functional benefits shows a moderate reduction in non-fatal symptoms or side effects. 4 - An additional benefit exists but is not quantifiable because there no scientific evidence base is possible 5 - There is no demonstration of value added benefit. 6 - The benefits of the drug to be evaluated is less than the benefit of the appropriate comparison treatment.	All decisions made by the G-BA are documented on the website (Federal Joint Committee, 2011c).

			This directly determines the price negotiations that are undertaken by the national confederation of statutory health insurance (orphan drugs are excluded from this process). An assessment of the cost-effectiveness can be requested by the manufacturer and this is performed by IQWIG using the efficiency frontier is used 15+ months post the initial marketing authorisation for the product (Federal Ministry of Health, 2011, Leverkus, 2011).	
Ireland	The NCPE provides the critical appraisal, rapid reviews and pharmacoeconomic analysis, The Corporate Pharmaceutical Unit products committee selects medicines to be assessed by the NCPE and uses this information to appraise and provide the final reimbursement decision (Tilson et al., 2010).	The NCPE review group critically appraises the manufacturer submission. The group consists of a clinician, pharmacist, scientist, health economist and statistician. Local expert opinion is sought with regards the place of the new medicine (NCPE, 2011a).	Manufacturers must first submit for a rapid review and the criteria at this stage are as follows (NCPE, 2009): 1. Number of eligible patients in the population 2. Medicine replaces or adds to the available medicines 3. Potential budget impact 4. Price compared with available comparators 5. Clinical-effectiveness 6. Cost-effectiveness (if available) from other jurisdictions A recommendation maybe made for reimbursement or this maybe referred for a full pharmacoeconomic analysis if they are high cost medicines or are high budget impact. The economic evaluation is critically appraised using the Drummond 10 point checklist. The decision criteria considered for the recommendation are (NCPE, 2010): 1. Cost-effectiveness – There is no fixed cost-effectiveness threshold in practice and if the cost-effectiveness estimate is significantly higher other factors will be considered. However previous recommendations have shown that a medicine with an ICER of less than €45,000/QALY is more likely to be reimbursed. 2. The level of uncertainty associated with the clinical and cost-effectiveness evidence 3. Budget impact 4. Innovative nature of the medicine 5. Lack of available alternatives.	The summary of the recommendation provided by the NCPE is available on the website (NCPE, 2011c).
Israel	The manufacturer submits and the Medical Technologies Administration (MTA) of	The manufacturer submits and PNAC makes the final decision for inclusion on the NLHS. The PNAC is appointed by the Ministry of Health	The committee takes into account the following factors: 1. Life Saving technology 2. Potential for the technology to prevent mortality and morbidity	The PNAC decisions and deliberations are available on the Ministry of Health website but the details with regards to the impact on the budget are not

	the Ministry of Health screens the submission and provides a rapid assessment. A list of technologies is provided to the Medical Technologies Forum and they put together an evaluation and consider evidence from other professional bodies and other jurisdictions agencies. The MTA provides a prioritised list of medicines in three groups (A,B,C) for which the Public National Advisory Committee (PNAC) makes the final decision on inclusion (Greenberg et al., 2009).	and is composed of twenty representatives, including the Ministry of Health, Ministry of Finance, Health Maintenance Organisation, experts in health economics and representatives of the public at large (Greenberg et al., 2009).	3. Number of patients who might benefit from the technology 4. Financial burden of illness 5. The available treatment alternatives 6. Degree of extension of life and quality of life 7. Degree of financial savings 8. Budget impact 9. Economic evaluation (from 2007) A score is provided and if there is an estimate of cost/benefit of the new medicine in the form of cost-effectiveness (Cost per QALY) then this is also taken into account alongside these other criterion. Cost-effectiveness is not however a specific criterion in the decision-making and is rarely provided by the manufacturer. The score is provided on a scale from 1 to 10 and the medicines are classified into three groups. Group 1 consists of high priority technologies (grades 8-10), group 2 consists of intermediate priority technologies (4-7) and group 3 consist of low priority technologies (grades 1 -3). Relative criteria of the decisions on the grades are not disclosed to the general public (Ministry of Health, 2010).	disclosed (Greenberg et al., 2009).
Italy	The manufacturer, the two sub committees of the AIFA; Scientific technical committee (CTS) and the Pricing and Reimbursement Committee (CPR) make recommendations for provision on the PFN formulary. The Executive Board comprised of 5 members makes the final decision on inclusion on the list (AIFA, 2011b).	The Scientific Technical Commission consists of 17 members that include medical practitioners and pharmacologists. The Pricing and reimbursement committee (CPR) consists of 12 expert members of 5 are nominated by the Ministry of Health, 5 are nominated by the regions, 1 representative of the Ministry of Economy and 1 representative of the Ministry of Production Activity. These members have proven experience in negotiation of prices and particular expertise in health economics (AIFA, 2011d).	The CTS takes into account the level of therapeutic innovation using an algorithm of defined characteristics, including (AIFA, 2007): 1. Severity of disease, 2. Availability of treatments 3. Added therapeutic effect. The scores for each of these components is combined to assess whether the medicine represents an Important, moderate or modest therapeutic innovation. Those representing a therapeutic innovation undergo price negotiations with the CPR and those that are equivalent must be priced below or at a similar level to the other relevant available medicines. The manufacturer's negotiated price is based on the following criteria (Folino-Gallo et al., 2008): 1. The cost-effectiveness of the treatment, regarded as useful for treatment of the disease and whether the drug is more appropriate than those drugs already available for the same therapeutic indication. There is no cost-effectiveness	The final decisions of the Executive Board are published in the Official Journal of Italy. The medicines lists are provided on the AIFA website (AIFA, 2011c).

			threshold in Italy; 2. The risk-benefit is ,pre favourable than drugs available for the same indication; 3. Economic impact assessment on the National Health Service; 4. Cost of treatment per day compared to medicines of the same effectiveness; 5. Market shares of drug acquired; 6. Comparison of prices and consumption in other European countries.	
Hungary	The Office of Health Technology Assessment (OHTA) provides a critical appraisal of the manufacturer submission. The TAC committee of the NHIFA uses information from their recommendations to make a final decision for the medicine (PPRI, 2007b).	The TAC members include members from the HIFA, Ministry of Health, Ministry of Finance Ministry of Economy and Transport, Hungarian Chamber of Pharmacists, Hungarian Medical Association, College presidents that have voting rights. It also consists of members that do not have voting rights such as the secretary, National Institute for Heath Information and Library (ESKI) and National Health insurance individual (Gulácsi et al., 2009).	The criteria for inclusion on the reimbursement list are as follows (PPRI, 2007b): 1. Clinical efficacy 2. Safety 3. Lack of alternative therapy 4. Cost-effectiveness 5. Price 6. Budget Impact	The appraisals are not published on the website.
Korea	The Drug Reimbursement Committee of HIRA is responsible for reviewing the HTA report for recommendation in the positive list (Bae and Lee, 2009).	The Drug Reimbursement Committee consists of 18 members that are appointed by the MOHW (Bae and Lee, 2009). The DREC includes healthcare professionals, academics, patient representatives, HIRA staff and other government department staff (Yang, 2009).	The Drug Reimbursement Committee considers the following factors (Bae and Lee, 2009): 1. Clinical usefulness/value 2. Pharmacoeconomics – there are Guidelines for Economic Evaluation of Pharmaceuticals in Korea (KPEG). There is no threshold reported for the inclusion of medicines. Although Yang (2008) reports discussion of a range of x0.8-1.2 of GDP. 3. International countries reimbursement status 4. International treatment guidelines 5. Budget Impact. The NHIC considers the following factors in the price negotiations (Bae and Lee, 2009): 1. The total cost of alternative medicines	The appraisal documents are not available publically.

			2. Budget impact 3. Reference price 4. The HIRA Drug Reimbursement Committee Evaluation.	
Mexico	The General Health Council makes the final decision and is informed by the Interinstitutional working group (Moise and Docteur, 2007).	The General Health Council of Mexico is composed of representatives of thirteen public health institutions as well as other government offices, non-governmental organizations, representatives from health professional's academies and health-related education representatives. The final decision is made on majority vote (General Health Council, 2011a).	There are three criteria that all medicines must meet for inclusion into the Basic Formulary of Inputs (Moise and Docteur, 2007): 1. The medicine must have a marketing authorisation 2. The medicine must meet all safety and clinical tests. 3. The medicines should be cost-effective.	The basic inputs table is published on the website with details of those medicines included. This does not include details of the deliberations for each of the medicines appraised (General Health Council, 2010).
Netherlands	The CFH report is considered by the CVD board that prepare the final advice. The Board must also advise the Minister of Health of any social consequences as a result of the package recommendation. These meetings occur in public and are called Advisory Package (ACP) meetings. Other stakeholders such as clinician, patients and insurers may be consulted at other stages in the process (CVZ and Ministry of Health Welfare and Sport, 2010).	The CFH committee consists of 22 external independent experts that can serve for a maximum term of eight years. The CFH membership includes pharmacist's physicians, health economists, health researchers/scientists, and representatives of the Ministry of Health. The Executive Board (CVZ) has three members that are appointed by the Minister of Public Health, Welfare and Sport. The ACP committee (Appraisal committee) includes the three executive board members and also has six expert members with practical knowledge of social security issues (CVZ and Ministry of Health Welfare and Sport, 2010).	The CVZ has four criteria for assessing what should be included in the basic insured package: 1. Necessity: does the illness or the required care – given the context in society – justify a claim on solidarity. This may include burden of disease or rarity of disease? 2. Effectiveness: does the form of care deliver what is basically expected to do? 3. Cost-effectiveness: is the relationship between costs/benefits broadly acceptable? This is appraised for medicines of added therapeutic value. 4. Feasibility: is inclusion in the package feasible, now and in the long term? The Council are allowed to also take into account personal responsibility, incidental effects on society and temporary nature of the interventions. The appraisal must consider the therapeutic value provided by the medicine (CVZ and Ministry of Health Welfare and Sport, 2010). The therapeutic value is categorised into three groups depending on the properties of the medicine. The	CVZ advice and CFH report including annexes are published on the website of the CVD among publications of CFH Reports (CVZ, 2011b).

			properties included when assessing therapeutic value are the positive benefits provided (RCT evidence) and adverse events, experience (the use of the medicine in practice by patients), usability (administration time) and applicability (the medicine may benefit different groups of patients for the same disease). The criteria are assessed in relation to morbidity, chronic nature of the disease and availability of alternatives. The medicines are classified into three categories: 1. Medicines with a therapeutic loss in comparison with other included treatment options; 2. Medicines which have equivalent therapeutic value compared to those of others in the package 3. Medicines with a therapeutic value in comparison to other medicines already in the insurance package. Budget impact is submitted but it is not a formal appraisal criteria. The appraisal phase is conducted by the Advisory Package Commission that considers the societal implications of any recommendation. The Minister makes the final decision and there is no explicitly stated threshold. However in 2009 the CVZ published guidance of a threshold range depending on severity of illness. (A background study on the 'cost-effectiveness' package principle for the benefit of the appraisal phase in package management CVZ report 2010). The threshold stated was EURO10,000 per QALY for less severe illness up to EURO80,000 per QALY for severe illness. The Minister of Health has not confirmed this threshold. The Inpatient Expensive medicines are appraised for therapeutic value and a plan made for assessment of the real-life cost-effectiveness at four years. The medicine is temporarily listed during this period (van Halteren, 2011).	
New Zealand	The PTAC committee reviews and appraises the evidence provided by the manufacturer and	The Pharmacology and Therapeutics Advisory Committee (PTAC) is a clinical advisory committee that has a role to	PHARMAC uses the following decision criteria (PHARMAC, 2010): 1. The health needs of all eligible people within New Zealand.	The minutes of the PTAC meetings are provided on the website (PHARMAC, 2011b).

	PHARMAC (when additional analysis undertaken). The PHARMAC board appraises the medicine following 9 criteria (PHARMAC, 2010).	provide objective clinical advice to the PHARMAC Board. The committee consists of 12 Medical Practitioners that are nominated by the professional medical bodies (PTAC, 2010). The PHARMAC board consists of five members (including the chairperson). The Board makes the final decisions for inclusion on the Pharmaceutical Schedule. The Minister of Health appoints each member of the Board for a period of 3 years (PHARMAC, 2011d). The Therapeutic Group Managers are responsible for negotiating the listing and commercial agreements which may include price negotiations special authority, expenditure caps, rebates on pharmaceutical price and multi-product agreements (bundling). The negotiations may lead to a re-prioritisation of the medicine.	2. The particular needs of Māori and Pacific peoples. 3. The availability and suitability of existing medicines and related products 4. The clinical benefits and risks of pharmaceuticals. 5. The cost-effectiveness of meeting health needs by funding pharmaceuticals, rather than by using other publicly funded health and 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 Pharmaceutical 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, in PHARMAC's Funding Agreement, or elsewhere. 9. Any other criteria that PHARMAC thinks are relevant. PHARMAC conduct a consultation whenever taking into account other criteria. PHARMAC has no threshold below which a medicine will be considered cost-effective. This is because cost-effectiveness is only one of nine criteria. The threshold is also likely to vary year on year with changes to the fixed budget.	
Norway	The Drug Administration of NoMA can assess and approve applications that do not exceed certain budget restrictions. The application may be referred to the blue prescription board if the drugs budget impact exceeds NOK 5 million or is a major therapeutic innovation. The board help to ensure the quality of decision-making on important reimbursement issues. This will be	The Blue prescription board is comprised of seven members that include health economists, pharmacists, physicians and GPs. The experts are appointed for a period of two years (NoMA, 2011b).	The approval of a blue prescription relies on the following criteria being met. The Blue Board will consider these points for those medicines referred (PPRI, 2008b): 1. The medicine is used to treat serious diseases or risk factors with high probability will lead to or aggravate a serious illness, 2. There is prolonged treatment or risk of prolonged treatment, 3. The medicinal product has a scientifically well-documented and clinically relevant effect in a defined, appropriate patient population, and 4. The cost of medicine is in a reasonable relation to the therapeutic value and the costs associated with alternative therapies.	The details of the available medicines are provided on the NoMA website: (NoMA, 2011d).

	particularly relevant in cases of therapeutic innovations that can lead to significant changes in treatment and thus the use of resources. The Board should be consulted if the drug is claimed to represent a major therapeutic innovation (PPRI, 2008b).			
Poland	The Consultative council makes recommendations after considering the HTA analysis prepared by members of AHTAPol. The Ministry of Health makes the final recommendation (Lipska, 2010).	The Consultative Council consists of 12 members that are appointed by the Minister of Health for a period of 6 years. The members include Presidents of Medical Schools, the Supreme Medical Chamber, the Chief of the Pharmaceutical Council, the Supreme Council of Nurses and Midwives and the National Health Fund. The Council votes on the recommendations for new medicines. The AHTAPol consults National Organisations in the medical specialism and the National Health Fund for any financial concerns. The two groups have 30 days to issues their opinions for consideration by the Consultative Council (AHTAPol, 2011b).	The Consultative Council takes into account the following factors: (Niewada et al., 2011): 1. Clinical effectiveness/efficacy 2. Safety 3. Cost-effectiveness 4. Impact on health system (budget impact) 5. Wider social and ethical aspects	The appraisals are provided on the website (AHTAPol, 2011c).
Portugal	The DGAE firstly makes the maximum pricing decision. The INFARMED board makes the final reimbursement recommendation (PPRI, 2008a).	The INFARMED has an executive board that contains five members that are appointed by the Ministry of Health. External pharmacologists and economists are involved in the assessment but no other stakeholders are involved in the appraisal (INFARMED, 2011a).	The appraisal of medicines for inclusion in the list of medicines reimbursed by the NHS is based upon scientific evidence demonstrating the efficacy and effectiveness of the medicine within the indication. A medicine maybe listed if it meets one of the following criteria (PPRI, 2008a): 1. The medicine is a new substance or has an innovative mechanism of pharmacological action with greater efficacy or tolerance than the alternative listed treatment	The listing recommendations are provided on the INFARMED website alongside the evaluation reports (INFARMED, 2011b).

			2. The new medicine is of similar composition to the other reimbursed medicines with a price 5% lower than the non-reimbursed generics 3. The new pharmaceutical form has a greater therapeutic benefit or cost-benefit ratio than those medicines that are already reimbursed 4. The new medicine is not a therapeutic innovation but has an economic benefit with the same therapeutic benefit as those medicines already reimbursed 5. A combination of medicines that are already reimbursed and demonstrate a therapeutic advantage but price does not exceed the sum of those already reimbursed. 6. Combination of active substances that are not individually provided on the market but demonstrate an advantage over medicines in the same therapeutic group using RCT evidence.	
Spain	The Ministry of Health is involved in the reimbursement decision and the Inter-ministerial Commission for Pharmaceutical Prices is involved in the pricing of medicines (Vogler, 2009)	The Ministry of Health, Minister of Health and members of the Spanish Agency for Medicines and Health Products (Vogler et al., 2009). The composition skills could not be identified from the documentation and website.	The following criteria are used when the Ministry of Health considers a medicine for reimbursement: 1. The severity, duration and sequence of different pathologies for which the medicine is indicated 2. The specific necessities of certain patient groups 3. The therapeutic and social usefulness of the pharmaceutical 4. The budget impact of the medicine and price of medicine 5. The existence of alternative medicines to treat the disease 6. The degree of innovation of the medicine A report is prepared by the Spanish Agency for Medicines and Health product, which summarises the clinical efficacy of the medicine (Vogler et al., 2009). Pharmacoeconomic studies have been used by regional HTA agencies but this is not a mandatory requirement for the reimbursement and pricing of medicines in Spain.	The details of the appraisal cannot be found on the agency website. A list of medicines approved can be found on the Ministry of Health website (Ministry of Health & Social Affairs, 2011).
Sweden	The Pharmaceuticals Benefit Board is responsible for making	There are ten board members and chairman who is appointed by the government to serve on the expert	There are three criteria that must be fulfilled if a medicine should be reimbursed. The criteria are provided in the Health and Medical Services Act 15 (LFN, 2008):	The minutes of the meetings are published on the TLV website. If the assessment can be made public (no

	decisions on the reimbursement of medicines. The Board may consult with expert advice from the 18 county councils and may require expert advice from the Swedish Council on Technology Assessment in Health Care (SBU). However, SBU has no official influence on pricing and reimbursement. The manufacturer is invited to deliberations when they are proposing more restrictive or to not recommend the medicine. The manufacturer is sent the assessment prior to the meeting. The manufacturer may decide to verbally present the case to the Board. The manufacturer has 30 minutes to put forward the case on the assessment. There is no requirement for attendance at the deliberations and details maybe submitted by the manufacturer in writing (LFN, 2008).	board for two years (each has their own deputy appointed) (LFN, 2007) In 2010 the number of members on the board was reduced to six plus the chairperson (with deputies). The Director General is also able to attend the meeting but cannot vote. The Board includes one pharmacologist. One health economist one patient group representative and three members of the County councils. The Chairman must also be able to provide legal advice to the Board (TLV, 2011b).	1. The Human Value Principle: Underlies the respect for equality of all human beings and the integrity of every individual. The TLV may not discriminate against people because of sex, race, age etc. when making a decision for reimbursement. 2. The need and solidarity principle: Those in greatest need take precedence when considering reimbursement of pharmaceuticals. Individuals with more severe diseases are prioritised over people with less severe conditions. 3. The cost-effectiveness principle that states that the cost of using a medicine should be reasonable from a medical, humanitarian and social-economic perspective. There is no formal cost-effectiveness range. Budget impact is not formally assessed or appraised. Cost-effectiveness is a crucial principle and is analysed from a societal perspective. The Board must ensure that none of the three criteria are contravened. The Board primarily weights up the need and solidarity principle with the cost-effectiveness principle. They must be weighed equally against each other. The Cost-effectiveness criteria must be therefore weighed against the severity of disease. The severity of the disease is considered using five categories, relevant, initial condition, prevent injury or death without treatment with the medicine.	commercially sensitive data) this will also be provided on the TLV website. The details of the not recommended decision may not be completely provided because the manufacturer requests removal of confidential information (TLV, 2011a).
Switzerland	The Federal Drugs Commission reviews the manufacturer submission and makes an advisory recommendation. The Federal Office for Public Health (BAG) makes the	The Federal Drug Commission advices the FOPH on the Pharmaceutical Speciality List (SL-List). The FDC consists of 20 members, four members of the faculty of medicine and pharmacy, three medical professionals, three	The framework for reimbursement and pricing sets out the following main elements to be considered: 1. The price of the new applicant medicines in other countries – The ex-factory price of a listed medicine cannot exceed the average ex-factory price of a set of main countries (Germany, Denmark, United Kingdom and the Netherlands).	There are no summary details of the appraisals performed by the Federal Drug Commission. A press release is provided on the Federal Office of Public Health (Federal Office of Public Health, 2011).

	final decision for inclusion in the list of medicines (Paris and Docteur, 2007).	pharmacist, one hospital representative, three members from the health insurers, two people covered by the insurance, two pharmaceutical representatives, one person from the Cantons and one person from the medicine regulatory agency, Swiss Agency for Therapeutic Products (SATP) (Paris and Docteur, 2007).	2. Relative effectiveness of the medicine – The relative effectiveness of the medicine should be classified by the Federal Drug Commission on the following levels of innovation: 1. Therapeutic breakthrough 2. Therapeutic progress 3. Savings compared to other medicines 4. No therapeutic progress and no savings 5. Inappropriate for social insurance 3. R&D costs – The medicines the either demonstrate (1) therapeutic breakthrough or (2) therapeutic progress are eligible to gain an "innovation premium". The price may be 10% to 20% of the existing price of the therapeutic comparator (Paris and Docteur, 2007).	
United Kingdom - England	The manufacturer submits and an ERG or assessment group reviews the submission depending on the type of process followed The appraisal committee is responsible for the decisions. The Guidance Executive (consisting of the NICE Executive Directors) signs off the guidance and implementation for publication. The Secretary of State appointment individuals to the Guidance Executive and can provide direction to the Guidance Executive. The Guidance Executive provides final approval for the guidance and its implementation. The Guidance Executive can provide clarification on procedural issues prior to	There are four appraisal committees and each committee will normally consist of 33 voting members including the chair. The decisions of the committee will normally be arrived at by a consensus of the members. The members vote anonymously and a simple majority vote determines the decision. Committee members are appointed for a 3-year term and are drawn for the NHS, patient and carer organisations, academia (Health economists, statisticians, biostatisticians) and the pharmaceutical and medical device industries (NICE, 2011a).	The committee is expected to consider the following under the direction of the Secretary of State for Health (Secretary of State, 2005): 1. Broad balance of clinical benefits and costs 2. Degree of clinical need to patients with conditions or diseases under consideration 3. Any guidance issued by the Secretary of State (End of life supplementary guidance 2009) 4. The potential for long-term benefits to the NHS from the innovation. Social value judgements are elicited from a separate citizen's council. The committee is not able to make recommendations on price of technologies to the NHS. There are normally two appraisal meetings for each technology considered (NICE, 2008): 1. Appraisal of clinical effectiveness –The committee may take into account with discretion to the weight of each factor: nature and quality of the evidence, uncertainty regarding the evidence differential benefits in different groups, the patient perspective on risks and benefits. 2. Appraisal of cost-effectiveness – The strength of the supporting clinical effectiveness evidence, robustness of the economic model, plausibility of the inputs, preferred modelling, range and	The full details and documents of the appraisals are provided on the website. This is date stamped and includes the ACD document FAD document and the final guidance issued. NICE has detailed documentation provided of the entire process (NICE, 2011e).

	approval of the technology (NICE, 2008).		plausibility of ICER's and the likelihood of decision error and consequences. The appropriate threshold to be considered by the appraisal committee is the opportunity cost of the programmes displaced by new more costly technologies. The committee uses an explicit threshold range: - Below a most plausible ICER of £20,000, the committee decision to recommend will normally be based on the cost-effectiveness and the estimate and the acceptability of the medicine as an effective use of resources. When not recommended the committee will make reference to the robustness (inputs into the model) and certainty around the estimated ICER. This maybe demonstrated by sensitivity analysis. - Above a most plausible ICER of £20,000, judgements will take into account the following factors (These factors will be more explicitly referenced as the ICER increases within this range): 1. The degree of certainty around the ICER. In particular a committee will be more cautious to recommend when ICERs are uncertain. 2. The assessment of changes in HRQL has been inadequately captured and may misrepresent the utility gained. 3. The innovative nature of the technology, if it adds to the demonstrable and distinctive benefits that may not have been captured in the QALY measure. - Above a most plausible ICER of £30,000 the committee will need to identify an increasingly stronger case for supporting the technology as an effective use of NHS resources.	
United Kingdom - Scotland	The NDC receive a submission from the manufacturer of the relevant evidence and in contrast to NICE in England, do not commission a third party to provide a separate review of the clinical evidence and economic evidence (in the	The SMC process includes two committees. The NDC includes clinicians and pharmacists – nominated by the ADTCs a health economist, a statistician and two industry representatives. The SMC includes a wider representation including a Chief Executive, Finance Directors, patient and public representation, Association of	Clinical effectiveness: The NDC reports a qualitative description of the efficacy and relative-effectiveness considerations. This has been informed by six questions asked to a number of independent experts on the following (SMC, 2011a): 1. Are there guidelines, available or in preparation, which do (or could) influence Scottish prescribing in this area? 2. Do you wish to highlight any areas of unmet need in relation to the relevant condition(s)? 3. What are the current treatment options? In particular,	The recommendations and the appraisal considerations can be found on the SMC website (SMC, 2011h).

	case of SMC). The recommendation is advice and the final reimbursement decision is made by the Health Boards.	British Pharmaceutical Industry (ABPI), together with the clinical and public health members. There is no third party synthesis of evidence and/or provision of economic evaluation (SMC, 2011d).	what is the predominant treatment in Scotland? 4. What is your preferred treatment (if different to predominant treatment)? Please explain? 5. Disease prevalence: Please estimate how many patients currently receive treatment in your catchment area and/or in Scotland? (Please state population numbers if you have given an estimate for your catchment area.) 6. If you have knowledge of this particular new product for this indication, please describe how it might fit into your treatment plan. Cost-effectiveness: The fitness for purpose of the economic evidence and the interpretation of the estimate of cost-effectiveness in the context of the medicine's use in practice is considered. The economic evaluation is one criterion considered in the draft advice by the NDC to the SMC with respect to the threshold reported by NICE but other criteria are considered in the context of each decision such as the absence of alternatives, bridging to other therapies, emergence of other therapies and special issues that are specific to the medicine. The manufacturer may submit a Patient Access Scheme (PAS) to an independent group called the Patient Access Scheme Assessment Group (PASAG) to improve the cost-effectiveness of a medicine by reducing the cost of the new medicine and allowing patient access to clinically effective medicines. Factors considered in the presence of a high cost per QALY (SMC, 2011c): 1. More uncertainty in the economic analysis for Orphan drugs may be acceptable. 2. Substantial improvement in life expectancy evidence (with sufficient quality of life to make the extra survival desirable). Substantial improvement in life expectancy would normally be a median gain of 3 months but the SMC assesses the particular clinical context in reaching its decision; 3. A substantial improvement in quality of life (with or without survival benefit);	

			4. Evidence that a sub-group of patients may derive specific or extra benefit and that the medicine in question can, in practice, be targeted at this sub-group; 5. Absence of other therapeutic options of proven benefit for the disease in question and provided by the NHS; 6. Possible bridging to another definitive therapy (e.g. bone marrow transplantation or curative surgery) in a defined proportion of patients; 7. Emergence of a licensed alternative to an unlicensed therapy which is established in clinical practice in NHS Scotland as the only therapeutic option for a specific indication. 8. SMC also looks at any other special issues which may have been highlighted by the manufacturer of the medicine, by clinical experts and/or by Patient Interest Groups. These special issues are usually very specific to the drug or disease under consideration and are thus not readily categorised.	

Table A4.16: Technology assessment level: Outputs and Implementation of decision

Country	Decision outcomes	Status of decision	Opportunity to appeal/dissent	Requirements for re-appraisal of medicines
Australia	Positive list: List (unrestricted benefit): The medicine has no restriction on the therapeutic use List (restricted benefit): Can only be prescribed for certain therapeutic uses List (authority required): Two categories; 1. Restricted benefit that requires approval from Medicare Australia or DVA; 2. Restricted benefit that does no require Medicare/DVA but requires recording of streamlined authority required code. Do not list: not recommended Defer listing: The listing can be deferred pending the provision of certain information on the medicine (PBAC, 2008).	The recommendation is advisory to the Minister of Health and Ageing. The Government cannot list a medicine on the PBS without a PBAC recommendation to do so. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine and is subject to review whenever a new submission is lodged. If the listing is expected to add more than $AUS10 million the cabinet must provide approval (PBAC, 2008).	Manufacturers may resubmit to PBAC to reconsider matters from relevant previous submissions. Even if such a submission is based entirely on new data, modifies the previously requested restriction or changes the comparator, it will be regarded as a resubmission. This is because the information in the resubmission will have to provide the basis for any change to PBACs earlier decision (PBAC, 2008).	The manufacturer may re-submit when new evidence or information becomes available. In the circumstances where no new evidence is available and the manufacturer submits an independent review is undertaken. The manufacturer must identify the main issue. A single independent reviewer, whose findings are submitted to the PBAC for consideration, generally reviews this. The PBAC will then amend if necessary the recommendation accordingly (PBAC, 2008).
Austria	Positive list: The Reimbursement Code (EKO) is categorised as a traffic light system (positive list). There is also a negative list for those not included for general reimbursement. The traffic light system is as follows (PPRI, 2007a): Red Box: Newly launched medicines that have applied for inclusion in the yellow or green box Medicines remain in the box for a period of 24-36 months Awaiting established price of EU countries and time taken depends on whether an EU price can be	The HEK provides an advisory recommendation. The Federation or Austrian Social Security Institutions (HVB) makes the final decision for inclusion on the Reimbursement Code (Austrian Federation of Social Insurance Institutions, 2004).	The HVB will justify rejection decisions. The manufacturer can appeal to the Independent Drug Commission (UHK) on initial listing and if the Federation decides to delist the medicine. The UHK can veto decisions cannot amend decisions by the HVB. The manufacturer can present on the basis of a negative decision. The UHK comprises 8 expert members each with their own deputies and is accountable to the BFGMJ. The sessions of the UHK are open to the public and meetings are scheduled monthly (PPRI, 2007a).	Amendments to the reimbursement code may be made with respect to the deletion from the code (de-listing) inclusion in another area of the reimbursement code, change to the usage, or changes to the package size. The Federation will initiate this procedure either on request from the manufacturer or by itself. The Federation may decide to reassess if it believes the medicine to no longer meet the requirements of the medico-therapeutic or health economic criteria. The Federation (HVB) gives the manufacturer 30 days to present the case when they have requested a

	established Advice taken from the HEK board The Head Physician must approve the medicine for the doctor prescribing to the patient Yellow Box: Medicine considered an important therapeutic innovation Medicine is only reimbursed for a specific disease or age group, specialist doctor or limited quantities The Head Physician must approve the prescription Light Yellow Box: Pharmaceuticals maybe freely prescribed by doctors of the sickness fund. A schedule of the reasons for prescription should be kept for the lead physician Green Box: Medicines considered medically and health economically robust In general no conditions but maybe conditions in some circumstances (patient group, age etc.). A flat rate per prescription is paid for all medicines on the general reimbursement list. Negative list includes medicines that are unsuitable for outpatient care.			change to the Reimbursement Code. The manufacturer maybe requested to present a case to demonstrate that the medicine still meets these criteria. The HVB decides on the changes to the listing and justifies the decision. The manufacturer can appeal changes to the Reimbursement Code to the UHK (PPRI, 2007a).
Belgium	Three classes of medicines (Adriaens and Soete, 2010): Class 1: added therapeutic value Class 2: comparable value	The Minister of Health may make the following decisions within 30 days of receiving the CRM recommendation (Gerkens and Merkur, 2010):	The decisions can be appealed at the relevant court on grounds that procedure was not correctly followed (KCE, 2010).	There are two reasons for reappraisal to occur across the medicine classes that the initial appraisal was based on a number of hypothetical factors and new

	Class 3: generics Positive list (Package list by chapter) for inclusion: Unrestricted reimbursement in line with the SPC (chapter I) Restricted reimbursement: Chapters II – reimbursement for all common indications and prescribers keeps this on file and Chapter IV – reimbursement subject to particular reimbursement conditions and requires prior approval by health insurance. Do not list. The recommendations also include 5 categories of coverage with regards to cost-sharing (A(100%), B(85%, max EU7.20), C(50%, max EU8.90), Cs(40%), Cx(20%)).	1. Positive decision for inclusion on the list of pharmaceuticals 2.Negative decision.		evidence was required to reduce the uncertainty and budgetary concerns. Those medicines that are categorised as class 1 follow a mandatory reappraisal between 18 and 36 months. The re-assessment report is submitted along with any new evidence and real life cost-effectiveness evidence. The CRM decision may be modified and this can even result in the de-listing of the medicine. The Minister may also decide when there are budgetary concerns to provide a multiple medicine appraisal of those medicines covering similar indications (KCE, 2010).
Canada	The listing procedure is described in the procedure for common drug review (CADTH, 2010): List: in line with licensed indication List with criteria: to a specific patient population Do not list Defer: pending clarification of information.	The drug plans make final benefit listing and coverage decisions based on the CADTH recommendations and other factors, such as drug plan mandates, jurisdictional priorities, and financial resources (CADTH, 2010).	The manufacturer may request for reconsideration (CADTH, 2010). The request must comprise the reasons and grounds for the request, the relief sought and the supporting evidence. This cannot be made just because the manufacturer disagrees with the recommendation. The acceptable grounds are: the CDR/CEDAC failed to operate under the stated procedures, the CEDAC recommendation is not supported by the evidence in the reviewer's reports. The CEDAC reconsideration will result in a final recommendation. A drug plan can also request clarification of a recommendation 10 working days following notification of the recommendation.	The manufacturer may re-submit with a reduced price during the embargo period and may provide a resubmission when new clinical evidence becomes available (CADTH, 2010).
Denmark	Details of general reimbursement are	The recommendations by the	A final decision provided by the Danish	The reimbursement status of medicines

	provided on the website (DMA, 2011a): Positive list: When a medicine has general reimbursement it means that all citizens receive reimbursement from the Danish regions. General reimbursement General reimbursement with conditions (To obtain reimbursement, it may be a condition that the medicine is prescribed to certain patient groups or for the treatment of specific diseases. Not eligible for general reimbursement Individual reimbursement There is a reimbursement co-payment rate depending on the previous 12 months expenditure on medicines.	reimbursement committee are advisory and the final decision is made by the Danish Medicines Agency (Danish Medicines Agency, 2008).	Medicines Agency may be appealed to the Danish Ministry of Interior and Health. The Ministry cannot reassess the medicine agency scientific estimate (Danish Medicines Agency, 2008).	is reassessed regularly because it is acknowledged that the status of a general reimbursement medicine may change over time. The reappraisal ensures that those medicines on the general reimbursement list are still meeting the criteria and those not do not satisfy the criteria. The reappraisal process was introduced in 2004. There is set prioritisation criteria to decide which medicines should be reassessed and this includes: significance of the medicines to primary sector, public health aspects, new evidence based recommendations and high costs or high consumption. The reimbursement committee then makes the recommendation to the Danish Medicines agency and details of the assessment are provided on the website (Danish Medicines Agency, 2008).
Finland	There are three categories of reimbursement which have different levels of co-payment (Ministry of Social Affairs and Health, 2005). Basic: 58% copayment, Special (low): 28% copayment and Special (High): 0% copayment. The lower special category includes 10 diseases that are categorised as chronic illnesses. The high special category includes 26 illnesses for severe diseases (PPB, 2011). Basic reimbursement Basic restricted reimbursement Special (low) reimbursement Special (low) restricted reimbursement Special (high) reimbursement Special (high) restricted reimbursement	The recommendations by the experts are advisory and the PPB makes the final decision, which is implemented through the Social Insurance Institution, KELA. There is a positive list provided rather than those not recommended (Kivioja, 2008).	If there are no appeals the decision of the PPB is final. Stakeholders unhappy with the decision of the PPB may appeal to the Supreme Administrative Court in Finland (Kivioja, 2008).	The decisions of the PPB are provided for a fixed term period (maximum of 5 years and 3 years for a new active substance). A renewed confirmation is required when this period lapses and this should document any changes that have occurred during the reimbursement period with respect to experience of use, new clinical studies and treatment practices. A manufacturer may also propose an increase in the wholesale price but this must be accompanied by a grounded proposal to inform the proposed price changes (Ministry of Social Affairs and Health, 2005).

France	Positive list: HAS opinions are either positive or negative (conditions may also be imposed for additional studies or a target patient population) and are produced for the CEPS of the Ministry of Health where decisions are made on the price for outpatient medicines and hospital medicines that are not covered within the DRG (Meyer, 2011).	The CEPS of the Ministry of Health provides the final reimbursement decision. The recommendations of HAS are advisory (Meyer, 2011).	The manufacturer has a period of eight days from receipt of the notice of the advice to request a hearing. At the end of the 8 days in the absence of comments the opinion becomes final. The manufacturer has 15 minutes to present its cases and reasons for the hearing should be submitted. The recommendation may then be amended and a final notice sent to the Ministry of Health and stakeholders (Rochaix and Xerri, 2009).	HAS can self-refer medicines in the presence of new evidence, reviews all medicines at 5 years post-listing and assess the evidence from any post-listing studies. The recommendations at the 5-year review may result in the SMR being revised and an opinion for de-listing the medicine. Manufacturers may submit new evidence for medicines at any point in a new dossier and the Transparency committee will provide reassessment of the medicine (Rochaix and Xerri, 2009).
Germany	The early benefits assessment details whether a medicine can be added to a reference price group (Federal Joint Committee, 2011b). The early benefit assessment will result in an assessment of added therapeutic value. This means that G-BA will not reject medicines outright because of the negotiations that occur with the price of the medicine. Prescribing restrictions can be set by the FJC. The G-BA can exclude items from reimbursement (negative list) if it does not show any improvement in benefit.	Once a decision has been made on the therapeutic benefit the statutory health insurance funds and the specific pharmaceutical company then negotiates the reimbursement price for pharmaceuticals that have proven additional benefit as a discount on the original selling price within six months. If negotiations do not achieve an agreement, an arbitration commission does not reach agreement then IQWIG will be commissioned to perform a Cost benefit analysis (Leverkus, 2011).	Following the publication of the benefit assessment on the website of the Federal Joint Committee, medical and pharmaceutical experts, pharmaceutical companies and their associated organisations, the relevant pharmaceutical manufacturer, the professional representatives of the pharmacists and the relevant umbrella organisations of doctors' associations for special therapies at the federal level are consulted and given the opportunity to respond in writing to the benefit assessment of the pharmaceutical, using the templates on the website. The manufacturer can also provide verbal participation at the hearing for the decision (Federal Joint Committee, 2011b). There is an arbitration stage if a price cannot be negotiated between the two parties (Leverkus, 2011).	After one year of the final G-BA decision, the manufacturer can request a new benefit assessment if there is new scientific knowledge. It is also possible that the G-BA decides that there is new scientific evidence that makes it necessary to perform a new assessment (Federal Joint Committee, 2011e).
Hungary	Hungary operates both a positive and negative list for pharmaceuticals (PPRI, 2007b). Recommended The recommended for subsidy category	The Technology Appraisal Committee makes a recommendation and final recommendations are made in the National Health Insurance Fund's Pharmaceutical Division. These are	The manufacturer has the right to appeal if the decision made by the NIHFA is to not recommend the medicine. The appeal Committee consists of a member from the Ministry	The manufacturer may resubmit for a price change through the regular procedure (PPRI, 2007b).

	involves a copayment by patients dependent on the disease severity. Not recommended Those products that cannot demonstrate cost-effectiveness or it is deemed not proven will not be recommended. Performance linked reimbursement schemes operate alongside price volume agreements (Dankó, 2010).	then disseminated in the form of legislation by the Minister of health in agreement with the Minister of finance (PPRI, 2007b).	of Health, one Minister of Finance, one member form the Ministry of Economy and Transport, a member of the National Institute of Pharmacy, President of the Health Insurance Supervisory body and the Director of the NIHFA. The decision will be made within 60 days of the appeal. The decision will be made by the appeal panel within 60 days of receiving the appeal (PPRI, 2007b).	
Ireland	There are three recommendation outcomes used by the NCPE (Tilson et al., 2010): 1. Recommended in line with marketing authorisation 2. Recommended with restriction 3. Not recommended	The recommendation by the NCPE is advisory and is sent to the HSE CPU unit which makes the final decision for the Community Drug Scheme (Tilson et al., 2010).	The reimbursement decision will be usually made within 90 days of receipt of the manufacturer submission. If reimbursement has been refused an appeal can be lodged with an expert committee (NCPE, 2011c). The expert committee will arranged by the Health Service Executive and the Irish Pharmaceutical Health Care Association (IHPA). The expert committee will take the views of different stakeholders and a final decision provided within a further 90 days (Tilson et al., 2010).	If a new medicine is refused after appeal and the manufacturer finds new evidence, the manufacturer may provide a new submission for the pharmacoeconomics to the NCPE (Tilson et al., 2010).
Israel	Positive list (National List of Health Services) (Greenberg et al., 2009): There are three groups for which medicines maybe categorised for potential listing: Group A: consists of high priority technologies Group B: consists of intermediate priority technologies Group C: consists of low priority technologies. PNAC makes the final decision on whether the medicine is included in the annual list of new technologies. The yearly updating of the list is a unique aspect of this reimbursement system.	The Medical Technologies Forum lists are advisory but generally the PNAC only adds to the list those score A10 or A9. The Ministry of Health makes the final approval of the list produced for the additions for the year. All HMO's are required by law to provide those technologies that are added to the list (Greenberg et al., 2009).	The stakeholders in the process are not allowed to appeal decisions made by PNAC on additions to the list of technologies. There is no process to resolve any disputes that stakeholders have with regards the decision or adherence to the specified procedure (Greenberg et al., 2009).	The manufacturer must resubmit to the next cycle (next year) when new evidence appears so that the medicine can then be considered for adding to the list. The technologies already on the list have never been delisted and therefore obsolete or ineffective treatments do not get removed (Greenberg et al., 2009).

Italy	A positive list exists in Italy (Folino-Gallo et al., 2008): The medicines maybe included in the National Pharmaceutical Formulary (PFN), a positive list. Special limitations can be applied by the AFIA committee called AFIA Notes. These are restrictions based on the patient population or characteristics of the disease. These are grouped as Class A medicines (essential medicines and medicines for serious and chronic diseases): 1. Inclusion on the list 2. Inclusion on the list with AIFA Notes. Class C: Diseases of slight importance. Theses medicines are not reimbursed by the NHS. Class H: Drugs that are provided only by hospitals.	The national decision is provided to the regions. Regions have to provide Class A medicines but may decide a different level of co-payment. In 2010 a new regulation was introduced for the mandatory listing of some medicines on regional hospital formularies to reduce variation in regions provision of innovative medicines. This was to promote equal access to these medicines regardless of the regional location of the patient (Gori et al., 2010).	The regions can appeal against the compulsory listing of innovative medicines on the grounds that the criteria have not been followed. It is not clear whether manufacturers can submit an appeal in the process (AIFA, 2010). Removal of the marketing authorisation can be appealed to the Regional Administrative tribunal.	The agreement between the manufacturer and the AIFA is for two years. On expiration of the term, each party can request a renegotiation. The manufacturer can apply for a variation in reimbursement category if new evidence is found following the initial assessment and also renegotiate for a change in the price. Conditional reimbursement was first introduced in 2006 either by a payment for performance or risk sharing. Data is collected in drug monitoring registries to monitor outcomes and provide payment on this basis (Jommi, 2009).
Korea	There is Positive List System (PLS) in operation in South Korea (Kyung Lee, 2011, Moo Lee, 2011): 1. Reimbursed 2. Not reimbursed HIRA classifies medicines as 1. List 2. Not Reimbursed Decisions may be based upon Coverage with evidence development but this is limited by the number of resources available (Moo Lee, 2011).	The reimbursement assessment is made by HIRA, price negotiations are undertaken by NHIC and the Ministry of Health makes final reimbursement listing decisions (Jang, 2010).	The manufacturer can request a re-evaluation by the HIRA. The final reimbursement listing decision provided by the Ministry of Health can be appealed to the courts (Kim & Chang, 2011). There is no judicial system/law to enable an appeal of the intermediary recommendations of the DREC.	The manufacturer can request a re-evaluation of the medicine. Existing medicines are reviewed overtime to ensure that they meet the criteria for the PLS. The medicines are reassessed by therapeutic class and this is based on the growth in use of the medicines and the budget impact of the medicines. Those medicines that are not considered cost-effective are delisted (Bae and Lee, 2009).
Mexico	There are two positive lists is provided of recommendations for medicines called the Basic Formulary (Cuadro Básico) and the Catalogue of Inputs (Catálogo de Insumos). The Basic	The final listing decision made is published in the Official Journal of the Federation. The public institutions must observe the recommendations made in the basic table (Moise and Docteur,	The draft update of the table of Basic Inputs for medicines is placed on the General Health Councils website and stakeholders may comment on this within 10 working days of the draft	The basic inputs list is regularly reviewed to modify for inclusion and exclusion of medicines. A medicine maybe de-listed for a number of reasons 1.) It is not longer prescribed;

	Formulary is designed for medical care at the primary level and the Catalogue of Inputs is for medical care at the secondary and tertiary level. These provide the basis for the institution specific formularies (Moise and Docteur, 2007).	2007).	decision. The Commission will respond to the comments and inform of the technical justification for the comment received (Moise and Docteur, 2007). If a decision is unfavourable, the manufacturer cannot submit a new manufacturer submission until 4 months after the previous decision. The manufacturer may then resubmit. A formal separate appeal process could not be identified from the documentation.	2.) Medicine will not be used; 3) Awareness of another product of greater efficacy or lower toxicity (Moise and Docteur, 2007).
Netherlands	There are two separate lists for outpatient medicines and hospital use medicines. Outpatient medicines fall under the Drug reimbursement System (GVS). The medicines are classified under: 1A: Therapeutic equivalent value (equivalent price) 1B: Therapeutic added value (fully reimbursed) 2: Condition reimbursement (restrictions apply. The restrictions may be as follows: 1. A particular condition 2. Within a specific age group 3. Delivery by specialist doctor or pharmacist 4. Special permission is required. Those medicines for hospital use are categorised as normal medicines or expensive medicines. Expensive Medicines are temporarily admitted to the Expensive Drug List. This was introduced in 2006. Coverage with Evidence Development collects real life	The CFH committee provides advice to the Board that will also consider the social consequences of the decision. The final advice of the Health Board (CVZ) is sent to the Minister of Health who makes the final decision (van Halteren, 2011).	If it is considered that there are possible procedural deficiencies in the conduct of the assessment the advice can be reconsidered. A consultation can be put in place where the interested parties are given the opportunity to comment. The Chairman of the council may also consider a hearing appropriate. The intention of the hearing is not to discuss the medicines therapeutic value, or cost-effectiveness values (CVZ and Ministry of Health Welfare and Sport, 2010). Any concerned party can appeal to the Administrative court with respect to the recommendation of the CVZ or the Minister on procedural grounds [Art 116 of Health Insurance Act] (Overheid, 2011).	The manufacturer may request a review of the decision by writing to the Minister. The facts and new data should be provided. Only evidence after the previous decision can be considered. The manufacturer may also request a review if there are changes to the treatment guidelines within the indication. The request for re-assessment cannot be any earlier than 6 months after the Ministers previous decision (CVZ and Ministry of Health Welfare and Sport, 2010). Those medicines on the Expensive inpatient Medicines are assessed for real-life cost-effectiveness four years after the decision (van Halteren, 2011).

	data so that real-life cost-effectiveness can be assessed at four years (van Halteren, 2011).			
New Zealand	Positive list (Pharmaceutical Schedule) (PHARMAC, 2011a): 1. Listing for medicines (community and hospital medicines subject to national contract. 2. Listing of medicines with restrictions (conditions on prescribing and special authority required). There is cost-sharing for some medicines provided in the community. The listing schedule is provided on the PHARMAC website (PHARMAC, 2011c).	The decision provided by the PTAC is advisory and the decision provided by the Executive Board of the PHARMAC provides a decision on listing which is mandatory (PTAC, 2010).	The courts of New Zealand can review PHARMAC decisions where it has been alleged that PHARMAC has breached its public law obligations (PHARMAC, 2006).	A manufacturer may provide a reapplication (resubmission) to the PHARMAC for the following reasons: 1. New information/data becomes available (clinical trial or cost-utility analysis). 2. The manufacturer wishes to respond to issues that were raised by the PTAC with regards to the original application. The PHARMAC can make decisions to delist medicine on the Pharmaceutical Schedule (PHARMAC, 2010).
Norway	Positive list (PPRI, 2008b): The listing decision for blue prescription may be as follows: List for indication of the marketing authorisation List with limited reimbursement – This includes limiting for certain parts of the indication or a particular patient group.	The reimbursement decision for inclusion in the list can be made by NoMA for inclusion as long as the budget impact does not exceed 5 million. The Minister of Health and Parliament must make a decision for the approval of medicines under law that exceed this value for inclusion by the National Insurance Administration (PPRI, 2008b).	Interested parties may appeal against decisions made by the NoMA and this will be forwarded to the Ministry of Health within 60 days of receiving the appeal. This can be extended by 30 days if the NoMA considers it necessary to consult with the Blue prescription committee. The Ministry of Health will make a decision on the appeal within 30 days of receiving this from NoMA. This procedural timeframe maybe suspended if new information is requested from the complainant (Lovdata, 2009).	All medicines that are included in the list must meet the criteria which includes a) a medicine which is used to treat a serious disease or risk factor, b) the disease or risk of disease requires prolonged treatment, c) the medicine has scientifically well documented evidence of the clinically relevant effect, d) the cost of the medicine is reasonable in terms of the therapeutic value. The NoMA may reconsider whether the requirements are met for individual medicines in the list. The NOMA may include new conditions for these to be met or may delist the medicine because it can no longer meet the criteria. The manufacturer has the opportunity to submit documentation to demonstrate that the medicine still meets the criteria. The removal of a medicine from the list is justified and

				documentation included on the agency website (Ministry of Health and Care Services, 2004, Lovdata, 2009).
Poland	There are a number of recommendations provided by the President of AHTAPol (Matusewicz and Lipska, 2009): 1. Finance 2. Finance temporarily, provided that data are gathered for a final decision (coverage with evidence development) 3. Finance provided if particular criteria are met in the particular condition 4. Finance provided a cost-effective way of financing was assessed following negotiations on price 5. Not to Finance 6. Increase Financing 7. Decrease Financing 8. Do not change Financing	The recommendation provided by the President of AHTAPol is advisory. The Ministry of Health for inclusion in the formulary makes the final decision (Lipska, 2010).	No formal appeal process was identified from the website or literature.	The Ministry of Health provides the reimbursement decision for two years and may remove the medicine after 2 years. There is no explicit provision in the reimbursement law for the procedure on expiry of the decision. The Ministry of Health may commission AHTAPol to reassess the medicine or may decide to prolong the term of the decision provided. There may be new legislation very soon on the procedure for reassessment of medicines (Personal Communication: Gabriela Ofierska-Sujkowska Head of Recommendation Division AHTAPol).
Portugal	Positive list: There is a positive reimbursement list called the Prontuario list used in the outpatient setting. The positive list is updated on a monthly basis on the INFARMED website (Vogler and Leopold, 2009): 1. List 2. List with restriction for certain therapeutic indications which are set out in the order of reimbursement Medicines are categories under four types, which determine the level of co-payment (Vogler, 2009): 1. Category A: Includes life	The recommendations provided by the INFARMED are advisory and the Minister of Health makes the final decision (PPRI, 2008a).	If the INFARMED committee decides not to list the medicine the manufacturer is informed of the decision and given the opportunity to present additional data. If the manufacturer has concerns with the final negative recommendation they can appeal to the Supreme Administrative Court in Portugal (PPRI, 2008a).	INFARMED reappraises medicines at three years to ensure that they still meet the criteria that are specified within the law. Price adjustment may take place if it is believed that the medicine is of excess costs. The manufacturer is notified and given the opportunity to adjust the price. Those medicines that do not meet the criteria can be delisted and the reasons are made publically available. The decision to exclude medicines is based on (PPRI, 2008a): 1. Excessive cost 2. Therapeutic efficacy doubtful or too expensive 3. Lower comparative

	saving medicines (100%) and reimbursed for chronic disease indications 2. Category B: Medicines for serious diseases (63%) 3. Category C: Non-priority medicine (31%) 4. Category D: New medicines whose therapeutic value has not yet been determined (15%)			effectiveness in relation to medicine reimbursed in comparison to those approved in the same indication 4. Reduced therapeutic efficacy
Spain	There is both a positive and negative reimbursement list in Spain (Vogler et al., 2009). There are four reimbursement categories: 1. 100% reimbursement for hospital pharmaceuticals 2. 90% reimbursement for pharmaceuticals for the management of chronic illnesses 3. 60% reimbursement for the majority of prescription only pharmaceuticals 4. 0% for pharmaceuticals on the negative list	The reimbursement process is administered by the Directorate General for Pharmacy and Health Products in the Ministry of Health. The Ministry of Health makes the final listing decision (Vogler et al., 2009).	The Inter-ministerial commission on Pharmaceutical prices sets the price of the manufacturer medicine. A maximum price is set and manufacturers receive notification of this, which they can appeal if they disagree with the maximum price. An appeal can be made for the regional funding of medicines (Vogler et al., 2009).	Re-assessment may occur after one year of the reimbursement and price decision. There may have been new medicines added to the list, which are at a lower price. The Directorate General for Pharmacy and Health Products may decide to de-list the medicine (Noticias Juridicas, 2011, Vallejo, 2009).
Sweden	The following recommendations maybe made under the General Subsidy positive list (TLV, 2011d): 1. Recommended as per license 2. Restricted recommendation limited to area or special patient group 3. Not recommended The recommendations may be conditioned: 1. Reimbursement can be	The Pharmaceutical Benefits Board makes the decisions on reimbursement. These decisions are mandatory (LFN, 2007).	The decisions maybe appealed against to the General Administrative Court, which is the county Administrative Court in the County of Stockholm. In the appeal, the manufacturer must indicate the reasons for the decision being appealed and the proposed changes to the decision. The appeal must be made within 3 weeks of the decision. An individual private person cannot appeal against a decision made by the TLV (LFN, 2007).	The manufacturer may resubmit to the process with a different price or new evidence but will need to go through the entire process again (LFN, 2008). TLV will reappraise those medicines that have been given conditional reimbursement. The manufacturer may resubmit for a price change, which is a simple procedure for a lower price. A manufacturer must demonstrate that two criteria are met if it is to propose a price increase (LFN, 2008):

	limited in time to make it possible for new data to be provided to the TLV 2. The company has to specify the restrictions set by the TLV in the marketing of the medicine.			1. Urgent treatment alternative for which the condition risks the patients life or future health 2. There is considerable risk of the manufacturer removing the medicine from the Swedish market. The TLV may decide to remove the medicine as either part of the reimbursement review (2002) by therapeutic group or by the ad hoc consideration of individual medicines. The manufacturer is contacted with regards to individual cases that are reviewed for reimbursement (TLV, 2011c).
Switzerland	A positive list (Federal Office of Public Health, 2011): Called the Pharmaceutical Specialities List (SL-List): List recommended List recommended with limitations. The limitation can refer in particular to the quantity or patient medical indications.	The listing recommendations result in a change in the SL list within 30 days after the meeting by the Federal Drugs Commission. If the conditions for inclusion are not fulfilled the FOPH will provide reasons for why this has not been listed. The details are published in the Bulletin of the Federal Office of Public Health (Federal Office of Public Health, 2011).	If the medicine is not judged to meet the criteria medicine will not be approved for listing. The manufacturer can submit a reconsideration request or it can appeal to the Federal Appeal Commission within 30 days of the decision. The manufacturer must prepare a letter with the reasons for disagreeing with the recommendation (Federal Office of Public Health, 2011)	The manufacturer may apply for a price increase at least 2 years after the inclusion on the SL list. The manufacturer should submit an application with the price increase request from a therapeutic comparison and a foreign price comparison. The manufacturer may also apply for a price decrease or change to the limitations on the listing. Medicines are reviewed at 36 months after they have been included in the SL list. The medicine will be appraised to consider whether it still remains value for money. The documents must be submitted by the manufacturer 30 months prior to the review of the medicine. If the review shows the price is too high in comparison to the appropriate alternatives the FOPH can request a price reduction. Alternatively, if the medicine is found to be significantly cheaper in comparison to

				other countries, a price increase may occur. The FOPH also reviews the medicines listed for 15 years or after the expiration of the patent. The conditions of effectiveness, appropriateness and efficiency will be assessed to ensure these are still met (Federal Office of Public Health, 2011, Paris and Docteur, 2007)
United Kingdom - England	NICE classifies each decision into one of four categories: 1. Recommended, 2. Optimised, 3. Only in Research and 4. Not Recommended in 2010 (NICE, 2011f). There was an informal categorisation of decisions prior to 2010 of Recommended in line with the marketing authorisation, Restricted and Not Recommended: 1. Recommended – A medicine is recommended if the medicine is inline with the marketing authorisation from the European Medicines Agency (EMA) or Medicines and Healthcare Products Regulatory Agency (MHRA) OR inline with how it is used in clinical practice in the NHS; 2. Optimised – The recommendations have a material effect on the use of the medicine and it is recommended in a smaller subset of the patient population than the marketing authorisation. The test of materiality takes into account advice from clinical experts on the anticipated use of the medicine in routine clinical practice. 3. Only in Research – the medicine is recommended for use only in the	NICE guidance for technology appraisals apply to England and Wales. When NICE guidance is published, health professional are expected to take if fully into account. The Secretary of State in England has states that the NHS is required to provide funding and resources for medicines recommended through Single Technology Appraisals and Multiple Technology Appraisals. It is normally enforceable three months from the date of publication of each technology appraisal (NICE, 2011c).	The stakeholders have an involvement throughout the technology appraisal process. Consultees are invited to make submissions and comment on consultation documents. All consultees (national groups representing patients and carers, organisations representing health care professionals, manufacturers and sponsors, the Department of Health, Welsh Assembly, specialised commissioning groups and local health boards) may appeal against the FAD (NICE, 2009b, NICE, 2009a). The appeal process can take a total of 8 weeks to complete (NICE, 2011b). There is a standing committee called the appeal committee which is chaired by the vice chair of NICE and non-executive directors of NICE, NHS representatives, representatives with experience of the relevant industry and lay members. Consultees have 15 working days from the FAD being issued to appeal. Appeals should be submitted in writing and must fall within the three specified procedural grounds for appeal. The appeal can be heard by oral submission or written submission and the decision will be made by the Chair of the appeal panel (Written	A review date is listed on the guidance for when the review process will commence. Evidence is collected to inform the review process and the views of stakeholders are sought to identify additional evidence. If a large amount of new evidence is available the guidance will be reviewed, in contrast if there is little new evidence the review will be delayed (NICE, 2009b, NICE, 2009a). Only in research recommendations: The medicine or treatment is recommended for use only in the context of a research study, for example a clinical trial (NICE, 2011f).

	context of a research study for example a clinical trial. 4. Not recommended – The treatment is not recommended. It will not be recommended if there is a lack of evidence of its clinical effectiveness and cost-effectiveness.		submissions are usually for where there are a limited number of appeal points). The appeal must relate to sections 1 to 4 of the FAD. The grounds for appeal are: 1. Ground one: The Institute has failed to act fairly. 2. Ground two: The Institute has formulated guidance, which cannot reasonably be justified in the light of the evidence submitted. 3. Ground three: The Institute has exceeded its powers. New evidence cannot be presented in the appeal hearing. Oral hearings are open to the public, consultees, commentators, members of the public and the press. If the appeal is upheld the FAD will be returned to the appraisal committee, the appeal panel may decide that small changes are required but this does not need to be sent to the appraisal committee or the appeal is dismissed. There are no further appeal possibilities. The decision maybe challenged by applying to the High Court for permission to apply for judicial review. This must be made within 3 months of the decision (NICE, 2011b).	
United Kingdom - Scotland	Three categories of advice are provided by the SMC to the Area Drug and Therapeutic Committees (ADTC) for listing; accepted for use; accepted for restricted use and not recommended (SMC, 2011h).	The details of the recommendations are provided in an advice document for the SMC within 12 weeks of the products being made available (non-legally binding) (SMC, 2011i). The Health Boards have the final decision with regards to reimbursement (Health Policy and Strategy Directorate, 2010).	The manufacturer may ask the SMC to convene an Independent Review Panel (IRP) to look again over existing data and analyses. An IRP will review the original submission and views of the NDC and SMC. The IRP consists of three member of the SMC that were not involved previously with the submission	Manufacturers may resubmit to the SMC in the light of new evidence or a new analysis of existing evidence but the SMC does not periodically review existing advice (SMC, 2011g).

			and four members of the Scottish Area Drug and Therapeutics Committees. The IRP reports back to the SMC who is the final judge following a review (SMC, 2011g).	

Box A4.1: The Efficiency Frontier

The Institute for Quality and Efficiency in Health Care (IQWIG) convened a panel of experts in 2007 to develop the economic methods for the assessment of technologies in Germany in line with the legal requirement (§ 35b Social Code Book (SGB) V). The panel produced a document on the general methods for evaluating the relation between cost and benefits in 2009 recommending the use of an alternative approach called the 'Efficiency Frontier' in the evaluation of technologies. The method concerns finding a maximum price at which a medicine in a given therapeutic area should be recommended for reimbursement. The analysis aims to inform the decision maker about the efficiency of a given medicine in the therapeutic area, but does not attempt to judge whether the condition deserves treatment or the willingness to pay for the medicine.

The efficiency frontier is an extension to the approach of incremental cost-effectiveness ratios and concerns the use of resources in a therapeutic area. The efficiency frontier approach is defined in the guide as follows:

"The efficiency frontier plot compares the therapeutic benefit of available interventions within a given therapeutic area with the outcome-related net costs of these interventions. The additional therapeutic benefit derived from a previous benefit assessment may be transferred into an approximately cardinally scaled measure. Interventions on the efficiency frontier denote the net cost for any given benefit that is consistent with the efficiency that can be achieved by the package of interventions on the current market. Prices can lead to health technologies being positioned on an already existing segment of the efficiency frontier, showing thereby consistent efficiency with already existing interventions. If a price results in an intervention being positioned below the efficiency frontier, this indicates a lower efficiency. This price is deemed too high and needs to be adjusted, or at least justified. Interventions above the efficiency frontier indicate improved efficiency and thus redefine the frontier."

(General Methods for the Assessment of the Relation of Benefits to Costs – Version 1.0 19/11/2009)

The approach requires that the health effects of the medicines are considered in terms of actual clinical measures such as mortality, morbidity, health-related quality of life and validated surrogates meeting the IQWIG criteria. The key requirement in the definition above is that the benefits must be transformed to an approximately cardinal scale or interval properties because units along the scale have similar value (for example twice the benefit is twice as valuable). The

efficiency frontier allows the decision maker to examine the existing medicines in relation to each other in a given therapeutic area but does not establish what *should be* paid for a given level of benefit for the new medicine. The process of considering those medicines with added therapeutic benefit means that many of the medicines assessed by IQWIG are likely to lie in the right hand quadrant representing those with greater benefit at a higher cost compared with the most efficient comparator. There are three regions in this quadrant, (i) those to above the efficiency frontier line that represent more efficient medicines (more benefit at a lower cost); (ii) those on the efficiency frontier line which represent the same efficiency as the existing intervention and (iii) those below the efficiency frontier in this quadrant that represent lower efficiency than the previous intervention. The decision on medicines falling in areas (i) and (ii) are fairly straightforward whereas those in (iii) require an appraisal of the willingness to pay for the health benefit. In the cases where the medicine provides superior benefit but a lower efficiency than the next best intervention the decision maker would need to consider whether there is justification for the decrease. Caro et al. (2010) suggests that in many cases diminishing marginal returns will be operating and past decreases could be assessed to consider a reasonable level of decline. The authors also suggest that willingness to pay for the additional benefits could be used for each therapeutic area but this would be potentially challenging in practice (Caro et al. 2010 – The Efficiency Frontier Approach to Economic, Health Economics).

The divergence from using standard cost-benefit or cost-effectiveness methods for using the efficiency frontier is justified by the panel on three grounds (Caro et al. 2010, Dintsios and Gerber 2010):

The evaluations performed by IQWIG are not the same as other reimbursement systems because they have a narrower remit. IQWIG is required to consider the maximum reimbursement amount in a given therapeutic area and therefore there is not a need for prioritising across the health care system

Those interventions should only be addressed that are judged as superior using the principles of Evidence Based Medicine (EBM) for the effectiveness of the medicine

Patients should not be excluded from therapeutic benefits in cost grounds alone

The introduction of this new approach for the economic analysis in the reimbursement of medicines have been controversial and subjected to criticism (Schulpher and Claxton (2010), Brouwer and Rutten (2010)) and the approach has been defended by the panel that

recommended the efficiency frontier and IQWIG – the agency responsible for implementing the approach (Dintsios and Gerber 2010, Caro et al. 2010).

Brouwer and Rutten comment that the nature and origins of the restrictive approach to economic analysis is not clear in Germany, (Brouwer and Rutten, 2010). The authors point to the fact that there is no single 'universally accepted' method but there seems to be no statement in German law against the use of cost-effectiveness comparisons between diseases or therapeutic areas. It is pointed out that the conventional cost-effectiveness approach can be used to consider whether a specific medicine in a specific disease area offers value for money and does not necessarily have to be used across disease areas.

Sculpher and Claxton emphasise the failure to define value because the methods fail to consider the implications of scarce resources and the concept of opportunity cost even if there is no explicit budget constraint. This is because additional costs will displace private consumption outside of the health sector. The authors explain that a lack of a definition of value across therapeutic area may have implications for providing appropriate signals of value and providing incentives for the development of future treatments. The authors suggest that the methods may be providing an indication of value through the 'going rate' – the additional cost per unit of health benefit implied by current clinical practice and this can only describe a lower bound on the value of health benefits If past decisions fully reflect health effects, costs and social values. If the going rate signals a lower bound then it is suggested that some sufficiently valuable medicines will be wrongly rejected. This is echoed by Brouwer and Rutten who comment that "...an efficiency frontier only describes what *is*, not what *should be*. A relevant ceiling must be imposed separately." The efficiency frontier is therefore a good approach for identifying those inefficient interventions but cannot describe the necessary price for those more effective and more costly. Along the lines made by Sculpher and Claxton they describe the danger that decision makers may be misguided assuming resource constraints because they might accept unfavourable cost-effectiveness ratios in some areas because the medicine is relatively inefficient (high prices), and reject some medicines in relatively efficient areas because of the fact that other relatively efficient medicines are available (low price). They also comment on the difficulties and complexities in constructing the efficiency frontier and both sets of authors do not perceive the approach to offer any value over conventional approaches. Schulpher and Claxton go on further to criticise the experts that developed the methods. "Even if the plea that the guidance reflects constraints imposed on them is credible, it poses the question of whether a group of independent experts should have accepted such a remit. Whether the critical constraints are exogenous or self

inflicted, they have failed to explore fully and to effectively communicate their severe limitations and often perverse implications." (Sculpher and Claxton, 2010).

IQWIG defends the approach by criticising the commentators for considering the efficiency frontier in terms of their country specific setting (Dintsios and Gerber 2010). They state that "In Germany, however, best allocation of scarce resources is by law solely pursued within a therapeutic area." The authors state that there is no international standard because numerous authors, including prominent British health economists have commented that there are a number of differences in approaches across countries and no necessarily best approach internationally. They propose that the international standard is that these elements are transparently stated (perspective etc). They also refer to the arbitrary nature of explicit/implied threshold ranges in operation in countries using conventional cost-effectiveness and cost-utility analysis and the equity implications of using cost-utility analysis in rare diseases.

The expert panel's response to these criticisms refers to the original aim of that was to outline a method that would allow a judgement of whether the price of a technology was reasonable in the therapeutic area. It reiterates that there is not a common standard for economic analysis because each country has its own procedures in line with each countries cultural and legal context. It goes onto state that the issue of whether the benefit is worth the price to society is something that remains unresolved by reimbursement agencies internationally, (Caro et al. 2010).

Box A4.2: Chapter 4 appendix references

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Chapter 5 appendix

Table A5.1: Summary of variable definition and description

Data	Variable	Description
Dependent variables		
Decision outcome (multinomial regression)	Dummy: Recommended, Restricted recommended, not recommended.	*Decision on reimbursement:* The guidance for each of the decisions was classified into three categories of decision which were "recommended", "restricted recommended" or "not recommended". The guidance categorised as recommended were for all patients that met the licence indication. The restricted recommended were categorised as those recommended for a specific patient sub-group. Those studies that were not recommended outside of clinical trials were categorised as "not recommended". A small sample of countries guidance that did not specify a specific decision. In these circumstances a decision was inferred from the conclusion.
Independent variables		
Diseasearea	Dummy: Cardiovascular Disease, Cancer	*Disease Area:* This variable identified whether the drug was for cardiovascular disease or cancer in the technology evaluation
Timesinceguidance	Numeric: Months	*Time since publication:* The number of months since the guidance document was published. This was taken as the number of months from the publication date to 20th May 2008.
Review	Dummy: Review of previous evaluation	*Review:* This indicates that the technology evaluation was a review of a previous evaluation of the medicine. This was identified by checking the technology evaluation to see whether it explicitly identified the evaluation as a review or by considering each countries previous evaluations within the indication.
RCTno	Numeric	*Number of RCTs:* The RCT number are taken from the documents presented for each of the countries
Studyrct	Dummy: RCT, no RCT	*RCT studies included:* This captures whether the document stated that the data on which the decision was based was taken from RCT data.
Studyobs	Dummy: Observational, no observational	Observational studies included: This captures whether the document stated that the data on which the decision was based was taken from observational studies.
Eccua	Dummy: Cost-utility analysis, no cost-utility analysis	*Cost-utility analysis*; This variable identified whether cost-utility analysis was used within the technology evaluation.
Eccea	Dummy: cost-effectiveness analysis, no cost-effectiveness analysis	*Cost-effectiveness analysis*; This variable identified whether cost-effectiveness analysis was used within the technology evaluation.
Eccma	Dummy: cost minimisation analysis, no cost minimisation analysis.	*Cost minimisation analysis*; This variable identified whether cost minimisation analysis was used within the technology evaluation.
Eccc	Dummy: cost consequence, no cost consequence analysis.	*Cost consequence analysis*; This variable identified whether cost consequence analysis was used within the technology evaluation.
Sensanalysis	Dummy: Sensitivity analysis, no sensitivity analysis	*Sensitivity analysis:* This identified whether sensitivity analysis was presented within the technology evaluation

Table A5.1: Summary of variable definition and description Continued..../

Icercqg	Numeric: cost per QALY (£)	*Cost per QALY gained.* The third model included the cost per QALY for the assessments where this was available. Where agencies reported ICER's in a different currency these were exchanged at the exchange rate for the date of the guidance into pounds (GBP). The ICER value appropriate to the decision-making was selected when this was specified for the indication and recommendation made. In the case of NICE where there were a number of groups submitting evidence on the ICER, the first choice was the one specified for the indication either found in the discussion or the 'consideration of evidence' section. In circumstances where this was not stated for NICE, the assessment group/ERG ICER dominated the sponsors ICER with respect to the recommended indication. Further to this in circumstances where the appropriate decision ICER was not stated and a range of assessment group/ERG ICER's were presented the mid-point of the ICER range was taken for assumptions with regards to an indication. Those drugs that were found to dominate the comparator were given an ICER of zero as a negative ICER is considered uninformative.
Budgetimpact	Dummy: Budget impact reported, no budget impact reported.	*Budget Impact:* This variable identifies whether a budget impact was reported in the analyses. This was used as an indication of whether the committee explicitly considered the budget impact of a medicine.
Patientgroupsub	Dummy: Patient group submission, no patient group submission.	*Patient group submission:* This variable identifies whether any patient group submissions were reported within the technology evaluation documentation.
Nopatientgroup	Numeric: Number of patient groups	*Number of patient groups:* This was identified by a count of the number of patient groups that were included within the technology evaluation documentation.
Publicinterest	Numeric: No of newspaper articles reporting public interest.	*News coverage prior to technology evaluation publication:* An assessment was made of the news coverage in a sample of two newspapers in each of the countries for the generic and brand name of the drug within the specific indication. Two newspapers were selected for the two highest circulation newspapers for each of the countries. The rationale for searching two newspapers was on a pragmatic basis because the number of newspapers in each country is different, countries differ in size and not all papers are indexed within databases. A search of the Nexis database was conducted on the number of mentions of either the generic or brand name in the indication reported prior to the date of release of the technology evaluation. This was to identify the level of media interest prior to the publication of any decision on the drug. The number of appearances was then recorded for each of the medicines for each technology evaluation.
Australia	Dummy: 0/1= Australia	*Australia HTA:* The impact of a Australian decision in comparison to England (reference group.)
Canada	Dummy: 0/1= Canada	*Canada HTA:* The impact of a Canada decision in comparison to England (reference group.)
Scotland	Dummy: 0/1= Scotland	*Scotland HTA:* The impact of a Scotland decision in comparison to England (reference group.)

Chapter 6 appendix

Table A6.1: Reimbursement system classification

	France	Scotland
Policy Implementation Level		
Establishment	Haute Autorité de santé (HAS) was established in 2004 by the Ministry of Health and Solidarity. Funding is raised through social health insurance in France.	The Scottish Medicines Consortium (SMC) was established in 2001 by the 15 Health Boards. Funding for public provision is funded through taxation in Scotland.
Objectives	The aim of the agency is to improve the quality of care and guarantee equity within the healthcare system.	The aim of the agency is to accept those newly licensed drugs which clearly represent good value for money and reduce postcode prescribing.
Implementation	Provides one of the two stages of advice regarding the case for reimbursement which includes clinical efficacy. Economic considerations made by the Economic Committee for Health Products (CEPS). the HAS opinion informs the pricing and volume agreements that are negotiated between the manufacturer and the Economic Committee for Health Products (CEPS) for outpatient medicines and medicines on top of DRG. Prices for those medicines for hospital use included in the DRG are negotiated directly with the individual hospitals.	Provides one stage advice to the health boards and Area Drug Therapeutic Committees with regards value for money. The health boards choose whether to include the medicine following advice from the SMC. Manufacturer is free to set price prior to the evaluation by the SMC.
Accountability	Legally required to provide advice to Ministry of Health in 90 days	NHS Scotland and the Ministry of Health
Technology Decision Level		
(i) Assessment		
Consultation and stakeholder involvement	Transparency committee includes physicians, pharmacist, specialist in methodology and epidemiology. There is no third party synthesis of evidence.	The SMC process includes two committees. The NDC includes clinicians and pharmacists – nominated by the ADTCs a health economist, a statistician and two industry representatives. The SMC includes a wider representation including a Chief Executive, Finance Directors, patient and public representation, Association of British Pharmaceutical Industry (ABPI), together with the clinical and public health members. There is no third party synthesis of evidence and/or provision of economic evaluation
Evidence base for assessment	HAS considers all pharmaceuticals once marketing authorisation has been granted. The manufacturer is required to present relevant data on clinical efficacy, comparative safety and relative effectiveness.	The SMC considers all newly licensed medicines, new formulations of existing medicines and new indications for established products (SMC excludes assessment of vaccines, branded generics, non-prescription-only medicines (POMs), blood products, plasma substitutes and diagnostic

		medicines) once marketing authorisation has been granted. The manufacturer is required to submit evidence on clinical efficacy, comparative effectiveness, clinical effectiveness, cost-effectiveness and budget impact.
Clinical-effectiveness assessment	HAS requires the manufacturer to submit all relevant studies for the clinical efficacy of the medicine but there are no requirements for these to be identified by a systematic review of the evidence. In the absence of head to head trials a network meta-analysis is permitted. The HAS commission a separate literature review of the evidence. The manufacturer provides a claimed score for the Service Médical Rendu (SMR) and L'amélioration du Service Medical (ASMR). The transparency committee is given information from a literature review and the manufacturer's submission.	The SMC requires the manufacturer to provide evidence assembled systematically for the indication(s) of the medicine including details of RCTs (active controlled most relevant), meta-analyses, and most relevant effects of a medicine. The manufacturer provides evidence of clinical efficacy and is required to consider the medicine in terms of the applicability to clinical practice in Scotland, guidelines and relevant protocols for the most relevant active comparator medicines. In the absence of head to head evidence a network meta-analysis is required by the SMC. The network meta-analyses should be described with reference to a systematic review for studies included and the search strategy for trials included and clinical/statistical heterogeneity between data sources.
Cost-effectiveness assessment	Not required or presented by manufacturer.	The responsibility for demonstrating the cost-effectiveness and any further analysis relevant to Scottish practice rests with the manufacturer and failure to submit cost-effectiveness automatically results in a not recommended decision. A reference case is not provided but the SMC specifies that cost-utility analysis is the preferred form of economic evaluation and health effects should be expressed in Quality-Adjusted Life Years (QALYs). Modelling is the main framework used to synthesise data of clinical and cost-effectiveness, in the absence of real-life effectiveness data. Manufacturers are required to provide sensitivity analysis in the form of single and multi-way analysis to allow the committee to explore the uncertainty in the estimates.
Presentation and communication of results	The manufacturer submits a dossier to the HAS but this is not published on the website. A fee of 2,875 EURO is required for the processing of the submission, HAS provides a 'opinion' document published on their website which contains an assessment of evidence, details of the appraisal and recommendation. http://www.has-sante.fr/portail/jcms/c_5268/medicaments?cid=c_5268	The manufacturer submits a New Product Assessment Form (NPAF) but no fee is required for the processing of the submission. The NPAF is not published on the SMC website. An advice document is published on the SMC website. http://www.scottishmedicines.org.uk/Home
(ii) Decision		
Who makes the decision	The HAS committee is called the Transparency committee and considers the dossier from the manufacturer and a review of the literature. A recommendation is produced along with a judgement of the ASMR and SMR are provided for the second stage where price is negotiated by the CEPS. The final reimbursement recommendation and price is made by CEPS in the Ministry of Health,	The NDC and Transparency committee solely receive a submission from the manufacturer of the relevant evidence and in contrast to NICE in England, do not commission a third party to provide a separate review of the clinical evidence and economic evidence (in the case of SMC). The recommendation is advice and the final reimbursement decision is made by the Health Boards.
Decision-making process	The decision making process is summarised in Figure 1. The HAS is one	The decision making process is summarised in Figure 1. The SMC is one

	agency involved in the process of decision making, which also involves CEPS and the Ministry of Health. The HAS committee is called the Transparency committee and considers the dossier from the manufacturer and a review of the literature. There is no consultation with stakeholders prior to the final recommendation.	agency involved in the decision process. The Health Boards make the final reimbursement decision. The SMC process includes two committees. The NDC includes clinicians and pharmacists – nominated by the ADTCs a health economist, a statistician and two industry representatives. The SMC includes a wider representation including a Chief Executive, Finance Directors, patient and public representation, Association of British Pharmaceutical Industry (ABPI), together with the clinical and public health members. There is no consultation with stakeholders prior to the final recommendation.
Appraisal of clinical evidence	The committee judges the SMR and ASMR for the medicines. This is performed by a majority vote for the two criteria. SMR (Medical Benefit): The score takes into account the severity of the condition and other data specific to the drug such as the effectiveness and adverse reactions, place in the therapeutic strategy, existence of other therapeutic alternatives and importance for public health. The SMR determines the level of cost-sharing paid by members of the health insurance system and whether the medicine justifies reimbursement. The SMR takes four categories; Major, Moderate, Low and insufficient (does not justify reimbursement). ASMR (Improvement in Medical Benefit): The Improvement in Medical Benefit is first provided in the manufacturer submission as a claimed score for the medicine. The ASMR is a score of the relative-effectiveness of the medicine compared to the medicine used in practice. There are five different levels of ASMR from Major Improvement (I), Important (II), Moderate (III), Minor (IV) and no improvement (V). The ASMR determines the pricing that is negotiated between the manufacturer and CEPS. A separate ASMR may be rewarded to a medicine that has different benefits in different indications or patient subgroups. The ASMR determines the price negotiated by the CEPS. CEPS negotiates price for outpatient medicines and those medicines that are used in hospital but not included in the DRG (those included in the DRG are negotiated with individual hospitals). Those rated on the ASMR of I, II or III are allowed to set a price higher than the comparator, IV depends on the context and V must be cost-saving in relation to the relevant comparator (s). The CEPS also sets price volume agreements with the manufacturer where in the event that sales exceed the forecasts for the four years the company is required to provide a claw back for the additional costs.	The NDC reports a qualitative description of the efficacy and relative-effectiveness considerations. This has been informed by six questions asked to a number of independent experts on the following: 1. Are there guidelines, available or in preparation, which do (or could) influence Scottish prescribing in this area? 2. Do you wish to highlight any areas of unmet need in relation to the relevant condition(s)? 3. What are the current treatment options? In particular, what is the predominant treatment in Scotland? 4. What is your preferred treatment (if different to predominant treatment)? Please explain? 5. Disease prevalence: Please estimate how many patients currently receive treatment in your catchment area and/or in Scotland? (Please state population numbers if you have given an estimate for your catchment area.) 6. If you have knowledge of this particular new product for this indication, please describe how it might fit into your treatment plan.
Appraisal of economic evidence	No appraisal performed of health economic evidence.	The fitness for purpose of the economic evidence and the interpretation of

		the estimate of cost-effectiveness in the context of the medicine's use in practice is considered. The economic evaluation is one criterion considered in the draft advice by the NDC to the SMC with respect to the threshold reported by NICE but other criteria are considered in the context of each decision such as the absence of alternatives, bridging to other therapies, emergence of other therapies and special issues that are specific to the medicine. The manufacturer may submit a Patient Access Scheme (PAS) to an independent group called the Patient Access Scheme Assessment Group (PASAG) to improve the cost-effectiveness of a medicine by reducing the cost of the new medicine and allowing patient access to clinically effective medicines.
(iii) Outputs and implementation		
Appeal and dissent	The manufacturer has a period of eight days from receipt of the notice of the advice to request a hearing. At the end of the 8 days in the absence of comments the opinion becomes final. The manufacturer has 15 minutes to present its cases and reasons for the hearing should be submitted. The recommendation may then be amended and a final notice sent to the Ministry of Health and stakeholders.	The manufacturer may ask the SMC to convene an Independent Review Panel (IRP) to look again over existing data and analyses. An IRP will review the original submission and views of the NDC and SMC. The IRP consists of here member of the SMC that were not involved previously with the submission and four members of the Scottish Area Drug and Therapeutics Committees. The IRP reports back to the SMC who is the final judge following a review.
Implementation and communication	HAS opinions are either positive or negative (conditions may also be imposed for additional studies or a target patient population) and are produced for the CEPS of the Ministry of Health where decisions are made on the price for outpatient medicines and hospital medicines that are not covered within the DRG.	The details of the recommendations are provided in an advice document for the SMC within 120 days (non-legally binding) and an opinion document for the HAS in 90 days (legally binding). Neither of the agencies publishes the manufacturer submission. Three categories of advice are provided by the SMC to the Area Drug and Therapeutic Committees (ADTC) for listing; accepted for use; accepted for restricted use and not recommended
Monitoring and reappraisal	HAS can self-refer medicines in the presence of new evidence, reviews all medicines at 5 years post-listing and assess the evidence from any post-listing studies. The recommendations at the 5-year review may result in the SMR being revised and an opinion for de-listing the medicine. Manufacturers may submit new evidence for medicines at any point in a new dossier and the Transparency committee will provide reassessment of the medicine.	Manufacturers may resubmit to the SMC in the light of new evidence or a new analysis of existing evidence but the SMC does not periodically review existing advice.
Evidence of impact of the decision	HAS is an advisory body and only part of the reimbursement decision process. The authors are unaware of any published studies reporting the impact of HAS advice on the final reimbursement decisions. Although the majority of reimbursement decisions made by the Ministry of Health are positive. HAS influence the price through the judgement of ASMR.	There is one study that has identified the effect of a not recommended SMC on use within primary care and found the impact to be variable, Bennie et al. An investigation into the effect of advice from the Scottish Medicines Consortium on the use of medicines in Scotland's Health Service (2011). The study reported that there is a complex relationship between advice following an SMC recommendation and changes in clinical practice.
	France	**Scotland**

Policy Implementation Level		
Establishment	Haute Autorité de santé (HAS) was established in 2004 by the Ministry of Health and Solidarity. Funding is raised through social health insurance in France.	The Scottish Medicines Consortium (SMC) was established in 2001 by the 15 Health Boards. Funding for public provision is funded through taxation in Scotland.
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Accountability	Legally required to provide advice to Ministry of Health in 90 days	NHS Scotland and the Ministry of Health
Technology Decision Level		
(i) Assessment		
Consultation and stakeholder involvement	Transparency committee includes physicians, pharmacist, specialist in methodology and epidemiology. There is no third party synthesis of evidence.	The SMC process includes two committees. The NDC includes clinicians and pharmacists – nominated by the ADTCs a health economist, a statistician and two industry representatives. The SMC includes a wider representation including a Chief Executive, Finance Directors, patient and public representation, Association of British Pharmaceutical Industry (ABPI), together with the clinical and public health members. There is no third party synthesis of evidence and/or provision of economic evaluation
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	separate literature review of the evidence. The manufacturer provides a claimed score for the Service Médical Rendu (SMR) and L'amélioration du Service Medical (ASMR). The transparency committee is given information from a literature review and the manufacturer's submission.	is required to consider the medicine in terms of the applicability to clinical practice in Scotland, guidelines and relevant protocols for the most relevant active comparator medicines. In the absence of head to head evidence a network meta-analysis is required by the SMC. The network meta-analyses should be described with reference to a systematic review for studies included and the search strategy for trials included and clinical/statistical heterogeneity between data sources.
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Presentation and communication of results	The manufacturer submits a dossier to the HAS but this is not published on the website. A fee of 2,875 EURO is required for the processing of the submission, HAS provides a 'opinion' document published on their website which contains an assessment of evidence, details of the appraisal and recommendation. http://www.has-sante.fr/portail/jcms/c_5268/medicaments?cid=c_5268	The manufacturer submits a New Product Assessment Form (NPAF) but no fee is required for the processing of the submission. The NPAF is not published on the SMC website. An advice document is published on the SMC website. http://www.scottishmedicines.org.uk/Home
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Who makes the decision	The HAS committee is called the Transparency committee and considers the dossier from the manufacturer and a review of the literature. A recommendation is produced along with a judgement of the ASMR and SMR are provided for the second stage where price is negotiated by the CEPS. The final reimbursement recommendation and price is made by CEPS in the Ministry of Health,	The NDC and Transparency committee solely receive a submission from the manufacturer of the relevant evidence and in contrast to NICE in England, do not commission a third party to provide a separate review of the clinical evidence and economic evidence (in the case of SMC). The recommendation is advice and the final reimbursement decision is made by the Health Boards.
Decision-making process	The decision making process is summarised in Figure 1. The HAS is one agency involved in the process of decision making, which also involves CEPS and the Ministry of Health. The HAS committee is called the Transparency committee and considers the dossier from the manufacturer and a review of the literature. There is no consultation with stakeholders prior to the final recommendation.	The decision making process is summarised in Figure 1. The SMC is one agency involved in the decision process. The Health Boards make the final reimbursement decision. The SMC process includes two committees. The NDC includes clinicians and pharmacists – nominated by the ADTCs a health economist, a statistician and two industry representatives. The SMC includes a wider representation including a Chief Executive, Finance Directors, patient and public representation, Association of British Pharmaceutical Industry (ABPI), together with the clinical and public health members. There is no consultation with stakeholders prior to the final

		recommendation.
Appraisal of clinical evidence	The committee judges the SMR and ASMR for the medicines. This is performed by a majority vote for the two criteria. SMR (Medical Benefit): The score takes into account the severity of the condition and other data specific to the drug such as the effectiveness and adverse reactions, place in the therapeutic strategy, existence of other therapeutic alternatives and importance for public health. The SMR determines the level of cost-sharing paid by members of the health insurance system and whether the medicine justifies reimbursement. The SMR takes four categories; Major, Moderate, Low and insufficient (does not justify reimbursement). ASMR (Improvement in Medical Benefit): The Improvement in Medical Benefit is first provided in the manufacturer submission as a claimed score for the medicine. The ASMR is a score of the relative-effectiveness of the medicine compared to the medicine used in practice. There are five different levels of ASMR from Major Improvement (I), Important (II), Moderate (III), Minor (IV) and no improvement (V). The ASMR determines the pricing that is negotiated between the manufacturer and CEPS. A separate ASMR may be rewarded to a medicine that has different benefits in different indications or patient subgroups. The ASMR determines the price negotiated by the CEPS. CEPS negotiates price for outpatient medicines and those medicines that are used in hospital but not included in the DRG (those included in the DRG are negotiated with individual hospitals). Those rated on the ASMR of I, II or III are allowed to set a price higher than the comparator, IV depends on the context and V must be cost-saving in relation to the relevant comparator (s). The CEPS also sets price volume agreements with the manufacturer where in the event that sales exceed the forecasts for the four years the company is required to provide a claw back for the additional costs.	The NDC reports a qualitative description of the efficacy and relative-effectiveness considerations. This has been informed by six questions asked to a number of independent experts on the following: 1. Are there guidelines, available or in preparation, which do (or could) influence Scottish prescribing in this area? 2. Do you wish to highlight any areas of unmet need in relation to the relevant condition(s)? 3. What are the current treatment options? In particular, what is the predominant treatment in Scotland? 4. What is your preferred treatment (if different to predominant treatment)? Please explain? 5. Disease prevalence: Please estimate how many patients currently receive treatment in your catchment area and/or in Scotland? (Please state population numbers if you have given an estimate for your catchment area.) 6. If you have knowledge of this particular new product for this indication, please describe how it might fit into your treatment plan.
Appraisal of economic evidence	No appraisal performed of health economic evidence.	The fitness for purpose of the economic evidence and the interpretation of the estimate of cost-effectiveness in the context of the medicine's use in practice is considered. The economic evaluation is one criterion considered in the draft advice by the NDC to the SMC with respect to the threshold reported by NICE but other criteria are considered in the context of each decision such as the absence of alternatives, bridging to other therapies, emergence of other therapies and special issues that are specific to the medicine. The manufacturer may submit a Patient Access Scheme (PAS) to an independent group called the Patient Access Scheme Assessment Group

		(PASAG) to improve the cost-effectiveness of a medicine by reducing the cost of the new medicine and allowing patient access to clinically effective medicines.
(iii) Outputs and implementation		
Appeal and dissent	The manufacturer has a period of eight days from receipt of the notice of the advice to request a hearing. At the end of the 8 days in the absence of comments the opinion becomes final. The manufacturer has 15 minutes to present its cases and reasons for the hearing should be submitted. The recommendation may then be amended and a final notice sent to the Ministry of Health and stakeholders.	The manufacturer may ask the SMC to convene an Independent Review Panel (IRP) to look again over existing data and analyses. An IRP will review the original submission and views of the NDC and SMC. The IRP consists of here member of the SMC that were not involved previously with the submission and four members of the Scottish Area Drug and Therapeutics Committees. The IRP reports back to the SMC who is the final judge following a review.
Implementation and communication	HAS opinions are either positive or negative (conditions may also be imposed for additional studies or a target patient population) and are produced for the CEPS of the Ministry of Health where decisions are made on the price for outpatient medicines and hospital medicines that are not covered within the DRG.	The details of the recommendations are provided in an advice document for the SMC within 120 days (non-legally binding) and an opinion document for the HAS in 90 days (legally binding). Neither of the agencies publishes the manufacturer submission. Three categories of advice are provided by the SMC to the Area Drug and Therapeutic Committees (ADTC) for listing; accepted for use; accepted for restricted use and not recommended
Monitoring and reappraisal	HAS can self-refer medicines in the presence of new evidence, reviews all medicines at 5 years post-listing and assess the evidence from any post-listing studies. The recommendations at the 5-year review may result in the SMR being revised and an opinion for de-listing the medicine. Manufacturers may submit new evidence for medicines at any point in a new dossier and the Transparency committee will provide reassessment of the medicine.	Manufacturers may resubmit to the SMC in the light of new evidence or a new analysis of existing evidence but the SMC does not periodically review existing advice.
Evidence of impact of the decision	HAS is an advisory body and only part of the reimbursement decision process. The authors are unaware of any published studies reporting the impact of HAS advice on the final reimbursement decisions. Although the majority of reimbursement decisions made by the Ministry of Health are positive. HAS influence the price through the judgement of ASMR.	There is one study that has identified the effect of a not recommended SMC on use within primary care and found the impact to be variable, Bennie et al. An investigation into the effect of advice from the Scottish Medicines Consortium on the use of medicines in Scotland's Health Service (2011). The study reported that there is a complex relationship between advice following an SMC recommendation and changes in clinical practice.

Table A6.2: 2010 recommendations by HAS and SMC

	HAS - 2010	SMC - 2010
Recommendations (all submissions on website excluding HAS simplified procedure)	410	86
Recommendations subset (Full submission for new medicine, indication, extension)	122 (30%)	57 (66%)
Recommendations for new medicine, indication or extension		
Recommended listing (including major/minor restriction)	115 (94%)	32 (56%)
Not Recommended Listing	7 (6%)	25 (44%)
Common medicines assessed	17 (14%)	17 (30%)
Disease treated (ICD 10 codes by chapter)		
Certain infectious and parasitic diseases	15 (12%)	1 (1%)
Neoplasms	16 (13%)	17 (30%)
Diseases of the blood and immune mechanism	6 (5%)	4 (7%)
Endocrine, nutritional and metabolic diseases	9 (7%)	8 (14%)
Mental and behavioural disorders	4 (3%)	2 (4%)
Diseases of the nervous system	9 (7%)	2 (4%)
Diseases of the eye and adnexa	4 (3%)	1 (2%)
Diseases of the circulatory system	16 (13%)	5 (9%)
Diseases of the respiratory system	5 (4%)	3 (5%)
Diseases of the digestive system	7 (6%)	1 (2%)
Diseases of the skin and subcutaneous tissue	3 (2%)	4 (7%)
Diseases of the musculoskeletal system and connective tissue	4 (3%)	6 (11%)
Diseases of the genitourinary system	2 (1%)	0 (0%)
Pregnancy, childbirth and the puerperium	1 (1%)	0 (0%)
Certain conditions originating in the perinatal period	1 (1%)	0 (0%)
Congenital malformations and chromosomal abnormalities	1 (1%)	0 (0%)
Symptoms, signs and abnormal clinical and laboratory findings	4 (4%)	2 (3%)

Injury, poisoning and certain other consequences of external causes	2 (2%)				0 (0%)		
Factors influencing health status and contact with health services	13 (11%)				1 (1%)		
Evidence judgments by HAS and SMC	HAS - SMR		HAS - ASMR			SMC - Clinically-effectiveness demonstrated	SMC - Cost-effectiveness demonstrated
	Substantial - 1	14 (12%)	1	3 (3%)	Yes	47 (82%)	32 (56%)
	Important – 2	83 (68%)	2	2 (2%)	No	10 (18%)	25 (44%)
	Moderate - 3	14 (11%)	3	9 (7%)	Type of Economic analysis performed		
	Low – 4	4 (3%)	4	20 (16%)	Cost utility	45 (79%)	
	Insufficient – 5	7 (6%)	5	81 (66%)	Cost effectiveness	2 (3%)	
			Insufficient	7 (6%)	Cost minimisation	9 (16%)	
					Not provided	1 (2%)	

Table A6.3: Concerns with clinical evidence and economic evidence

ID	Drug	Efficacy Trials	SMC Clinical Evidence	HAS Clinical Evidence	ASMR	SMC Economic Model Issues
C001	Botulinum type A 500 units powder solution for injection	SMC: Bakheit (2000), Bakheit (2001) & Bakheit (2004) HAS: Smith (2000), Bakheit (2001), Hesse (1998) The same Phase III supporting trial but additional different supporting trials.	There are difficulties in assessing the benefits: (1) Dosage - individualised for each patient according to muscle spasticity. (2) Comparators – no details for comparison with physiotherapy. (3) Patient population – short time period to post stroke. (4) Assessment of primary outcome by investigator assessment. (5) Clinical trial studies for post-stroke patients even though indication is wider.	The main issues reported were (1) No trials available comparing with active comparator drugs (phenol, alcohol, dantrolene or baclofen) or functional rehabilitation. (2) No safety or efficacy data lasting more than 12 weeks.	5	Not recommended - license The model structure was deemed appropriate and extensive sensitivity analysis. The issues reported were: (1) Improvement in MAS scores lead to improvements in quality of life. Clinical expert opinion confirmed that changes in MAS and quality of life are poorly reported. A Health Outcomes Data Repository (HODaR) was used but deemed a poor substitute for direct measurement.
C002	Ribavirin 200mg	Same trials: Gonzalez-Peralta (2002) Fried (2002)	The clinical issues related to: (1) Dosage – for lighter patients where oral solution is unavailable.	The clinical issues: (1) Uncontrolled design of trials not allowing demonstration of impact on morbidity or mortality.	3	Recommended – License No issues reported. The analysis was well conducted and demonstrated ribavirin to be a cost-effective treatment option compared to no treatment.
C003	Docetaxel 20mg/80mg concentrate and solvent	Same trials Martin (2005), Roche (2006)	The clinical issues related to: (1) Comparator – The trial compared TAC with FAC. This is not the commonly used regime in France. An indirect comparison was considered against FEC.	The clinical issues: (1) Comparator – The comparator used in the trial as according to American design rather than FEC100.	2	Recommended - License No issues reported. The economic study was well designed. An indirect comparison was used for the comparator regime.

C004	Candesartan cilexetil 2,4,8,16 & 32mg	Same trials CHARM-Alternative, CHARM-Added	No issues reported.	No issues reported.	2	Recommended - License No issues reported. The comparator reflected Scottish practice and demonstrated that candesartan is a cost-effective treatment when used as an alternative to ACE-inhibitors or when used as an add-on.
C005	Solifenacin succinate tablets 5mg, 10mg	SMC: Chapple (2004), Cardozo (2004), Haab (2005), x1 unpublished, Chapple (2005) HAS: Chapple (2004), Cardozo(2004), x2 unpublished, Chapple (2005)	The issues reported were: (1) Trial attrition. (2) Dosage – Dose reduction not permitted for those intolerant. (3) Trial population – patients were predominantly female (4) Other comparators – solifenacin has not been compared to other medicinal products.	The issues reported were: (1) Lack of active comparator studies – The committee does not have access to studies comparing with an active comparator in France. (2) Trial representation – The trial population was not representative of the older patients	5	Recommended - License Issues noted: (1) The analysis was complicated by the omission of 1mg tolterodine which would reduce the average weighted cost.
C007	Rasagiline 1mg	Same trials: TEMPO study	The issues reported were: (1) Lack of comparator trials – No trials compare with selegiline or other dopamine agonists. (2) Delayed trial start design – There is no convincing evidence that it causes disease modifying or neuroprotective effects.	The issues reported were; (1) The studies assessed the short term benefit of 6 to 12 months. (2) Lack of active comparator trials – No trials compare with selegiline or other dopamine agonists.	5	Not recommended - Subgroup Issues noted: (1) Limited consideration of comparator regimes. (2) The interpolated transition probabilities. (3) Structure of the model for first and second line therapy.
C008	Rasagiline 1mg	Same trials: LARGO study, PRESTO study	The issues reported were: (1) Lack of active comparator trials - There were no trials directly comparing	The issues reported were; (1) The studies assessed the short term benefit of 6 to 12 months.	5	Not recommended – license Issues noted: (1) The most relevant comparator was not

			rasagiline with other COMT inhibitors or selegiline.	(2) Lack of comparators– No trials compare with selegiline or other dopamine agonists. The indirect comparison was not relevant		considered which was considerably lower in cost.
C009	Lanthanum carbonate 250mg, 500mg, 750mg, 1000mg	Same trials: Joy (2003), Hutchison (2005)	The issues reported were: (1) Lack of active comparator trials – There were no head to head studies with other non-aluminium phosphate binder, sevelamer (2) Long term effects on bone have still to be fully established.	The issues reported: (1) The long term safety on bone has not yet been sufficiently established.	5	Restricted - Subgroup No issues reported. The survival analysis was deemed necessary and seems to have been robustly performed and sensitivity analysis gave the committee confidence in the results given the uncertainty in the clinical evidence.
C010	Omalizumab 150mg	Same trials: INNOVATE (2005)	The issues reported were: (1) Lack of active comparator trials – It has not been shown whether omalizumab is clinically beneficial to slow release theophyllines or anti-leukotriene agents.	The issues reported: (1) Short-term study period of 28 weeks. 23 month period would have been more appropriate. (2) Asthma severity was markedly more pronounced before the study.	4	Restricted – Subgroup The issues reported were: (1) Risk of death from severe exacerbation episode may be an overestimate (2) The assumption of no drop out (3) The baseline assuming divisible dosage may not always be feasible in clinical practice.
C011	Capecitabine 150 and 500 mg	Same trial: X-ACT study	The issues reported were: (1) Lack of direct comparisons – Whether the tolerability of capecitabine would be sustained in comparison to the de Gramont	The issues reported were: (1) The main study showed that capecitabine was not inferior to 5FU/FA regimen (bolus) but a different administration used in	5	Recommended – License No issues reported. The evaluation was well designed and seemed robust. It was notable for the use of a number of comparators.

			regimen.	Europe.		
C013	Erlotinib 25mg, 100mg & 150mg	SMC: BR21 study Indirect comparison included. HAS: BR21 study and Trial A248-1007 Phase II.	The issues reported were: (1) Comparator – Active supportive care in all performance status. Indirect comparison was needed with docetaxel. (2) Patient Population – Identification and pre-selection of patients most likely to respond	The issues reported were: (1) Lack of comparator with second line comparator drugs docetaxel and pemetrexed. (2) Patient population – patients included in the trial had to have already received at least one or two line of chemotherapy and it was not stated whether the disease was progressing or had stabilised.	5	Restricted - Subgroup The issues reported were: (1) The group of patients who would not be suitable to receive docetaxel was not compared to the appropriate comparator. (2) Weakness in the handling of resource use for the duration of treatment of 4-5 cycles of docetaxel may be greater than standard practice in Scotland.
C014	Sildenafil citrate 20mg *Orphan Indication.*	SMC: Galie (2005) & SERAPH study HAS: Galie (2005)	The issues reported: (1) Trial design with meaningful endpoints. (2) Patient population – only 58% of the study population were of functional class III, although treatment effects were consistent across subgroups. (3) Lack of data for second-line – The study excluded patients who had previously failed bosentan therapy.	Issues reported: (1) The effect of the treatment on mortality unknown and the benefit not established in more severe stages of PAH.	1	Restricted – License No issues noted.
C015	Ibrandronic acid 150mg	Same trials: Chesnut (2004) & Miller (2005)	The issues reported: (1) Lack of comparative trials – No comparative trials of	The issues reported: (1) Lack of comparative trials with other	5	Recommended - License No issues reported

		HAS: Indirect comparison includedc	ibandronic acid with other standard treatments for osteoporosis in postmenopausal women. (2) Patient population – the study included women that did not have osteoporosis.	bisphosphonates		
C016	Pegylated interferon alfa 2a, 180mcg subcutaneous injection	SMC: Lau (2004), Cooksley (2001), Marcellin (2004) HAS: Lau (2004), Marcellin (2004)	The issues reported were: (1) Patient population – data on patient subgroups and the trials were based in Australasia and the proportion of Asian patients exceeded 97%.	The issues reported were: (1) Lack of direct comparison with other comparators – establishing benefit in comparison to standard alpha interferon	5	Recommended - License There were no issues reported.
C018	Posaconazole 40mg/ml oral suspension	Same trials: SCH56592 (unpublished) + retrospective data SMC: Indirect comparison included.	The issues reported were: (1) The non-comparative study design and comparison with a retrospectively identified control group. (2) Patient population – The majority of the patients in the posaconazole group had received prior treatment with amphotericin.	The issues reported were: (1) The uncontrolled study did not allow a comparison of posaconazole with voriconazole.	5	Recommended - License The issues reported were: (1) The comparison of costs is based on median duration of treatment with very wide range for each drug.
C023	Tipranavir 250mg	Same trials: RESIST 1 study and RESIST 2 study.	The issues reported were: (1) Long term safety issues and adverse events profile require further information.	No issues reported.	3	Restricted - Subgroup No issues reported. The economic evaluation was well designed.
C024	Infliximab 100mg	SMC: Gottlieb (2004), Reich	The issues reported were: (1) Lack of direct	The issues reported were: (1) Lack of a direct	3	Restricted - Subgroup No issues reported.

		(2005) & Menter (2006) Indirect comparison included. HAS: Chaudhai (2001), Gottlieb (2004), Reich (2005) Indirect comparison included.	comparison– in comparison to etanercept or efalizumab.	comparison – with etanercept and methotrexate. Indirect comparison submitted by manufacturer but not deemed suitable.		
C025	Sodium oxybate 500mg/ml	SMC: XYREM (2002), XYREM (2003a), XYREM (2003b), XYREM (2005) HAS: XYREM (2002), XYREM (2003a), XYREM (2003b), SXB-6, SXB-7	The issues reported were: (1) Lack of direct comparison with other licensed products – A comparison between sodium oxybate and clomipramine which is the only other licensed product for the treatment of cataplexy in adults with narcolepsy. (2) Dosing regimen – The dosing regimen maybe problematic in practice.	The issues reported were: (1) Larger scale long term trials are necessary to clearly demonstrate the benefit (2) The effects of discontinuing sodium oxybate therapy.	4	Not recommended - License The issues reported were: (1) The utility values may not be representative of clomipramine treated patients (2) The resource savings (3) No costs for the treatment of adverse events were recorded (4) Non-responders maybe on sodium oxybate for more than 3 months.
C026	Levetiracetam 250, 500, 750 & 1000mg	Same trial: Glauser (2006)	The issues reported were: (1) Lack of direct comparisons with other anti-epileptic drugs. (2) Dosage mechanism – dose titration in practice is unlikely to follow such a rigid titration as in the trials.	No issues reported	3	Recommended - License The issues reported were: (1) There were some weaknesses in the submission but these are not expanded upon in the document.
C027	Exemestane	Same trial:	The issues reported were:	The issues reported were:	3	Restricted use license

	25mg tablets	Coombes (2004)	(1) Long term outcome studies (2) Lack of direct comparison with other aromatase inhibitors.	(1) The exclusion of patients with early recurrences. (2) Comparison with other comparator regimes – A comparison of the benefit of sequential treatment compared with treatment with an aromatase inhibitor prescribed immediately.		No issues reported. The choice of patient population, comparator and economic modelling approach all seem appropriate.
C028	Adalimumab 40mg solution for injection	Same trials: ATLAS study, Maksymowych (2005)	The issues reported were: (1) Patient population – Only 56% and 42% of the patient populations in the two trials had received treatment with at least two DMARDs. The populations may differ from Scottish patients. (2) Lack of direct comparisons – There are no direct comparisons of adalimumab with other TNF-antaginists for the treatment of arthritic and psoriatic symptoms in patients.	The issues reported were: (1) Lack of a direct comparison with other TNF antagonists etanercept and infliximab	2	Recommended - License No issues reported. The choice of comparator and modelling approach were broadly acceptable.
C029	Sorafenib 200mg	Same trials: Escudier (2007) phase III, Ratain (2006)	The issues reported were: (1) Lack of studies against the active comparator – sunitinib. (2) Patient cross-over in trial.	No issues reported.	2	Not recommended - License The issues reported were: (1) The extrapolation and reapplication of the 4th cycle transition probabilities substantially reduces

						the confidence in the long term cost-effectiveness.
C030	Voriconazole 50mg & 200mg tablet, 40mg/ml oral suspsension & 200mg vials for infusion.	Same trials: Kullberg (2005)	The issues reported were: (1) Dosage – The intravenous maintenance dose in the clinical study was 3mg/kg twice daily which is inconsistent with the maintenance dose, listed in the summary of product characteristics (SPC) of 4mg/kg twice daily. (2) Submitted indication – the indication was for second line following fluconazole where patients were fluconazole resistant or refractory to fluconazole. The study considered voriconazole with conventional amphotericin B followed by fluconazole for the primary treatment of non-neutropenic candidaemia.	The issues reported were: (1) Patient population – Patient characteristics at baseline were similar except for the mean APACHE II score which was higher in the amphotericin B/fluconazole than patients treated by voriconazole. The incidence of renal events was higher in the amphotericin B/fluconazole group than in the voriconazole group.	4	Restricted - Subgroup The issues reported were: (1) The use of the clinical trial data, lower maintenance dose and patient weight in clinical trials – manufacturer asked to produce additional analysis.
C032	Nebivolol 5mg	SMC: SENIORS (2005), Edes (2005) Indirect comparison included. HAS:	The issues reported were: (1) Lack of direct trials comparing nebivolol with other beta-blockers. (2) Intention to treat analysis – The ITT analysis should include all patients randomized, and no	No issues reported	3	Recommended - License The issues reported were: (1) The analysis compared nebivolol to carvedilol, which is the more expensive f the two available beta-blockers that could have been

		SENIORS (2005)	reason is given for the exclusion of a study centre.			used in the comparison. (2) The mean age in the model was 70, which was 6 years less than the mean age in the clinical trials and likely age of the population of interest in Scotland. This is likely to overestimate the gain in life.
C033	Daptomycin 350mg	Same trial: Arbeit (2004)	The issues reported: (1) Other direct comparisons – There are no directly comparative clinical data comparing daptomycin with linezolid or quinupristin/dalfopristin. (2) Types of infections included – The numbers of patients in some groups were small and these may affect the extrapolation of the trial results in terms of clinical success in the studies into practice.	The issues reported were: (1) Type of infections in the trials – The clinical efficacy of daptomycin against Enterococcus faecalis and Enterococcus faecium has not been established. The product cannot be positioned in the therapeutic management of severe infections.	5	Restricted - Subgroup No issues reported. It was appropriate to use a cost-minimisation approach because the submitted clinical evidence demonstrated equivalent efficacy of daptomycin and Vancomycin.
C034	Alglucosidase alfa 50mg *Orphan Drug*	SMC: Kishnani (2007), Trial 1702, AGL02804 HAS: Kishnani (2007), Trial 1702, AGL02804	The issues reported were: (1) Late onset – the available evidence does not demonstrate efficacy in this group of patients. It is not clear if the data can be extrapolated from infantile-onset disease. (2) Long term data –	The issues reported were: (1) There are no long-term efficacy and safety data available (2) Data on late-onset Pompe disease is very limited.	2	Not recommended - License No issues reported. The analysis was clear, concise and well conducted but given the extremely high cost for the health gain the economic case was not demonstrated. £244,450 - £318,283 per QALY.

			uncertainty whether patients remain in good long term health.			
C036	Tigecycline 50mg	Same trials: Ellis-Grosse (2005), Sacchidanand (2005)	The issues reported were: (1) Lack of other direct comparisons. The trials compared to Vancomycin and azetreonam. These antibiotics are not rountinely used in Scottish practice for skin and soft tissue infections. American study design. (2) Patient population – Patients were recruited in 2 of 65 centres participating in the global trial. It is not possible to determine from the data whether there are any differences between the Scottish population and total trial population.	This issues reported were: (1) Lack of other direct comparisons. The comparators used in the trials Vancomycin and azetreonam are not the reference comparators. (2) Patient population – There were patient groups excluded which would be important in this context. (immunodepressed patients).	5	Restricted - License The issues identified: (1) The evaluation considered clinical data that does not represent 2nd or 3rd line treatment usage rather first line.
C037	Tigecycline 50mg	Same trials: Olivia (2005) & Babinchak (2005)	The issues reported were: (1) Patient population – Patients from the UK were recruited in 2 of the 94 centres participating in one of the trials. It is not possible to determine whether there are any differences between the Scottish population and the total trial population. (2) Lack of other direct comparisons – The trials	The issues reported were: (1) Patient population included – The mean APACHE score was 6 and only 4% of patients had a score>15. The number of patients with a severe underlying pathology was limited. The patients not representative of those in practice.	5	Restricted - License The issues reported were: (1) The manufacturer's analysis used clinical effectiveness data from 2nd line or 3rd line therapy rather than first line. (2) The possibility that other factors other than bacterial resistance patterns might influence clinical

			compared with imipenem-cilastatin which is not routinely used in Scottish practice. (3) Limited number of infections – The trials described in the evidence submission gave a limited number of pathogens resistant to other antibiotics which were isolated.	(2) Lack of other direct comparisons – with other antibiotics.		response has not been considered.
C038	Pegaptanib 0,3mg	Same trial: VISION study	The issues reported were: (1) Patient population – entry requirements in the trial defined subfoveal neovascular AMD, implying that patients with extrafoveal or juxtafoveal disease were excluded from the trials. (2) Long term efficacy – The trial design may limit the analysis of efficacy in the second year compared to the first year.	The issues reported were: (1) Patient population – caution should be exercised in interpreting results as 13-35% of patients, based on the groups in both studies, also received verteporfin FPT treatment during the study. (2) Lack of direct comparison with verteporfin. The marketing authorisation was given 6 years earlier.	3	Restricted - Subgroup No issues reported. The key strength of the evaluation was that the clinical data has provided a targeted treatment option for Scottish practice.
C040	Testosterone undecanoate 1000mg/4ml oily solution	Same trial: Schubert (2004) SMC: Indirect comparison included	The issues reported were: (1) Dosage variations – comparative testosterone levels in the direct study are difficult to interpret because of variation in the dosing intervals and	The issues reported were: (1) There was no hypothesis formulated of superiority or equivalence and no determination of sample size. The study	5	Recommended - License No issues reported. The economic evaluation was generally adequately designed, with a plausible comparator.

			pharmacokinetic profile of different formulations relative to the sampling points for assay testosterone. (2) The indirect comparison had several weaknesses but clinical experts did not raise concerns about the comparative effectiveness.	is exploratory and descriptive and no statistical tests performed. (2) Lack of comparison with other routes of administration of testosterone.		
C043	Rituximab 10mg/ml	Same trial: Van Oers [EORTC 20981 study] (2006)	No issues reported.	No issues reported.	1	Restricted - License The issues reported were: (1) The model structure did not include adverse events. (2) Uncertainty stemming from the long-term nature of the disease
C045	Ivabradine 5mg & 7.5mg	SMC: Tardif (2005), Ruzyllo (2007), [x3 long term studies] HAS: Borer (2003), Tardif (2005), Ruzyllo (2007), CL03-018, [x3 long term safety studies]	The issues reported were: (1) Patient Population – The trial population may not be representative of the Scottish population that would be eligible for ivabradine. (2) The robustness of the non-inferiority trial questioned by the EMEA.	The issues reported were: (1) Lack of other direct comparisons – There is no study available versus other calcium inhibitors (especially diliazem and verapamil). (2) Patient population – There were no studies that enrolled patients with contraindications or intolerance to beta-blockers.	3	Restricted - subgroup The issues reported were: (1) The justification of primary care resource use estimates were not provided and costs of managing ivabradine related adverse events were not estimated. (2) Concerns over the comparator chosen of no treatment for those who are contraindicated or intolerant to beta-blockers and calcium

						channel blockers. No evidence for other possible treatment options.
C046	Natalizumab 300mg	Same trials: Polman [AFFIRM study] (2006), Rudick (2006)	The issues reported were: (1) The EMEA uncertainties highlighted with regards treating the trial subgroup analysis with caution. There is no documentation on the severity of relapses, either by clinical course or duration. (2) Lack of controlled comparative studies – with existing therapies such as beta-interferon or glatiramer acetate.	The issues reported were: (1) Lack of other direct comparison study. The committee regretted the absence of any comparative study with mitoantrone for the treatment of aggressive recurring-remitting forms of MS and the insufficient amount of data on natalizumab as a monotherapy in the population defined by the indication. (2) Long term safety concerns.	3	Restricted - Subgroup The issues reported were: (1) The case was only made in rapidly evolving severe RRMS. (2) The data used was taken from the trials in all patients with RRMS rather than the RES subgroup. (3) The assumption of assuming the treatment would continue irrespective of the time from start of treatment or EDSS state.
C047	Parathyroid hormone 100mcg	SMC: PATH study, TOP study Indirect comparison included. HAS: Top study, PATH study, OLES study, POWER study Indirect comparison included.	The issues reported were: (1) Primary outcome – The trial comparing parathyroid hormone with alendronate assessed BMD but not fracture rates. However anti-fracture efficacy is not solely related to BMD and estimates of the relative benefits on fracture rates with the drugs cannot be derived from this outcome. (2) Lack of other comparator	The issues reported were: (1) Lack of direct comparison – The committee would of liked to of been presented with a direct comparison with teriparatide or any other anti-osteoporosis drugs.	5	Restricted - License There were no issues reported. The evaluation was presented concisely, used a range of comparators and included adequate sensitivity analysis.

			trials – There are no trials directly comparing PTH with teriparatide.			
C048	Rituximab 100mg/10ml, 500mg/50ml	SMC: REFLEX study Indirect comparison included. HAS: REFLEX study, EDWARDS study, DANCER study.	The issues reported were: (1) Lack of other direct comparisons with other DMARDs or TNF-antagonists.	The issues reported were: (1) Lack of a direct comparison with another TNF antagonist.	2	Recommended - License There were no issues reported. The model structure was appropriate and the analysis was well described.
C049	Levetiracetam 250, 500, 1000mg & 100mg/ml oral solution, 100mg/ml diluted for infusion.	Same trial: Brodie (2007) SMC: Indirect comparison included.	There were no issues reported.	No issues were reported.	4	Restricted - License The issues reported were: (1) The manufacturers submission suffered from a lack of transparency and clarity (2) The use of a limited indirect comparison.
C050	Levetiracetam 250, 500, 1000mg & 100mg/ml oral solution, 100mg/ml diluted for infusion.	Same trial Berkovic (2007)	The issues reported were: (1) Lack of direct comparison with other anti-epileptic drugs for the licensed indication. (2) The selection criteria in those patients from age of four.	No issues were reported	3	Recommended - license There were some weaknesses raised with the submission. These were not explicitly raised. The sensitivity analysis gave reassurance.
C051	Palonosetron 250 mcg	Same trials: Gralla (2003), Eisenberg (2003), Aapro (2003)	There were no main issues raised	There were no issues reported.	4	Recommended - License The issues reported were: (1) The reliance on non-statistically significant treatment differences (2) The assumptions regarding dose and

						efficacy of comparator product
C052	Posconazole 40mg/ml oral suspension	Same trials: Ullmann (2007), Cornely (2007)	The issues reported were: (1) Infection Type – The comparative efficacy data relative to itraconazole, are limited by small group sizes.	The issues reported were: (1) The committee would of liked information on the method of isolation of patients in the studies. (2) Patient population – very few patients had grade 3-4 mucositis in the population studied. It is therefore difficult to draw conclusions on the efficacy of such prophylaxis in patients with severe mucositis.	3	Recommended - License The issues raised were: (1) Itraconazole may have been the more appropriate comparator in the trial.

Table A6.4: Data and reasons for differences in recommendations

Code	Medicine	Type	Discrepant rec	Trials similar	Comparators	Primary Outcome	HAS - ASMR	SMC – clinical effectiveness	Type of Economic Analysis	Economic estimate	Reason for discrepancy
C001	Botulinum type A	C-C-C	Yes	Yes – add ev SMC – Three placebo RCT, 1 Phase II, 2 Phase III	Different Trials – placebo SMC Usual Care HAS – Active comparator drugs	Modified Ashworth Score (MAS)	5	Clinical effective for endpoints but uncertainty about the transformation to QoL benefit	Cost utility	Dominates	Uncertainty surrounding the relative effectiveness and difference in comparators, HAS provides ASMR of 5 and list SMC not recommended
C002	ribavirin	C-C-NC	Yes	Yes Two uncontrolled trials	Trials -placebo SMC Best supportive care HAS Best supportive care	Sustained Viral Response (SVR)	3	Clinically effective for endpoints and QoL improvement.	Cost utility	£490	Both agree clinical effectiveness and Cost-effectiveness demonstrated – restriction imposed by HAS (minor restriction) on specialist and monitoring
C007	rasagiline	C-C-C	Yes	Yes 2 double blind RCT	Trials – placebo SMC: Selegine, levodopa plus a dopa decarboxylase inhibitor and dopamine receptor agonists.	UPDRS	5	Uncertainty regarding the relative effectiveness in comparison with other medicines	Cost effectiveness	Dominates	Uncertainty in the relative effectiveness for SMC and issues with fitness for purpose of model not sufficient to demonstrate economics (not

					HAS: Selegine, levodopa plus a dopa decarboxylase inhibitor and dopamine receptor agonists.						recommended) No improvement in relative effectiveness for HAS.
C008	rasagiline	C-C-C	Yes	Yes Two Double blind RCT (one placebo controlled, one active comparator)	Trials: placebo, active comparator (entacapone) SMC: Selegine, levodopa plus a dopa decarboxylase inhibitor and dopamine receptor agonists. HAS: Selegiline (MAO-B inhibitor)	Average change in mean off time	5 No indirect compar ison.	Indirect comparison demonstrates improvement of entacapone over other COMT inhibitors but no direct comparison of rasagline with selegiline. Equivalence to entacpone	Cost minimisati on	(£) saving	Both agencies come to the same conclusion regarding uncertainty of relative effectiveness with selegiline. SMC does not recommend because the economic evidence includes an inappropriate comparator.
C009	Lanthanu m carbonate	C-C-NC	Yes	Yes – Two Double blind RCTs Phase III (one placebo, one active comparator)	Trials: placebo and calcium carbonate SMC: Sevelamer, calcium carbonate HAS: Sevelamer	Serum Phosphate levels	5	Broad equivalence between lanthum carbonate and sevelamer even though no direct data. Modelled improvement in HrQoL in comparison to calcium carbonate.	Cost utility	£6,741	Both agree on clinical equivalence. The manufacturer's economic evidence submission to the SMC is in a subgroup of the licensed patient group (second line) and

											concludes cos-effectiveness has been demonstrated in this group against one of the comparators (calcium carbonate).
C010	omalizumab	C-C-C	Yes	Yes – One Double blind Multi Centre RCT	Different Trials: Placebo SMC: Leukotriene receptor antagonist, SR theophyline or ral beta-2-agonist HAS: Best Supportive Care	Rate of clinically significant asthma exacerbations	4	Relative effectiveness as an adjunctive therapy but not determined in relation to slow release theophyllines or anti-leukotriene agents.	Cost utility	£30,995	Both agree on the relative effectiveness with regards to best supportive care. A different relevant comparator in Scotland, which led to the analysis focusing on a subgroup (all other treatments failed.
C013	erlotinib	C-C-C	Yes	Yes add ev SMC: Double Blind RCT Phase III (placebo) HAS: Double Blind RCT Phase III (placebo) plus non-comparative Phase II study.	Trials: Placebo SMC: Docetaxel monotherapy, pemetrexed, Best Supportive Care HAS: Docetaxel, Permetrexed, Best Supportive Care	Overall Survival	5	Indirect comparison show a comparable overall survival outcome with docetaxel and a more favourable adverse event profile.	Cost utility	£22,500	Uncertainty regarding relative effectiveness for HAS (ASMR=5) and judged equivalent for overall survival in comparison to docetaxel. The economic evidence is considered by the SMC which involved an

											indirect comparison show comparable overall survival outcomes and improvement in adverse events resulting in quality of life benefits. Recommended in a restricted group of those eligible for docetaxel.
C015	Ibrandronic acid	C-C-NC	Yes	Yes Two Double Blind Phase III RCTs (Placebo)	Trials: Placebo SMC: Oral bisphosphonates Alendronate, risedronate sodium, raloxifene, disodium etidronate, calcitronin and teripartide HAS: Oral bisphosphonates.	Rate of morphometric vertebral fractures	5 – Indirect comparison provided but populations of trials had different populations	No active comparators with other standard treatments. Meta-analysis of 32 RCTs shows ibrandronic acid to be broadly equivalent to other bisphosphonates.	Cost minimisation	(£15) saving	Uncertainty regarding clinical efficacy for HAS. Clinical equivalence judged by a meta-analysis for SMC and economic evidence demonstrates cost-saving. HAS places restriction on reimbursed indication.
C016	Pegylated interferon alfa 2a	C-C-C	Yes	Yes – add ev SMC: Two Phase III studies (lamivudine monotherapy	Trials: (active comparators, lamivudine) SMC: conventional	Seroconversion	5	Trial shows clinical effectiveness in comparison to Lamivudine which is the most commonly used	Cost utility	£5,300	Both consider common comparators and reach similar conclusions surrounding the clinical efficacy in

				and combination of lamivudine and pegylated interferon alfa 2a) One Phase II dose finding (pegylated interferon alfa 2a versus conventional interferon alfa 2a) HAS: Two Phase III studies (lamivudine monotherapy and combination of lamivudine and pegylated interferon alfa 2a)	interferon alfa 2a and alfa 2b, Lamivudine, Adefovir dipivoxil. HAS: Interferon alfa 2a and alfa 2b, lamivudine.			in clinical practice. Data limited to a Phase II Australasian study for comparison with conventional interferon alfa 2a.			comparison to conventional alfa 2a and lamivudine. The economic evidence modelled showed improvement in quality of life and an acceptable cost-effectiveness. HAS minor restriction (specialist and monitoring)
C023	Tipranavir	C-NC-NC	Yes	Yes Two RCT Phase III (pre selected protease inhibitor plus ritonavir)	Trials: (active comparator – pre selected protease inhibitors) SMC: Other boosted proteases inhibitors; lopinavir/ritonavir	Reduction in viral load	3	Relative effectiveness against other protease inhibitors was established.	Cost utility	£28,000	Both agencies agreed on the relative effectiveness. The manufacturer submitted a cost-effectiveness analysis in highly pre-treated patients. The

					, atazanavir/ritonavir, saquinavir/ritonavir, amprenavir/ritonavir, fosamprenavir/ritonavir HAS: Boosted protease inhibitors						cost-effectiveness was demonstrated.
C024	infliximab	C-C-NC	Yes	Yes – add ev SMC: 3 Double Blind RCTs (placebo) HAS: X3 Double Blind trials (placebo)	Trials: placebo SMC: etanercept and efalizumab HAS: Etanercept and afalizumab	PASI 75	3 – Indirect comparison provided but committee judged was not possible to base conclusions because no assessment of heterogeneity	No active comparator trials comparing infliximab with etanercept and efalizumab. An indirect comparison was performed by NICE which demonstrated a greater response but this could be due to differences in trial populations.	Cost utility	£27,354	Both committees concur on the relative effectiveness. The economic model used the indirect comparison and extensive sensitivity analysis provided demonstrated cost-effectiveness for patients with severe plaque psoriasis. (restricted)

							, not conclusive whether trials were comprehensive. A direct comparison would be helpful.				
C025	Sodium oxybate	C-C-C	Yes	Yes – add ev SMC: Two RCTs Double Blind (placebo) HAS: Two RCTs Double Blind (placebo), and 6 month Open label RCT	Different Trials: placebo SMC: Clomipramine HAS: Best Supportive Care	Change in Cataplexy attacks	4	There is no direct comparison which compares sodium oxybate with clomipramine, uncertainty with regards the relative effectiveness	Cost utility	£65,980	The two agencies considered different comparators for practice in France and Scotland The economic analysis was not cost-effective at the current price and there were weaknesses with the submission. (not recommended)
C027	exemestane	C-C-NC	Yes	Yes Double Blind RCT (exemastane, tamoxifen)	Trial: (active comparator, tamoxifen, exemestane) SMC:Tamoxifen,	Disease Free survival	3	Advantages in terms of disease free survival. This translates into QALY gain overtime in the	Cost utility	£14,980	Both agencies agree on relative effectiveness of the medicine. Economic case demonstrated

					anastrozole, Letrozole. HAS: Tamoxifen, anastrozole and Letrozole.			economic model.			through a robust analysis (minor restriction)
C028	adalimumab	C-C-NC	Yes	Yes Two Double Blind RCT (placebo)	Trials: Placebo SMC: Etanercept, infliximab HAS: Etanercept, infliximab	ACR20	2 - Indirect comparison was not adopted because of weaknesses with the methodology	Relative effectiveness in comparison with placebo but uncertain with regards other TNF antagonists.	Cost utility	£29,000	Both agree on relative effectiveness with respect to placebo but uncertainty with respect to etanercept. The manufacturer's economic submission to the SMC explores the sensitivity of the modelling and concludes cost-effectiveness for adalimumab. (Minor restriction for HAS)
C029	Sorafenib	C-NC-C	Yes	Yes Double Blind RCT Phase III (placebo) and Phase II study.	Trials: Placebo SMC: Best Supportive Care HAS: Best Supportive Care	Progression Free Survival (PFS)	2	Relative effectiveness in terms of PFS but uncertainty regarding overall survival.	Cost utility	£35,523	Both agencies agree on relative effectiveness for PFS but await results of overall survival (ASMR =2). Concerns with extrapolation after the trial

											periods and too high cost-effectiveness (not recommended by SMC).
C030	voriconazole	C-C-C	Yes	Yes One open label RCT (voriconazole vs amphotericin B followed by fluconazole)	Trials: (active comparator) SMC: Amphoericin B, fluconazole and caspofungin. HAS: Amphotericin B, fluconazole, Caspofungin and Fluxytosine.	Successful response to treatment	4	Clinical study shows relative effectiveness versus the active comparator but does not support the submission for second line.	Cost minimisation	(£1,436) saving	HAS judge there to be an improvement on the basis of safety in comparison to Amphotericin second line (ASMR=4) Weaknesses in the model by use of clinical trial data, patient weight and maintenance. There was a need for treatment in those that do not respond. (restriction to this patient group in SMC)
C033	daptomyxin	C-C-NC	Yes	Yes Two Investigator blind RCTs (Daptomycin, or penicillinase-resistant penicillin or	Trials Different SMC: Vancomycin, teicoplanin, linezolid, quinupristin/dalfopristin.	Clinical Success	5 – population studies did not include severe infections	Non-inferiority demonstrated to comparators used. There are no studies comparing daptomycin with linezolid or quinupristin/dalfopristin which may	Cost minimisation	(25) saving	Both agree on relative effectiveness with regards to non-inferiority in trial population but cannot be placed in HAS severe infections because of lack of

				Vancomycin).	HAS: Beta lactams, quinolines, macrolides, glycopeptides, aminoglycosides, oxazolidinones and synergistins.			be used in Scottish practice.			severe infections in trial population which was also highlighted by SMC. The manufacturer submitted a cost-minimisation analysis to the SMC in a subgroup of patients with suspected or confirmed MSRA infection. (Major restriction SMC).
C034	Alglucosidase alfa	C-C-NC	Yes	Yes - Three non-comparative trials matched with a group without symptoms.	Trials: (alglucosidase-orphan drug) SMC: Best Supportive Care HAS: Best Supportive Care	Proportion of patients alive and free of invasive ventilation .	2	Relative effectiveness demonstrated against Best Supportive Care.	Cost utility	£318,283	Both committees concur on the improvement of relative effectiveness (ASMR=4) A well conducted analysis but not cost-effective at price (Not recommended).
C036	tigecycline	C-C-C	Yes	Yes Two Double Blind RCTs (vancomycin followed by aztreonam)	Trials: (active comparators) SMC: Flucloxacillin and Benzylpenicillin, beta-lacta antibiotics and macrolides	Test of Cure (TOC)	5	Studies show tigecycline to be non-inferior to Vancomycin-azetreonam. These are not routinely used in Scottish Practice and no direct	Cost utility	Not reported	Both agree that relative effectiveness shown in the study comparisons but relevance to clinical practice questionable.

					HAS: beta-lactam, quinolones, macrolides, glycopeptides. Aminoglycosides, oxazolidinones, synergistins.			comparisons with other antibiotic regimes.			There are weaknesses in the economic evidence and use of the clinical evidence. Restricted to use for second and third line (Major restriction SMC).
C037	Tigecycline	C-C-C	Yes	Yes Two Double Blind RCT (tigecycline vs imipenem-cilastatin)	Trials: (active comparator) HAS: beta-lactam, quinolones, macrolides, glycopeptides. Aminoglycosides, oxazolidinones, synergistins. SMC: Cefotaxime plus metronidazole, piperacillin-tazobactam, meropenem, Vancomycin.	Test of Cure (TOC)	5	The comparator in the trials is not routine in Scottish clinical practice. Uncertainty regarding other direct comparisons.	Cost utility	Not reported	Both agree relative effectiveness shown in the study comparison but relevance to clinical practice questionable. (ASMR=5). There are weaknesses in the economic evidence and use of the clinical evidence. Restricted to use for second and third line (Major restriction SMC).
C040	Testosterone undecanoate	C-C-NC	Yes	Yes One RCT (testosterone undecanoate vs enentate)	Trials (active comparator) SMC: Testosterone enantate,	Erthropoiesis and Grip strength	5	Similar relative efficacy in comparison to enanatate (clinical equivalence). A	Cost utility	£2,019	The Transparency committee discounted the trial evidence because of methodological

					Testosterone propionate, Testosterone esters. HAS: Testosterone enanthate, testosterone esters			indirect treatment comparison was provided that had several weaknesses.			weaknesses (ASMR=5) and restricted reimbursement to non age related androgenic deficiency. Uncertainty in indirect comparison but sensitivity analysis confirms likely cost-effectiveness. (Recommended listing)
C045	ivabradine	C-C-C	Yes	Yes – add ev SMC: Two Double blind RCT Phase III (ivabradine vs atenolol) and (ivabradine vs amlodipine) Three 1 year safety studies. HAS: Two Double blind RCT Phase III (ivabradine vs atenolol) and (ivabradine vs amlodipine), one Double	Trials (active comparator) SMC: Calcium-channel blockers, nitrates and potassium channel activators HAS: Calcium channel blockers, nitrates , nicrorandil	Total Exercise Duration (TED)	3	Non-inferiority of ivabradine vs atenolol and ivabradine versus amlodipine was shown.	Cost utility	£15,021	Both agree relative effectiveness established in the comparator drugs but ASMR (3) for the same indication as SMC. Manufacturer submitted within a subgroup of the licensed population. There were concerns over the comparator chosen but there may be a small group of patients

				blind RCT (placebo) Phase II and Double blind RCT (placebo) Phase III and three 1 year studies							with no other treatment option. (Major restriction)
C046	natalizumab	C-C-C	Yes	Yes Two studies – Double blind RCT (placebo) Phase III, One RCT (natalizumab vs beta interferon 1a)	Different Trials: SMC: Beta-interferon, glatiramer acetate HAS: Mitroxanatrone	Patient relapse	3	There is a clinically important reduction in clinical relapse. There are no active comparator studies resulting in uncertainty.	Cost-utility	£22,500	Both agree uncertainty with regards the active comparator of mitoxantrone in France and beta-interferon in Scotland. An (ASMR=3) was only provided for the RES group and requests an observational study be provided. Manufacturer submitted an economic analysis in the RES subgroup. There were concerns with model were explored through sensitivity analysis and considered cost-effective. (Restricted)

C049	Levetiracetam	NC-NC-C	Yes	Yes One Double Blind RCT (levetiracetam vs carbamazepine)	Trial: Active comparator SMC: oxacarbazepine, gabapentin, topiramate, sodium valproate, carbamazepine, lamotrigine, phenytoin. HAS: Phenytoin, Primidone, Gabapentin, Lamotrigne, Phenobarbital, Carbazepine, Valporic acid, Oxcarbazepine, Clonazepam	6 month seizure freedom	4	Non-inferiority demonstrated in comparison to carbamazepine. A limited indirect comparison was performed to compartor.	Cost utility	£413	Both agree on the non-inferiority in comparison with carbamazepine and HAS provides a ASMR=4. Manufacturer positioned as second line. There were a number of weaknesses with indirect comparison to derive the relative efficacy and high utility values but reassurance was provided by a number of sensitivity analyses (Major restriction).
C052	posaconazole	C-C-C	Yes	Yes Two studies: One Double Blind RCT (posaconazole vs fluconazole), one open label evaluator-blind RCT	Trials: Active comparator SMC: Fluconazole, itraconazole HAS: itraconazole, fluconazole and amphotericin B	Incidence of probable/proven Fungal infection	3	Posaconazole appears to be more effective than fluconazole, the comparative efficacy of posaconazole vs itraconazole is more limited due to small sample sizes.	Cost utility	£27,907	Both agree on the non-inferiority demonstrated against the active comparators in the trials and deemed an ASMR=3. The cost-effectiveness modelling was uncertain and

				(posaconazole vs fluconazole or itraconazole)							sensitive to changes in parameters (provided when other therapies not tolerated). (Major Restriction).

Table A6.5: Reasons for differences in recommendations

Reason	Codes	Number
The appropriate relevant comparators in France and Scotland are different. -1	C001, C010 C025, C046	4
Both agree on uncertainty in relative effectiveness (HAS: ASMR=5). There are uncertainties in the economic evaluation resulting in the SMC advising either a not recommended/major restriction. - 3	C007, C008, C036, C037	4
Both agree on improvement in relative effectiveness (HAS: ASMR≠5). Manufacturers economic evidence demonstrates cost effectiveness and minor restriction between agencies -2	C002, C027, C028	3
Both agree on improvement in relative effectiveness (HAS: ASMR≠5). Manufacturer submits a cost-utility analysis demonstrating cost-effectiveness in a subgroup where the SMC advises major restriction.- 4	C023, C024, C049	3
Both agree on improvement in relative effectiveness (HAS: ASMR≠5). The SMC advises to not recommended because the medicine is not cost-effective at the manufacturers supplied price. - 5	C029, C034	2
Both agree on improvement in relative effectiveness (HAS: ASMR≠5). Manufacturer submits cost-utility analysis with weaknesses in the evaluation resulting in SMC advising a major restriction. - 7	C045, C052	2
Both agree on uncertainty in relative effectiveness (HAS: ASMR=5). Manufacturer submits a cost-utility analysis for a number of scenarios and sensitivity analysis demonstrating likely cost-effectiveness. HAS advises major/minor restriction. - 8	C016, C040	2
Both agree on relative effectiveness (HAS: ASMR=5). Manufacturer submits a cost-utility analysis in a subgroup demonstrating a quality of life benefit and cost-effectiveness. SMC advises major restriction. - 9	C009, C013	2
Both agree uncertainty in relative effectiveness (HAS: ASMR=5). Manufacturer submits cost-minimisation in a subgroup resulting in SMC advising major restriction -6	C033	1
Both agree on relative effectiveness but ASMR=4 provided on ground of safety for HAS. The manufacturers economic submission to SMC contains weakness but advise listing in a restricted group because of no treatment alternative - 10	C015	1
Difference in judgement of clinical equivalence. HAS evaluates relative effectiveness to be uncertain in the presence of an indirect comparison whereas SMC considers a meta-analysis and find this to demonstrate equivalence in a restricted group. Cost-minimisation demonstrates the economic case and SMC advises major restriction. - 11	C030	1

Abbreviations

ABSMA	Advisory Board for Social Medical Affairs
ACD	Appraisal Consultation Document
ACP	Appraisal Committee
ADTC	Area Drug and Therapeutic Committees
AHTAPol	Agency for Health Technology Assessment in Poland
AIFA	The Italian Medicines Agency
AMNOG	Pharmaceutical Market Restructuring Act
ASMR	Improvement in Medical Benefit
AUnETS	The association of the Spanish HTA agencies
BMJ	British Medical Journal
BNF	British National Formulary
CADTH	Canadian Agency for Drugs and Technologies in Health
CDR	Common Drug Review
CEA	Cost-effectiveness analysis
CEDAC	Canadian Expert Drug Advisory Committee
CEEPS	Commission for Economic Evaluation and Public Health
CEPS	Economics Committee on Health Care Products
CER	Comparative Effectiveness Research
CFH	Pharmaceutical Assistance Commission
CLY	Cost per Life year gained
CMS	Centre for Medicare and Medicaid Services
CPU	Corporate Pharmaceutical Unit
CQG	Cost per QALY gained
CRM	Committee for Reimbursement of Medicines
CUA	Cost utility analysis
CVZ	Dutch Health Insurance Boards
DGHP	Directorate General of Pharmacy and Health Products
DPS	Drugs Payment Scheme (DPS)
DREC	Drug and Reimbursement Committee
DUSC	Drug Utilisation Sub-Committee
EBM	Evidence Based Medicine
EMA	European Marketing Authorisation
EMWGPO	European Medicines Agency Working Group with Patient Organisations
ERG	Evidence Review Group
ESC	Economic Sub-Committee
EUnetHTA	European network for Health Technology Assessment
FAD	Final Appraisal Determination
FDC	Federal Drugs Commission
FOPH	Federal Office of Public Health
G-BA	Federal Joint Committee and IQWIG
GDP	Gross Domestic Product

GHC	General Health Council
GMS	General Medical Services
HAS	Haute Autorité de santé
HEK	Medicines Evaluation Committee
HIRA	Health Insurance Review and Assessment
HMO	Health Maintenance Organisations
HOD	Ministry of Health Care Services
HRQOL	Health Related Quality of Life
HSE	Health Service Executive
HTA	Health Technology Assessment
HTAi	Health Technology Assessment International
HVB	Federation of Austrian Social Security Institutions
ICER	Incremental Cost-effectiveness Ratio
IIA	Independence of irrelevant alternatives
iJODR	Interim Joint Oncology Drug Review
IMSS	Mexican Social Security Institute
INAHTA	International Network of Agencies for Health Technology Assessment
INFARMED	National Authority of Medicines and Health Products
IPHA	Irish Pharmaceutical Healthcare Association
IQWIG	The Institute for Quality and Efficiency in Health Care
IRP	Independent Review Panel
ISSSTE	The Institute of Security and Social Services for Government Workers
KELA	Social Security Institutions
LTI	Long term illness scheme
MCDA	Multiple Criteria Decision Analysis
ML	Maximum Likelihood
MNLM	Multiple Logistic Regression Model
MTA	Multiple Technology Appraisal
MTA	Medical Technology Administration
MTN	Reimbursement Committee
NCE	New Chemical Entities
NCPE	National Centre for Pharmacoeconomics
NDC	New Drugs Committee
NHIC	National Health Insurance Corporation
NHIFA	National Health Insurance Fund Administration
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIHDI	National Institute for Health and Disability Insurance
NLHS	National List of Health Services
NoMA	Norwegian Medicines Agency
NPAF	New Product Assessment Form
OECD	Organisation for Economic Co-operation and Development
OHTA	Office for Health Technology Assessment
OTA	Office of Technology Assessment
PAPIG	Patient and Public Involvement Group

PBAC	Pharmaceutical Benefits Advisory Committee
PBPA	Pharmaceutical Benefits Pricing Authority
pCODR	pan Canadian Oncology Drug Review
PHARMAC	Pharmaceutical Management Agency
PMPRB	Patented Medicine Price Review Board
PNAC	Public National Advisory Committee
PPB	Pharmaceutical Pricing Board
PPIP	Patient and Public Involvement Programme
QALYs	Quality Adjusted Life Years
R&D	Research and Development
RCT	Randomised Controlled Trial
RVZ	Council for Public Health and Health Care
SEMESP	Assessment of Health Economics and Public Health
SIIF	Social Insurance Institution of Finland
SMC	Scottish Medicines Consortium
SMR	Medical Benefit
STA	Single Technology Appraisal
TAC	Technology Appraisal Committee
TAR	Technology Assessment Report
TLV	Pharmaceutical Benefits Board (previously LFN)
TSC	Technical and Scientific Committee
UK	United Kingdom
UNCAM	National Union of Health Insurance Funds
VBP	Value Based Approach
VIF	Variance Inflation Factors
WHO	World Health Organisation

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