



# eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

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## **EUnetHTA JA WP5: Relative Effectiveness Assessment (REA) of Pharmaceuticals**

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### **Background review July 2011 (version 5B)**

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## Summary

Upon the completion of the High Level Pharmaceutical Forum, the European Network for Health Technology Assessment (EUnetHTA) was identified as an appropriate candidate for developing scientific recommendations for improvements in relative effectiveness assessment<sup>1</sup>. The remit of Work Package 5 (WP5) of EUnetHTA is to develop methodology for relative effectiveness assessment of pharmaceuticals based on the existing tools within EUnetHTA. The aim of this background review is to provide an overview of the processes, the scope and the scientific methods used for relative effectiveness assessment in current national practice, as a starting point for the development of models and guidelines that have the best chance of acceptance/usage across the Member States. In addition, an overview is provided of current activities that have been identified in relation to relative effectiveness assessment of pharmaceuticals.

Data on national approaches for relative effectiveness assessment were gathered through a survey in 30 jurisdictions (26 European jurisdictions, Australia, Canada, the United States of America [USA] and New Zealand).

Except for the USA, all jurisdictions included perform evaluations that include a comparative analysis of efficacy and/or effectiveness of pharmaceutical(s) in comparison to alternative(s) to feed national reimbursement decisions on pharmaceuticals. This assessment is referred to with a variety of terms. In general these evaluations can be divided into (single) rapid assessments<sup>2</sup> and full assessments of pharmaceuticals<sup>3</sup>. Rapid assessments often have to be carried out within a specific timeframe whereas for full assessments a pre-specified timeframe is only applicable in a minority of jurisdictions. The methodological approaches used for rapid and full assessments do not differ much. The main differences seem to be the number of comparators (more comparators for a full assessment) and the timing of the assessment. The rapid assessment is often done after market authorisation whereas for a full assessment this is often performed when the pharmaceutical(s) is/are on the market for a number of years. Therefore, often more data are available for a full assessment as clinical effectiveness data are more likely to be available years after market authorisation.

In general, documents/guidelines in which the methods that are used for the comparative analysis are described, are not very detailed. Further, the survey showed that the similarities of the scientific methods used in the jurisdictions is greater than the difference. The jurisdictions use multiple (similar) sources for the assessment, however there seems to be some divergence between jurisdictions whether unpublished clinical data and/or confidential data are used. The definition of preferred choice of comparator is similar between most jurisdictions using definitions that are similar to 'usual care'. In the majority of the jurisdictions the choice of the comparator(s) for the assessment can also be a non-pharmaceutical intervention and is thus not limited to pharmaceuticals. The type of outcomes that can be included in the analysis are also similar for the included jurisdictions. In general, all clinically relevant outcomes are accepted for the assessment. Often outcomes related to mortality and/or morbidity and/or quality of life are preferred. Surrogate outcomes are in general not preferred, however they are accepted for the assessment if they are considered clinically relevant or are validated (this often depends on the indication/therapeutic area). There seems to be more variation in how the absence of effectiveness data is handled in terms of qualitative or quantitative extrapolation of efficacy data.

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<sup>1</sup> For details regarding the definition of relative effectiveness assessment we refer to section 1.2.3.

<sup>2</sup> (Single) rapid assessments are assessments of a new pharmaceutical at the time of introduction to the market in comparison to one or more alternative interventions.

<sup>3</sup> Full assessments of pharmaceuticals are assessments (non-rapid) of (all) available technolog(y)(ies) for a particular step in a treatment pathway or a specific condition.

The websites of a number of organisations were searched for activities related to relative effectiveness assessment. Internationally, there are various agencies all over the world that are involved in relative effectiveness or comparative effectiveness research/assessments. Guidelines on methodological issues that are relevant to relative effectiveness assessment are developed or are in development by the Agency for Health Research and Quality (AHRQ), Pharmaceutical Benefits Advisory Committee (PBAC), European Medicines Agency (EMA) and International Society for Pharmacoeconomics and Outcomes Research (ISPOR). In the future the Patient-Centered Outcomes Research Institute (PCORI, USA) will probably have a relevant role in guideline development as well.

Relative effectiveness assessments (broadly defined), amongst other criteria, are always considered by national decision-makers when making reimbursement decisions. This indicates that there is an element, this comparative analysis, that can be shared between jurisdictions. We conclude based on the results of our review that there is a common ground for the development of a shared methodology for this comparative analysis, the relative effectiveness assessment of pharmaceuticals. The purpose of such a relative effectiveness assessment is to assess the net therapeutic benefit of an intervention. The EUnetHTA HTA Core Model<sup>4</sup>, with a focus on the first four domains (Health problem and current use of technology, Description and technical characteristics of the technology, Safety and Effectiveness), can be used for such a purpose. However, some information from other domains, such as ethical, social, legal and organisational analysis may also be included in this model. As mentioned, the evaluation of pharmaceuticals can be divided into rapid assessments and full assessments of pharmaceuticals. Therefore WP5 will also develop 2 models, a Rapid Model and a Full model. The scope of the Full model will be all domains of the HTA Core Model except for the domain 'cost and economic considerations'. The scope of the Rapid model will also be all domains of the HTA Core Model except for the domain 'cost and economic considerations', however only a limited number of elements of the ethical analysis, the organisational analysis, the social aspects and the legal aspects will be included.

Finally, our results show that there are still a number of issues to be dealt with during development of methodology that can be used in Europe. The table below provides a summary of most relevant challenges for a common methodology on relative effectiveness assessment and how these will be addressed in WP5.

#### **Summary of most relevant challenges for a common methodology on relative effectiveness assessment and how these will be addressed in WP5**

<b>Challenge</b>	<b>WP5 activity</b>
Methodology to do assessments is often not explicitly reported	<ul style="list-style-type: none"> <li>• Production of guidelines on important methodological issues</li> <li>• Standardisation of reporting for assessments through using the Rapid/Full model for relative effectiveness assessment of pharmaceuticals</li> </ul>
Variation between jurisdictions in terminology and definitions	<ul style="list-style-type: none"> <li>• Production of guidelines on important methodological issues</li> </ul>
How to handle lack of effectiveness data	<ul style="list-style-type: none"> <li>• Production of guidelines on external validity and extrapolation of efficacy results;</li> <li>• Standardisation of reporting in Rapid/Full model</li> </ul>
How to present unintended and intended effects	<ul style="list-style-type: none"> <li>• Inclusion of section in Rapid/Full model that</li> </ul>

<sup>4</sup> The EUnetHTA HTA Core Model is a guidance document/model for producing extensive multi-dimensional assessments of health technologies that are reported in a structured format and that can be used as a foundation for local – e.g. national or regional – health technology assessment reports.

	aggregates intended and unintended effects
Variance in usual care between jurisdictions	<ul style="list-style-type: none"><li>• Production of guideline on 'Criteria for the choice of the most appropriate comparator(s)' as well as a guideline that provides methodology on direct and indirect comparisons in order to come to adjusted interpretations for jurisdictions with different forms of care</li></ul>





## List of abbreviations

AHRQ	Agency for Health Research and Quality
AHTApol	Agency for Health Technology Assessment in Poland
AIFA	Italian Medicines Agency
AT	Austria
ATC	Anatomical Therapeutic Chemical
AU	Australia
BE	Belgium
BU	Bulgaria
CA	Canada
CADTH	Canadian Agency for Drugs and Technologies in Health
CH	Switzerland
CHE	Centre of Health Economics of Latvia
CHMP	The Committee for Medicinal Products for Human Use
CNS	National Health Office of Luxembourg
CVZ	Dutch Healthcare Insurance Board
CZ	Czech Republic
DERP	Drug Effectiveness Review Project
DG Enterprise	Directorate General for Enterprise and Industry
DG Sanco	Directorate General for Health and Consumers
DMA	Danish Medicines Agency
DK	Denmark
EE	Estonia
EHC	Effective Health Care
EHIF	Estonian Health Insurance Fund
EMA	European Medicines Agency
EN/WA	England & Wales
EPAR	European Public Assessment Report
EPC	Evidence-based Practice Center
ES	Spain
ESKI	National Institute for Strategic Health Research
EU	European Union
EUnetHTA	European Network for Health Technology Assessment
FI	Finland
FR	France
GE	Germany
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAS	National Authority for Health
HILA	The Pharmaceuticals Pricing Board
HIQA	Health Information and Quality Authority
HRQL	Health-related quality of life
HTAi	Health Technology Assessment International
HU	Hungary
HVB	Association of Austrian Social Insurance Institutions
ICER	Institute for Clinical and Economic Review

ICMJE	International Committee of Medical Journal Editors
IE	Ireland
INAHTA	International Network of Agencies for Health Technology Assessment
INAMI-RIZIV	Belgian National Institute for Health and Disability Insurance
INFARMED	Portuguese National Authority of Medicines and Health Products
IOM	Institute of Medicine
IQWiG	German Institute for Quality and Efficiency in Health Care
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IT	Italy
LA	Latvia
LU	Luxembourg
MA	Malta
MEDEV	Medicines Evaluation Committee
MSAC	Medical Services Advisory Committee
NCPE	National Centre for Pharmacoeconomics
NGO	Non-governmental organisation
NICE	National Institute for Health and Clinical Excellence
NIH	National Institutes of Health
NL	Netherlands
NPAR	National Public Assessment Report
NO	Norway
NOKC	Norwegian Knowledge Centre for the Health Services
NZ	New Zealand
OS-DHHS	Office of the Secretary of the U.S. Department of Health and Human Services
OHSU	Oregon Health & Science University
PBAC	Pharmaceutical Benefits Advisory Committee
PCORI	Patient-Centered Outcomes Research Institute
PHARMAC	Pharmaceutical Management Agency
PHIS	Pharmaceutical Health Information System
PL	Poland
PPRI	Pharmaceutical Pricing and Reimbursement Information
PT	Portugal
QALY	Quality-adjusted life year
SBU	Swedish Council on Health Technology Assessment
SC	Scotland
SE	Sweden
SI	Slovenia
SIGN	Scottish Intercollegiate Guidelines Network
SK	Slovakia
SLOVATHA	Slovak Agency for Health Technology Assessment
SMC	Scottish Medicines Consortium
SUKL	Czech State Institute for Drug Control
SUPPORT	Supporting Policy-relevant Reviews and Trials
TLV	The Dental and Pharmaceutical Benefits Agency in Sweden
TU	Turkey
USA	United States of America
WHO	World Health Organization

WP4	Work package 4
WP5	Work package 5
ZZZS	The Health Insurance Institute of Slovenia



# 1 Introduction

## 1.1 Background

Several Member States of the European Union (EU) have expressed an interest in joint assessments of relative effectiveness of pharmaceuticals. The Directorates General for Health and Consumers (DG Sanco) and General Enterprise and Industry (DG Enterprise) of the European Commission have indicated in earlier communications that they have no intentions to develop new central institutions. Instead, they would prefer to make use of already available reports such as from the Working Group Relative Effectiveness of the High Level Pharmaceutical Forum and from existing networks like European Network for Health Technology Assessment (EUnetHTA) and the Medicines Evaluation Committee (MEDEV). Upon the completion of the High Level Pharmaceutical Forum, the EUnetHTA network was identified as an appropriate candidate for developing scientific recommendations for improvements in relative effectiveness assessment.

Work package 5 (WP5) on Relative Effectiveness Assessment in EUnetHTA WP5 was developed as part of the proposal for a EUnetHTA Joint Action between 2010-2012 that was filed to DG Sanco on May 20, 2009. The EUnetHTA Joint Action grant agreement was signed in December 2009 on behalf of 33 participating partners.

The objectives of WP5 (as defined in the EUnetHTA Grant Agreement 2010-2012) are:

- Development of health technology assessment tools and methods: Improved relative effectiveness assessments by identifying areas where methodological guidance is needed and by providing it, suggesting ways to integrate relative effectiveness assessment of pharmaceuticals as a special version of the HTA Core Model;
- Application and field testing of developed tools and methods: a relative effectiveness assessment of (a group of) pharmaceuticals in line with the core health technology assessment development.

WP5 has no intentions to develop a complete new assessment methodology for relative effectiveness assessment of pharmaceuticals, as the knowledge is already available. An overview of the processes, the scope and the scientific methods currently used by Member States for relative effectiveness assessment is necessary to set up common tools within WP5 that are based on and similar to what is already happening in daily practice in EU jurisdictions. Therefore this report focuses on a review of the current processes, methodologies and activities related to relative effectiveness assessment.

In chapter 1, information is provided on the work done by the High Level Pharmaceutical Forum (section 1.2.1) and the concept of relative effectiveness assessment (section 1.2.2 and 1.2.3). Chapter 2 describes the results of a survey on the processes and methodologies used for relative effectiveness assessment by health technology assessment organisations for the purpose of national reimbursement decisions in 26 European jurisdictions<sup>5</sup>, Australia, Canada, New Zealand and the United States of America (USA). Chapter 3 provides an overview of current activities that have been identified in relation to relative effectiveness assessment of pharmaceuticals. The report ends with a discussion of the implications of all the findings on WP5 (Chapter 4).

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<sup>5</sup> Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, United Kingdom.

## **1.2 Relative effectiveness assessment**

### **1.2.1 High Level Pharmaceutical Forum**

The High Level Pharmaceutical Forum was set up in 2005 as a three year process by Vice-President Verheugen and former Commissioner Kyprianou, in order to find relevant solutions to public health considerations regarding pharmaceuticals, while ensuring the competitiveness of the industry and the sustainability of the national health-care systems (<http://ec.europa.eu/pharmaforum/>).

The Working Group of the High Level Pharmaceutical Forum on Relative Effectiveness aimed to support Member States in applying relative effectiveness systems in order to allow containment of pharmaceutical costs as well as a fair reward for innovation. The Relative Effectiveness Working Group developed and agreed a number of documents:

- Core principles on relative effectiveness<sup>6</sup>;
- Availability of data to conduct relative effectiveness assessments<sup>7</sup>;
- Development of networking and collaboration<sup>8</sup>.

The final recommendations of the Relative Effectiveness Working Group for the Member States are presented below<sup>9</sup>:

#### ***Recommendation 5: Implement agreed good practice principles for relative effectiveness assessments***

5.1 Member States and stakeholders - the pharmaceutical industry, social insurers, health care professionals and patients' organisations- are encouraged to adopt the agreed working definitions on efficacy, relative efficacy, effectiveness and relative effectiveness and to use them in the scientific literature and reports of all kinds. The use of these common definitions will ensure a common understanding of the work done at national level and will facilitate the exchange of information between all parties involved.

5.2 Member States and stakeholders are encouraged to implement the agreed best practice principles for relative effectiveness assessment and to regularly communicate and exchange information on their adoption, where appropriate. Such implementation should also ensure medicines receive fast access to market and appropriate reward.

#### ***Recommendation 6: Promote the exchange of information on relative effectiveness assessments in order to improve the data availability and transferability***

6.1 Member States and stakeholders are encouraged to regularly exchange information in order to achieve the objectives set out in the conclusions, namely:

i) to consolidate the scientific evidence on relative effectiveness by collecting data, processes and conclusions reached at national level, for purposes of comparison, where appropriate,

<sup>6</sup> High Level Pharmaceutical Forum. Core principles on relative effectiveness. Available at URL: [http://ec.europa.eu/pharmaforum/docs/rea\\_principles\\_en.pdf](http://ec.europa.eu/pharmaforum/docs/rea_principles_en.pdf) (accessed December 2010).

<sup>7</sup> High Level Pharmaceutical Forum. Availability of data to conduct relative effectiveness assessments. Available at URL: [http://ec.europa.eu/pharmaforum/effectiveness\\_en.htm](http://ec.europa.eu/pharmaforum/effectiveness_en.htm) (accessed December 2010) .

<sup>8</sup> High Level Pharmaceutical Forum. Development of networking and collaboration. Available at URL: [http://ec.europa.eu/pharmaforum/docs/rea\\_networking\\_en.pdf](http://ec.europa.eu/pharmaforum/docs/rea_networking_en.pdf) (accessed December 2010).

<sup>9</sup> High Level Pharmaceutical Forum. High Level Pharmaceutical Forum 2005-2008. Final Conclusions and Recommendations of the High Level Pharmaceutical Forum. Available at URL [http://ec.europa.eu/pharmaforum/docs/final\\_conclusions\\_en.pdf](http://ec.europa.eu/pharmaforum/docs/final_conclusions_en.pdf) (accessed December 2010).

ii) to facilitate the work of the pricing and reimbursement authorities by providing them with this consolidated scientific evidence, focusing on their priority areas and  
iii) to inform health-care professionals and patients on the most effective drugs. This exchange should also aim to identify any barriers, whether scientific, technical or legal, that prevents all the parties involved from circulating the information easily.

6.2 In particular this exchange of scientific evidence should focus on the need to:

- i) improve the understanding of the scientific evidence generated that can be used for relative effectiveness by sharing best-practice in terms of data requirements and processes;
- ii) increase the understanding among those involved in relative effectiveness assessments of the possibilities and limitations in the generation of data that can be used for relative effectiveness assessments during and after the granting of marketing authorisation;
- iii) explore better avenues for dialogue between assessing bodies and/or decision-makers and the marketing authorisation holder to address point i);
- iv) strengthen the methodological quality and rigour of relative effectiveness assessments and identify any scope for common approaches in certain areas of assessment, as appropriate;
- v) inform health-care professionals and patients on the most effective medicines

6.3 National authorities and companies should also consider ways of having early dialogue during product development to improve the generation of appropriate data as far as possible.

6.4 Member States, with the involvement of the European Medicines Agency, should continue their efforts to consider how European Public Assessment Report and the National Public Assessment Report can further contribute to relative effectiveness assessments.

6.5 In an effort to streamline the exchange of such information and to ensure effective EU-wide coverage of relative effectiveness assessments, Member States and the Commission should identify how existing networks could be involved and any support that might be needed. Member States and the Commission should also address the issue of the involvement of stakeholders, while observing the above agreed principles.

### 1.2.2 Comparative effectiveness in the US

In 2009, comparative effectiveness research increased rapidly in the USA when The American Recovery and Reinvestment Act of 2009 (referred to as "Recovery Act" hereinafter) allocated \$1.1 billion for comparative effectiveness research<sup>10</sup>. When President Obama signed the bill, the recipients of the funds (the National Institutes of Health [NIH], Agency for Health Research and Quality [AHRQ], and Office of the Secretary of the U.S. Department of Health and Human Services [OS-DHHS]) issued requests for proposals to develop comparative effectiveness research infrastructure and to conduct comparative effectiveness research studies. The Recovery Act also mandated an Institute of Medicine (IOM) study to establish national priorities for comparative effectiveness research. Then, early in 2010, the health reform legislation established an ongoing national program in comparative effectiveness research: the Patient-Centered Outcomes Research Institute (PCORI). The roles and responsibilities of the PCORI are further discussed in chapter 3.

<sup>10</sup> Sox HC. Comparative effectiveness research: a progress report. Ann Intern Med. 2010 Oct 5;153(7):469-72.

In the USA the following definition is adopted by the IOM for comparative effectiveness research<sup>11</sup>:

"Comparative effectiveness research is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of comparative effectiveness research is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels."

The key words in this definition are "generation and synthesis of evidence" (which implies both original research and systematic reviews), "alternative methods" (which implies making comparisons in study populations), and "to make informed decisions" (which implies a focus on data that helps to decide between alternatives)<sup>11</sup>.

### 1.2.3 Relative effectiveness

The starting point for WP5 is the definition of relative effectiveness from the High Level Pharmaceutical Forum<sup>6</sup>:

- **Relative effectiveness:** can be defined as the extent to which an intervention does more good than harm compared to one or more intervention alternatives for achieving the desired results when provided under the usual circumstances of health care practice.

Essentially this definition contains three important elements:

1. The balance between doing more good than harm;
2. The intervention should be compared to one or more intervention alternatives. Hence the value of the intervention depends on its value relative to alternatives;
3. Results should be achieved when applied under usual circumstances of health care practice as opposed to within a clinical trial setting.

It should be noted that this definition is not without dispute. For example, there are discussions whether something defined as effectiveness should include benefits and harms. It is also considered disputable whether establishing how an intervention performs under usual circumstances of health care practice is at all feasible. Additionally, it has been indicated that the word 'relative' can have a mathematical meaning referring to a ratio, for example like in a relative risk calculation, whereas an additional clinical benefit could also be described as added life expectancy. The latter would be expressed as a difference in months, rather than a ratio. Although the definition may not be without debate this definition will form the basis for WP5, as it is a consensus between many relevant stakeholders in Europe.

#### 1.2.3.1 The efficacy/effectiveness spectrum

The following definition for relative efficacy was adopted by the High Level Pharmaceutical Forum<sup>6</sup>:

- **Relative efficacy:** can be defined as the extent to which an intervention does more good than harm, under ideal circumstances, compared to one or more alternative interventions.

The High Level Pharmaceutical Forum investigated the data availability to conduct relative effectiveness assessments<sup>7</sup>. It was concluded that there is no clear consensus as to whether clinical trials yield efficacy or effectiveness information. All data on pharmaceuticals yield

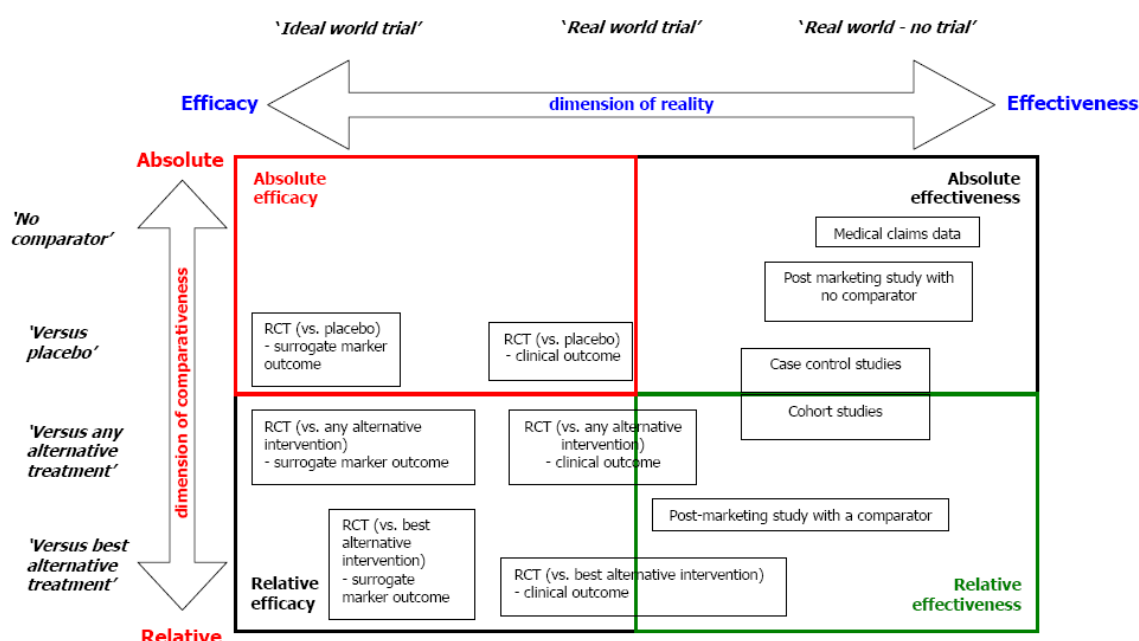
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<sup>11</sup> Sox HC. Defining comparative effectiveness research: the importance of getting it right. Med Care. 2010 Jun;48(6 Suppl):S7-8.



information that is somewhere on an efficacy/effectiveness spectrum, as illustrated in Figure 1 which is a simplified presentation of the spectrum. As a general rule, conventional clinical trials tend more to the efficacy side of the spectrum. The term effectiveness is used differently in EU Member States, which does not correspond with the High Level Pharmaceutical Forum definition. While some Member States use it to describe what is actually happening in real life (which is always theoretical to a certain extent), others stated to use it exclusively to describe clinical trials that are as far as possible to the effectiveness side of the spectrum. According to these Member States, this gives the best estimate of what happens in real life. There is no clear consensus on the interpretation among EU Member States.

**Figure 1. Efficacy/effectiveness spectrum.**



Source: High Level Pharmaceutical Forum 2008<sup>7</sup>

### 1.2.3.2 Confusing terminology

Many jurisdictions are becoming increasingly interested in evidence-based health care decision making because of their desire to improve the quality and efficiency of care provided to patients. Such activities are given various names, such as evidence-based medicine (EBM), health technology assessment (HTA), or more recently, comparative effectiveness research (CER). These terms are not used consistently, however, which has led to confusion in the medical and health policy communities<sup>12</sup>.

It has been pointed out that there is an important difference between comparative effectiveness research and evidence based medicine<sup>13</sup>. Evidence-based medicine is defined as, "The

<sup>12</sup> Luce BR, Drummond M, Jönsson B, Neumann PJ, Schwartz JS, Siebert U, Sullivan SD. EBM, HTA, and CER: clearing the confusion. *Milbank Q.* 2010 Jun;88(2):256-76.

<sup>13</sup> Manchikanti L, Falco FJ, Boswell MV, Hirsch JA. Facts, fallacies, and politics of comparative effectiveness research: Part 2 - implications for interventional pain management. *Pain Physician.* 2010 Jan;13(1):E55-79. Review.

conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients"<sup>14</sup>. Manchikanti et al. (2010) have described the difference between evidence based medicine and comparative effectiveness research as the following. Evidence based medicine is essentially focused upon the use of the right (types and extent of) knowledge to guide the right and good intentions and actions of medical practice, which is fundamental to prudential clinical decision-making. In contrast, comparative effectiveness research is to assist consumers, clinicians, purchasers, and policy-makers to make informed decisions that will improve health care at both the individual and population levels<sup>13</sup>. However, one can also position evidence based medicine as the methodological basis for both clinical decision making (at the level of individual patients) and comparative effectiveness research/relative effectiveness assessment (of the value of an intervention at the level of health care systems and/or society). It is emphasised by Manchikanti et al. (2010) that comparative effectiveness research and evidence based medicine share many similarities and goals and it is mentioned that they are analogous to religion and politics – meaning different things to different people<sup>13</sup>.

Health technology assessment has been defined as: '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. Health technology assessment is conducted by interdisciplinary groups using explicit analytical frameworks drawing from a variety of methods'<sup>15</sup>.

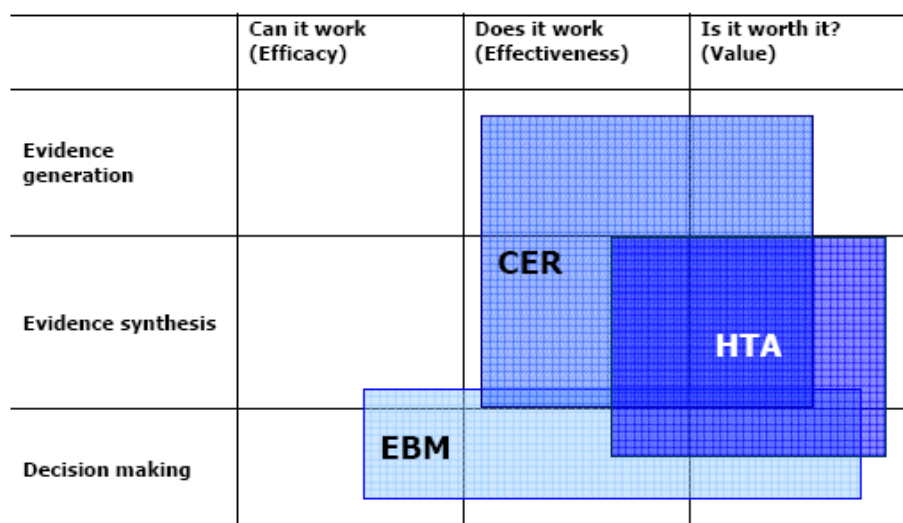
Luce et al. (2010) have developed a organising framework to help derive more precise definitions<sup>12</sup>. Along one axis are three questions that evidence-based processes in health care seek to answer about an intervention, namely, "Can it work" (i.e., efficacy), "Does it work?" (i.e., effectiveness), and "Is it worth it?" (i.e., economic value). Along the other axis are the three key functions of implementing evidence-based activities, namely, "Evidence Generation," "Evidence Synthesis," and "Decision Making." The graph below illustrates the current confusion of the various terms due to overlap in questions seeking to answer and key functions.

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<sup>14</sup> Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: What it is and what it isn't. *BMJ* 1996; 312:71-72.

<sup>15</sup> International Network of Agencies for Health Technology Assessment (INAHTA). URL: [http://www.inahta.org/HTA/Glossary/#\\_G](http://www.inahta.org/HTA/Glossary/#_G) (Accessed 18 December 2010).

**Figure 2. Current confusion of Views of EBM, CER and HTA.**

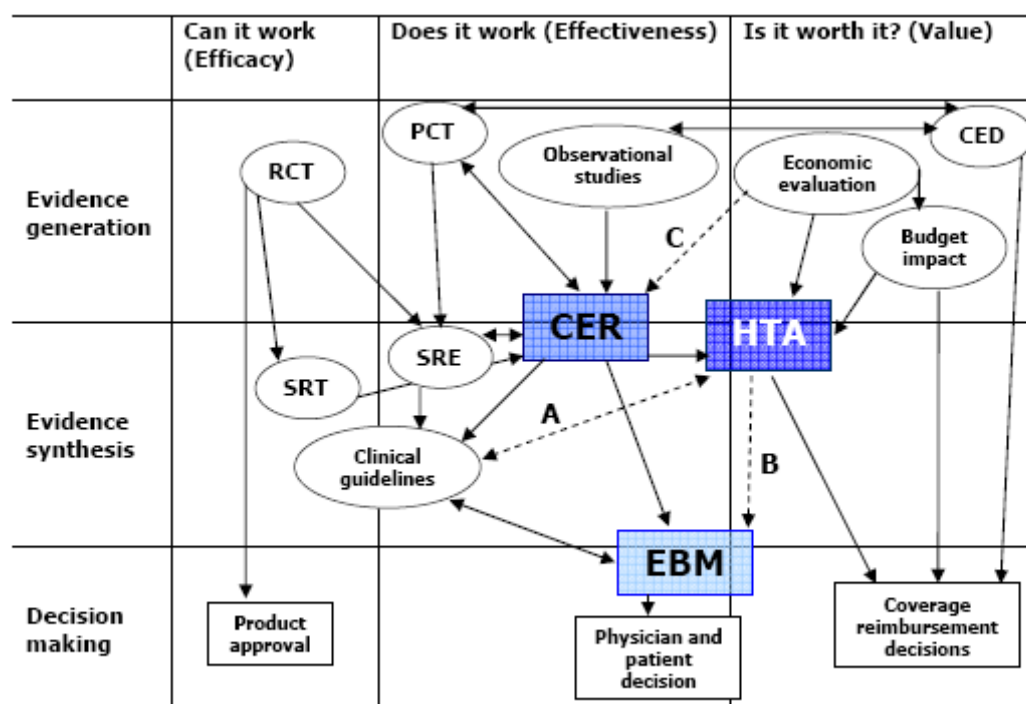


**Abbreviations:** CER=comparative effectiveness research; EBM=evidence based medicine; HTA=health technology assessment

**Source:** Luce BR, Drummond M, Jönsson B, Neumann PJ, Schwartz JS, Siebert U, Sullivan SD. EBM, HTA, and CER: clearing the confusion. *Milbank Q.* 2010 Jun;88(2):256-76.

The graph below was developed by Luce et al. (2010) to help derive more precise definitions.

**Figure 3. Redefined relationships of evidence processes**



**Abbreviations:** CED= coverage with evidence development; CER=comparative effectiveness research; EBM=evidence based medicine; HTA=health technology assessment; PCT=pragmatic clinical trial; RCT=randomised controlled trial; SRE= systematic review of evidence; SRT= systematic review of trials.

**Note:** Solid lines indicate clear relationships, and dotted lines indicate disputed relationships. White rectangles represent decision processes, and circles and ovals represent all other evidence activities, except for the coloured rectangles, which are reserved for EBM, HTA, and CER.

**Source:** Luce BR, Drummond M, Jönsson B, Neumann PJ, Schwartz JS, Siebert U, Sullivan SD. EBM, HTA, and CER: clearing the confusion. *Milbank Q.* 2010 Jun;88(2):256-76.

Based on this framework, they propose the following definitions of the three key terms<sup>12</sup>:

1. Evidence-based medicine is an evidence synthesis and decision process used to assist patients' and/or physicians' decisions. It considers evidence regarding the effectiveness of interventions and patients' values and is mainly concerned with individual patients' decisions, but is also useful for developing clinical guidelines as they pertain to individual patients.
2. Comparative effectiveness research includes both evidence generation and evidence synthesis. It is concerned with the comparative assessment of interventions in routine practice settings. The outputs of CER activities are useful for clinical guideline development, evidence-based medicine, and the broader social and economic assessment of health technologies (i.e., health technology assessment).
3. Health technology assessment is 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 health technologies. The precise balance of these inputs depends on the purpose of each individual health technology assessment. A major use of health technology assessment is informing reimbursement and coverage decisions, in which case HTAs should include benefit-harm assessment and economic evaluation.

Luce et al. (2010) prefer to distinguish between activities that concentrate primarily on benefits to the patient (evidence-based medicine) and those that concentrate primarily on benefits to

society at large (health technology assessment)<sup>12</sup>. The latter being often within budget constraints, meaning that not everyone may get everything he or she desires. In addition, they emphasise that although they differentiate, bind and relate evidence-based medicine, health technology assessment and comparative effectiveness research they do not contend that they all have a central unifying aspect.

How to position a relative effectiveness assessment within this framework? The purpose of a relative effectiveness assessment is to inform health care professionals, patients and decision makers about the net therapeutic benefit of an intervention compared with alternative interventions. Therefore, we would position relative effectiveness assessment as a specific element of a health technology assessment that focuses on the clinical implications of the intervention, whereas the concept of health technology assessment is broader and can also include for example social, ethical and cost aspects.

### 1.2.3.3 The HTA core Model and WP5

The HTA Core Model is a guidance document developed within EUnetHTA to foster a collaborative way of assessing health technologies, aiming at promoting international use of health technology assessment results and avoiding duplicate work<sup>16</sup>. The model is a guidance document/model for producing extensive multi-dimensional assessments of health technologies that are reported in a structured format and that can be used as a foundation for local – e.g. national or regional – health technology assessment reports. The HTA Core Model consists of 9 chapters, which are called domains (Table 1)<sup>17</sup>. Each domain is divided into more specific topics, and further into issues in the form of generic questions<sup>18</sup>. The combination of domain, topic, and issue defines an assessment element, the basic unit in the Model. The elements are divided into core and non-core elements based on their importance and transferability. The Model guides the health technology assessment doers first to consider the relevance of each assessment element for the technology. For each relevant element, the generic question is translated into a specific question concerning the technology. A Core HTA is the compilation of the questions and answers of relevant core elements for a specific technology, and a summary chapter.

**Table 1. Domains in the HTA Core Model.**

- 
- |  |
|--|
| 1. Health problem and current use of technology                |
| 2. Description and technical characteristics of the technology |
| 3. Safety  |
| 4. Effectiveness   |
| 5. Costs and economic evaluation                               |
| 6. Ethical analysis  |
| 7. Organisational aspects                                      |
| 8. Social aspects  |
| 9. Legal aspects   |
- 

<sup>16</sup> Lampe K, Mäkelä M, Garrido MV, Anttila H, Autti-Rämö I, et al. The HTA core model: a novel method for producing and reporting health technology assessments. *Int J Technol Assess Health Care*. 2009 Dec;25 Suppl 2:9-20.

<sup>17</sup> Pasternack I, Anttila H, Mäkelä M, Ikonen T, Räsänen P, et al. Testing the HTA core model: experiences from two pilot projects. *Int J Technol Assess Health Care*. 2009 Dec;25 Suppl 2:21-7..

<sup>18</sup> A Domain within the core model can be divided in individual topics which subsequently can be divided into issues. Example in *Health Problem and Current Use of the Technology* there is a topic *Target condition*. Within this topic target condition there is an issue *Which disease/health problem/potential health problem will the technology be used for?* These issues are called elements.

The remit of WP5 is to develop methodology for relative effectiveness assessment of pharmaceuticals based on the existing tools within EUnetHTA, the HTA Core model. This will result in two models for relative effectiveness assessment of pharmaceuticals using elements of the EUnetHTA Core Model under the umbrella of WP5, a model for rapid assessment of relative effectiveness of pharmaceuticals (from now on referred to as the **Rapid model**) and a model for a full assessment of relative effectiveness of pharmaceuticals (from now on referred to as the **Full model**). Development of the models will be in close collaboration with WP4 (HTA Core Model) of EUnetHTA. The basic methodology used for the Rapid and the Full model will be similar but, due to for example availability and maturity of data at the time of evaluation, there will be important differences as well. Keypoints for the development of the models are:

- be as close as possible to the national and international guidelines;
- be context non-specific (suitable to be shared internationally);
- follow the principles of the HTA Core Model, although the number of domains, topics and items may differ.

In line with the recommendation of the High Level Pharmaceutical Forum that relative effectiveness and cost-effectiveness should be considered as two entities<sup>9</sup>:

*'The High Level Pharmaceutical Forum acknowledges the distinction between the scientific assessment of the relative effectiveness of medicinal products and health-economic assessments of their costs and benefits'*

the domain of cost-effectiveness is excluded from the scope of WP5.

In addition, guidelines will be developed for methodological issues that will be referred to in the Rapid model and Full model.

The aim of this background review is to provide an overview of the processes, the scope and the scientific methods used for relative effectiveness assessment in current national practice, as a starting point for the development of models and guidelines that have the best chance of acceptance across the Member States.

#### 1.2.3.4 Other definitions

The following definitions of the High Level Pharmaceutical Forum are also used as a starting point for WP5:

- **Efficacy:** is the extent to which an intervention does more good than harm under ideal circumstances;
- **Effectiveness:** is the extent to which an intervention does more good than harm when provided under the usual circumstances of health care practice.

In addition WP5 members have added the following definitions:

- **(Single) rapid assessment of relative effectiveness of pharmaceuticals:** defined as rapid assessment of a new technology at the time of introduction to the market and comparing the new technology to standard care;

- **Full assessment of relative effectiveness of pharmaceuticals:** defined as full assessment (non-rapid) of (all) available technolog(y)(ies) for a particular step in a treatment pathway for a specific condition;





## 2 National approaches to and use of relative effectiveness assessment

### 2.1 Data gathering

WP5 of the EUnetHTA Joint Action aims to review methods used for the relative effectiveness assessment of pharmaceuticals and to develop, apply and field-test new tools and methods. As a first step towards this goal this report provides an overview of the processes and methodologies used for assessments by health technology assessment organisations for the purpose of national reimbursement decisions of pharmaceuticals. Health technology assessment is a tool to support healthcare decision-making, including access decisions. However, for the survey it was chosen to limit the analysis to assessments for the purpose of national reimbursement decisions. It was already indicated by the High Level Pharmaceutical Forum that European Member States currently are not using or working with common definitions regarding efficacy, relative efficacy, effectiveness and relative effectiveness. Hence, the assessments performed that provide input for reimbursement decisions regarding pharmaceuticals varies in content and scope between members states. In order not to exclude evaluations of pharmaceuticals of jurisdictions based on the definition of the High Level Pharmaceutical Forum of relative effectiveness the following type of assessments were included: all 'comparative analysis' assessing the efficacy and/or effectiveness of pharmaceutical(s) in comparison to alternatives that provide input for national reimbursement decisions on pharmaceuticals have been included.

#### Jurisdictions included

In total, 30 jurisdictions are included, including 26 European jurisdictions, Australia, Canada, New Zealand and the USA.

The jurisdictions included are: Australia, Austria, Belgium, Canada, Czech Republic, Denmark, England & Wales, Estonia, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Luxembourg, Malta, Netherlands, New Zealand, Norway, Poland, Portugal, Scotland, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey and USA.

Originally, it was planned to include data for Bulgaria, Cyprus, Greece, Lithuania and Romania as well. However, we were not able to gather data for these jurisdictions within the timelines of this report.

The overview is limited to assessments by health technology assessment organisations that provide input for *national reimbursement decisions* of pharmaceuticals. However, it should be noted that the following exceptions are applicable:

- For England and Wales the assessments are performed by the National Institute for Health and Clinical Excellence (NICE). Only a positive advice regarding a pharmaceutical is mandatory (legislative). If NICE recommends the use of a product, it becomes mandatory for primary care trusts to provide and fund it. However, in case of a negative advice it is up to the primary care trusts to decide whether they want to fund the pharmaceutical;
- For Scotland for which the assessments are performed by the Scottish Medicines Consortium (SMC). The SMC advises regarding the use of pharmaceutical however the decision to fund the pharmaceutical is up to the regional health authorities;

- For Canada the assessment is done nationally by the Canadian Agency for Drugs and Technologies in Health (CADTH) but the decision on reimbursement (based on the national assessment) is a regional responsibility.

They were included after all because the agencies referred to are known for their well established processes/methodology.

### Data abstraction

Data were captured with a standardised data abstraction form that was developed by seven agencies<sup>19</sup> that are involved in health technology assessment of pharmaceuticals. The data abstraction form contained four sections with questions regarding:

- Section A: General information on the health care system
- Section B: General information on reimbursement of pharmaceuticals
- Section C: Relative effectiveness assessment of pharmaceuticals as part of (single) rapid assessment
- Section D: Relative effectiveness assessment of pharmaceuticals as part of a full assessment

The questions of the data abstraction form are included in the results tables in Appendix I.

Data were initially abstracted from different types of literature (peer reviewed, grey literature, EU and national reports etc.). The sources that were used per jurisdiction are listed in Appendix II. The results of the literature review were complemented by data collected through directly contacting experts involved in national evaluation processes used to make reimbursement decisions. These experts were identified through contacts within the EUnetHTA network and/or through their positions in relevant organisations. The organisations per jurisdiction are listed in Table 2. If the (single) rapid assessment and full assessment are performed by different organisations more than one organisation was interviewed.

The USA were included as one jurisdiction. As there is no organisation that is involved in national assessment of pharmaceuticals or national reimbursement decisions of pharmaceuticals (all health plans/health insurers have their own list), no organisation was interviewed and section C and D of the data abstraction form were considered not applicable to this jurisdiction.

**Table 2. Organisations of interviewees**

Jurisdiction		Institution interviewed
1. Australia	AU	PBAC (Pharmaceutical Benefits Advisory Committee)
2. Austria	AT	HVB (Association of Austrian Social Insurance Institutions)
3. Belgium	BE	INAMI-RIZIV (National Institute for Health and Disability Insurance)
4. Canada	CA	CADTH (Canadian Agency for Drugs and Technologies in Health)
5. Czech Republic	CZ	SUKL (State Institute for Drug Control)
6. Denmark	DK	DMA (Danish Medicines Agency)
7. England& Wales (UK)	EN/WA	NICE (National Institute for Health and Clinical Excellence)
8. Estonia	EE	EHIF (Estonian Health Insurance Fund)
9. Finland	FI	HILA (The Pharmaceuticals Pricing Board)
10. France	FR	HAS (French National Authority for Health)

<sup>19</sup> AETSA (ES), AHTAPOL (PO), CVZ (NL), HAS (FR), ESKI (HU), IRF (DE), NICE (UK)

<b>Jurisdiction</b>		<b>Institution interviewed</b>
11. Germany	GE	IQWiG (Institute for Quality and Efficiency in Health Care)
12. Hungary	HU	ESKI (National Institute for Strategic Health Research)
13. Ireland	IE	NCPE (National Centre for Pharmacoeconomics) and HIQA (Health Information and Quality Authority)
14. Italy	IT	AIFA (Italian Medicines Agency)
15. Latvia	LA	CHE (Centre of Health Economics of Latvia)
16. Luxembourg	LU	CNS (National Health Office)
17. Malta	MA	Ministry for Health, the Elderly and Community Care
18. Netherlands	NL	CVZ (Dutch Healthcare Insurance Board)
19. New Zealand	NZ	PHARMAC (Pharmaceutical Management Agency)
20. Norway	NO	NOKC (Norwegian Knowledge Centre for the Health Services)
21. Poland	PL	AHTApol (Agency for Health Technology Assessment in Poland)
22. Portugal	PT	INFARMED (National Authority of Medicines and Health Products)
23. Scotland (UK)	SC	SMC (Scottish Medicines Consortium)
24. Slovakia	SK	SLOVATHA (Slovak Agency for Health Technology Assessment)
25. Slovenia	SI	ZZZS (The Health Insurance Institute of Slovenia)
26. Spain	ES	Ministry of Health, Social Policy and Equality, Directorate-General for Pharmacy and Healthcare Products
27. Sweden	SE	TLV (The Dental and Pharmaceutical Benefits Agency in Sweden) and SBU (Swedish Council on Health Technology Assessment) <sup>20</sup>
28. Switzerland	CH	Federal Medicines Commission
29. Turkey	TU	Ministry of Health of Turkey General Directorate of Pharmaceuticals and Pharmacy
30. United States of America	USA	No interview

A semi-structured questionnaire (based on the data abstraction form<sup>21</sup>), which focused on information unavailable in the literature, was used to elicit information from the experts. The semi-structured questionnaire was either mailed and filled in independently by the expert or administered through a telephone interview. In both cases the answers were checked by the researchers for inconsistencies and clarity and challenged if needed by asking queries. Due to the involvement of different institutions in several jurisdictions for relative effectiveness assessments, in some jurisdictions experts from more than one institution were contacted in order to gain all answers.

The data were gathered between 1 May 2010 and 1 May 2011.

### Validation of results

To ensure that the authors of this report have interpreted the answers correctly, the institutions were asked to validate the results..

<sup>20</sup> In Sweden the (single) rapid assessments are performed by THL. Full assessments can be performed by SBU and THL. For this background review it was chosen to include the methodology of SBU for the Full assessments. If important deviations were noticed between THL and SBU methodology this is included in footnotes in the appendix.

<sup>21</sup> The semi-structured questionnaire consisted of those questions of the data-abstraction form that could not be answered with the data that were found in literature or uncertainty existed regarding the data that were found in literature.

The aggregated results are described in section 2.2 and section 2.3. The raw data are presented in Appendix I.

## ***2.2 Reimbursement of pharmaceuticals***

### **2.2.1 Type of system**

The jurisdictions included are organised primarily either through a national health service (50%, 15/30) or through an insurance-based health care system, also often referred to as a third party payer system (about 50%, 16/30). In Turkey both are applicable. In most jurisdictions the insurance-based system is dominated by social health insurance<sup>22</sup> whereas only in three jurisdictions private health insurance<sup>23</sup> is the main type of health insurance (USA, Netherlands and Switzerland). The private health insurers in the Netherlands and Switzerland are operating under 'social' conditions (e.g. acceptance is mandatory). In the USA health insurance is primarily provided by the private sector, with the exception of programs such as Medicare, Medicaid, TRICARE, the Children's Health Insurance Program and the Veterans Health Administration. Some jurisdictions (Germany and Turkey) have private health insurance as a full alternative besides their social health insurance. Of those jurisdictions operating under a health insurance based system participation in health insurance is mandatory (everyone is obliged by law to be insured) in 75% (18/24) of the jurisdictions. Except for Estonia, private health insurance is available in all jurisdictions as supplementary/complementary health insurance (e.g. additional insurance to cover extra services and/or co-payment).

A detailed overview of the results per jurisdiction is provided in Appendix I, Result table 1 and Result table 2.

### **2.2.2 Reimbursement lists**

A positive list is a designation of a legally binding index of the pharmaceuticals that are funded/reimbursed by the national health service/health insurance system. On the contrary, pharmaceuticals classified in a negative list can not be prescribed at the expense of the health service/health insurance (they are explicitly excluded from funding/reimbursement). For inclusion on a positive list the decision is often based on a reimbursement evaluation (which in general includes some form of health technology assessment) whereas negative lists (e.g. Germany and England/Wales) are often exclusions of specific types of pharmaceuticals such as non-prescription or life style pharmaceuticals which are not per definition subject to a reimbursement evaluation before being placed on the negative list.

For the outpatient use, most jurisdictions work with a national positive (80%, 24/30) or a national negative reimbursement list for pharmaceuticals (20%, 6/30) (see Figure 4). Slovakia and Italy are the only jurisdictions who have both a positive and a negative list. For Italy, these lists are combined in one list with the positive list being reimbursement category A (reimbursed) and the negative list being category C (not reimbursed).

Of the jurisdictions included, Canada and the USA have neither a national positive or a negative list. In Canada the regions have their own list and in the USA all health plans have a separate

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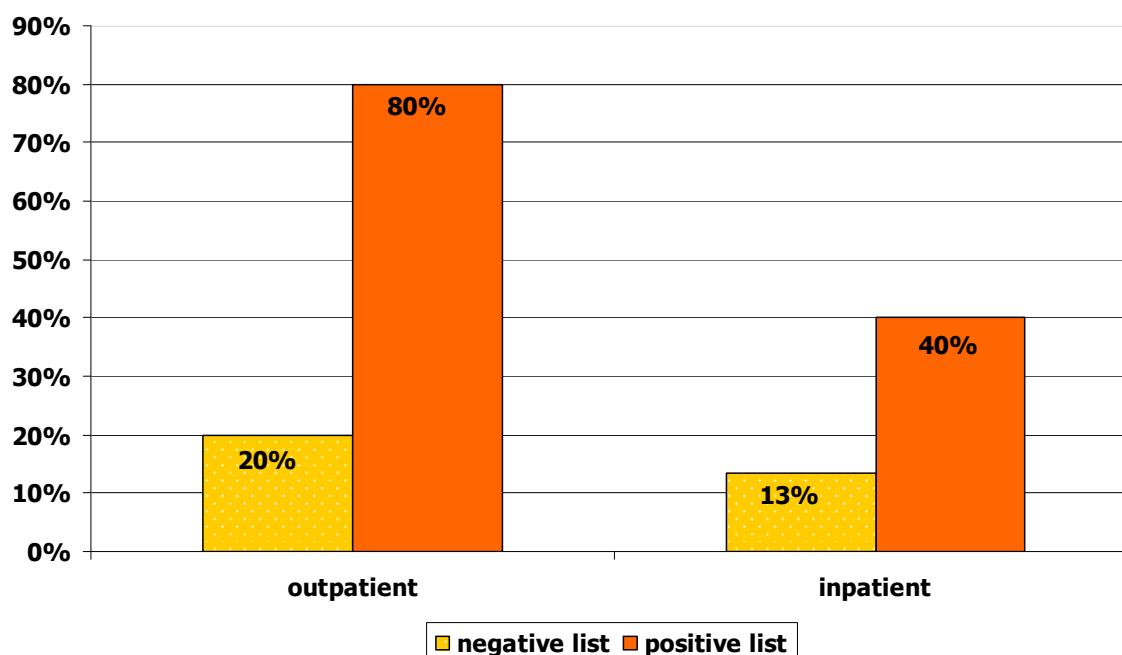
<sup>22</sup> Social health insurance is managed by a government agency, an agency for the government, or a not-for-profit institution.

<sup>23</sup> Private health insurance is operated by private companies.

pharmaceutical formulary that lists the prescription pharmaceuticals that are preferred by the health plan.

For the inpatient use, the number of jurisdictions with a national positive list for pharmaceuticals is substantially lower (40%, 12/30) and only 4 jurisdictions (England/Wales, Italy, Portugal and Scotland) have a national negative list for pharmaceuticals for inpatient use.

**Figure 4. Jurisdictions with national positive/negative reimbursement list (%)**



Number of jurisdictions: 30.

A detailed overview of the results per jurisdiction is provided in Appendix I, Result table 3.

### 2.2.3 Co-payment

At least some outpatient pharmaceuticals may be subject to some form of co-financing/patient co-payments in all jurisdictions, except for Malta. Malta is the only jurisdiction where no co-payment is applicable for any outpatient pharmaceuticals that are funded by the national health service. In the majority of the jurisdictions (60%, 18/30) a percentage of the price of the pharmaceutical has to be co-financed (see Table 3). Payment of the difference between reference price and retail price is applicable in more than 50% (16/30) of the jurisdictions. Arrangements such as fixed fee, prescription fee and deductibles are less frequent. 40% (12/30) of the jurisdictions have an annual co-payment ceiling protecting the patients from unlimited co-payment. It should be noted that different types of co-payment can be applicable in one jurisdiction to different types of pharmaceuticals. For example, payment of the difference between reference price and retail price is of course only applicable to pharmaceuticals that are included in the reference price system whereas in the same jurisdiction a percentage of the price may be applicable to reimbursed pharmaceuticals that do not fall under the reference price system.

Co-financing/co-payment is only applicable for pharmaceuticals for inpatient use in a limited number of jurisdictions (see Table 3). In some jurisdictions (20%, 6/30) fixed fees are applicable which can either be specifically for the pharmaceuticals consumed (Belgium) or a fixed fee per hospitalisation day (Austria, France, Germany, Sweden and Switzerland).

In Canada and the USA the co-financing arrangements vary across regions/ health plans. In Canada this is only applicable to pharmaceuticals for outpatient use as there is no co-payment for pharmaceuticals for inpatient use.

**Table 3. Methods used for co-financing/co-payment for pharmaceuticals (% of jurisdictions)**

Method of co-financing	Outpatient	Inpatient
Percentage of price of pharmaceutical	60%	0%
Fixed fee	17%	20%
Payment of difference between reference price* and retail price	53%	0%
Prescription fee	30%	0%
Deductible**	13%	3%
Annual co-payment ceiling***	40%	0%

Number of jurisdictions: 30.

\* A reference price limits the reimbursement of pharmaceuticals by establishing a maximum level of reimbursement for a group of pharmaceutical products

\*\* is a fixed amount which the patient has to pay for a defined period before the cost is fully or partially reimbursement

\*\*\* Annual co-payment ceiling: a limitation of the annual maximum amount of co-payment to be borne by a patient (e.g. a maximum co-payment per prescription like in Belgium, or annual ceilings of private expenses on pharmaceuticals and/or on health care in Germany and Luxembourg).

A detailed overview of the results per jurisdiction is provided in Appendix I, Result table 4.

## 2.2.4 Evaluations that provide input for reimbursement/funding decisions

Pricing and reimbursement decisions are in general based on an evaluation of the pharmaceutical that provides input for the decision.

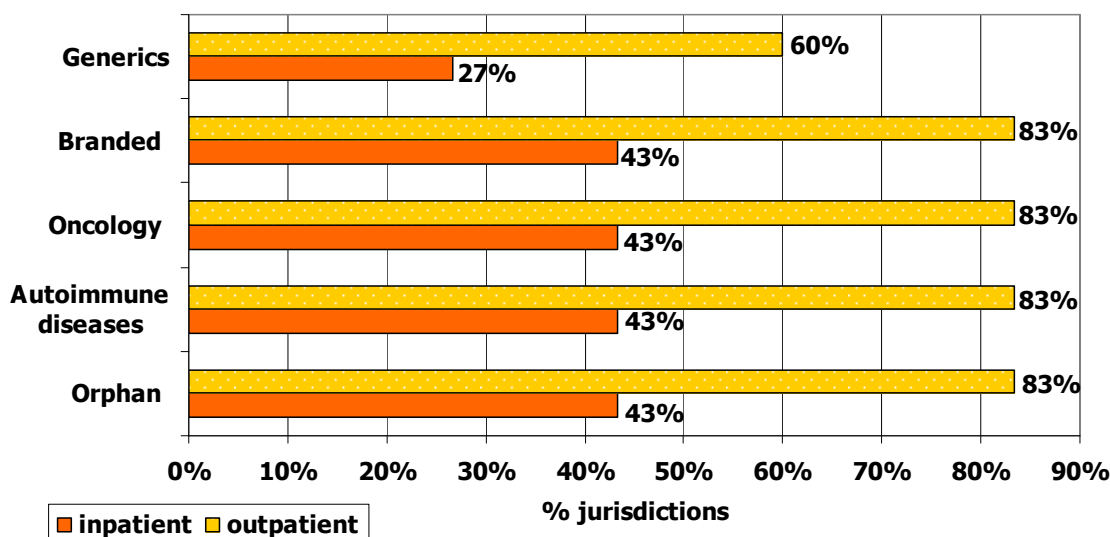
### 2.2.4.1 Type of pharmaceuticals and reimbursement criteria

There is variation across jurisdictions whether or not pharmaceuticals are subject to formal reimbursement evaluations prior to reimbursement. This strongly correlates with the existence of a positive list (section 2.2.2). In general, in jurisdictions with a positive list, pharmaceuticals must be evaluated before they can enter the list (e.g. France, Netherlands) in order to be reimbursed. Generics may be exempted from an evaluation (e.g. Netherlands, Scotland) or may be subject to a less extensive evaluation (e.g. Italy).

In jurisdictions with a negative list (and no positive list) in general pharmaceuticals are only evaluated in case there is a specific need (e.g. high costs, doubts about the relative effectiveness). Figure 6 shows the percentage of jurisdictions in which specific types of pharmaceuticals are always subject to a reimbursement evaluation before they are reimbursed.

The proportion of jurisdictions for which the various types of pharmaceuticals for inpatient use are always evaluated is about half of the proportion for pharmaceuticals for outpatient use.

**Figure 5. Jurisdictions in which specific types of reimbursed pharmaceuticals are always subject to a reimbursement evaluation (%)**



Number of jurisdictions: 30.

A detailed overview of the results per jurisdiction is provided in Appendix I, Result table 5.

### Reimbursement criteria

In general, each jurisdiction has defined a list with criteria that a product should adhere to in order to be reimbursed. Figure 6 presents the proportion of jurisdictions in which specific reimbursement criteria are applicable. A detailed overview of the results per jurisdiction is provided in Appendix I, Result table 6.

In all jurisdictions more than one criterion is used to inform reimbursement decisions. The criteria have been grouped according to commonly used names. However, it should be noted that the exact definitions of criteria differ in their wording and their nuances in each jurisdiction which makes the attribution to one of the names listed below difficult and susceptible to individual interpretation. In most jurisdictions at least some of the criteria that are applicable are stated in legal acts.

Effectiveness (effectiveness and efficacy are grouped) is stated to be used in all jurisdictions (see Figure 6). Safety is only stated not to be a criterion for pharmaceuticals for outpatient use in Norway. For Norway, safety can be assessed within the cost-effectiveness analysis, however this depends on whether data were provided by the marketing authorisation holder (hence they are not assessed on a regular or systematic basis). In order to be granted reimbursement in Norway, the marketing authorization holder has to demonstrate the seriousness of the disease/condition, that long-term treatment is necessary (more than 3 months) and the efficacy and cost-effectiveness.

France is the only jurisdiction for which no criterion related to cost (cost-effectiveness, cost containment, value for money or price) is stated to be applicable to reimbursement decisions of pharmaceuticals for outpatient use. It should be noted however that in France the price of the



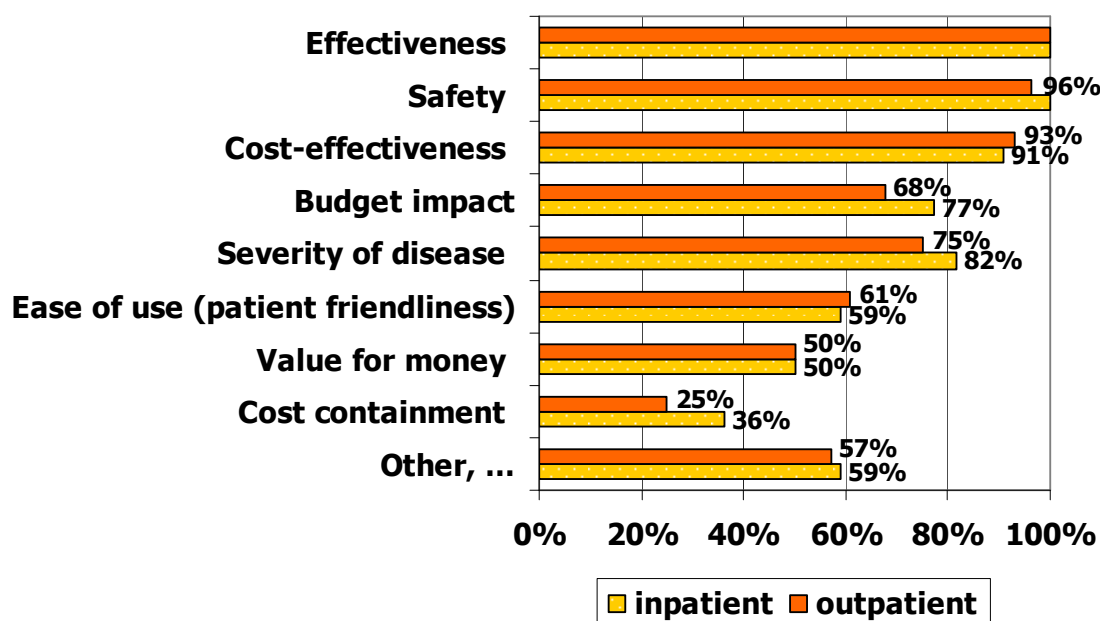
pharmaceutical is negotiated separately from the reimbursement decision, and this negotiation is also influenced by the therapeutic benefit. The greater the therapeutic improvement, the higher the potential price relative to similar products<sup>24</sup>.

Examples of other criteria that were mentioned but are not listed in Figure 6 are 'Impact in terms of public health' and 'the degree of innovation of the pharmaceutical'. The availability of alternative(s) is the most frequently mentioned other criteria.

In the USA criteria differ according to health plan, although many health plans adhere to the guidelines for formulary submission dossiers by the Academy of Managed Care Pharmacy (AMCP). In Canada, the criteria differ according to province.

It should be noted that as no predefined definitions were provided for the various criteria, the results are susceptible to individual interpretation of interviewees. Further investigation would be required to provide a more precise overview. In addition, it would be interesting to investigate the relative weight of various criteria in the national decision procedure. In some jurisdictions it is indicated that some of the criteria are not considered as major criteria for the final decision, such as 'severity of disease' in Scotland and 'ease of use' in the Netherlands.

**Figure 6. Jurisdictions in which specific reimbursement criteria are applicable (%)**



Number of jurisdictions: 30.

#### 2.2.4.2 Type of assessment

In general, assessments of pharmaceuticals that provide input for reimbursement decisions can be divided into (single) rapid assessment and full assessments of pharmaceuticals. (Single) rapid assessments are assessments of a new pharmaceutical at the time of introduction to the market in comparison with one or more alternative interventions. Full assessments of pharmaceuticals are assessments (non-rapid) of (all) available technology(ies) for a particular step in a

<sup>24</sup> Sorenson C. Use of comparative effectiveness research in drug coverage and pricing decisions: a six-country comparison. Issue Brief (Commonw Fund). 2010 Jul;91:1-14.



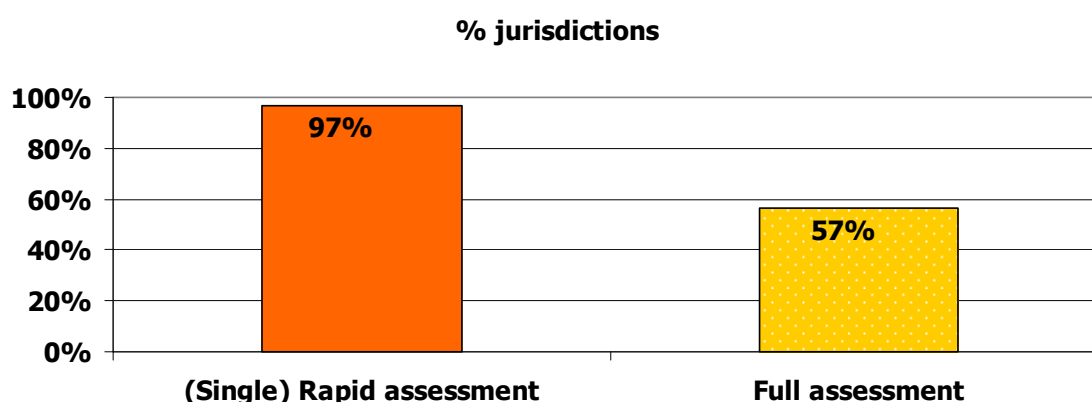
treatment pathway or a specific condition and are often conducted several years after introduction to the market. For a rapid assessment a limited number of comparators are used as opposed to a full assessment, where multiple technologies are considered. Additionally, even though similar methodology is followed in the collection of evidence, due to tim(e)(ing) and sometimes scope limitations, the rapid assessment is less comprehensive than the full assessment model. It should be noted that pricing and reimbursement decisions are not to the same as a rapid or full assessment. The latter are a tool to support, but not replace, these decisions.

Figure 7 shows that the first type, which from now on will be referred to as a 'rapid' assessment, is performed in all included countries, except the USA. In Germany, this type of evaluation was not common yet. However in 2011, a new law has come into force which determines that each pharmaceutical should be evaluated as soon as it enters the market. Therefore rapid assessments are becoming more common in Germany as well.

'full' assessments are performed in almost 60% (17/30) of the jurisdictions.

It should be noted that for this report only assessments that provide input for national reimbursement decisions are taken into account<sup>25</sup>.

**Figure 7. Jurisdictions that carry out assessments of pharmaceuticals to support reimbursement decisions (%)**



Number of jurisdictions: 30.

A detailed overview of the results per jurisdiction is provided in Appendix I, Result table 7.

Figure 8 shows that the rapid assessment has to be carried out within a specific timeframe in the majority of jurisdictions (>90%, 27/29) whereas for a full assessment this is only so in a minority of jurisdictions (12%, 2/17). Of the European jurisdictions included, most jurisdictions have implemented the timeframe specified in the Transparency Directive 89/105/EEC for the rapid assessment. The Transparency Directive 89/105/EEC is a harmonised legal instrument to guarantee the transparency of pricing and reimbursement measures. Part of the Transparency Directive is a strict timeframe of 90 or 180 days from receipt of application (90 days for pricing and 90 days for reimbursement, this in total 180 days). The Transparency Directive provisions

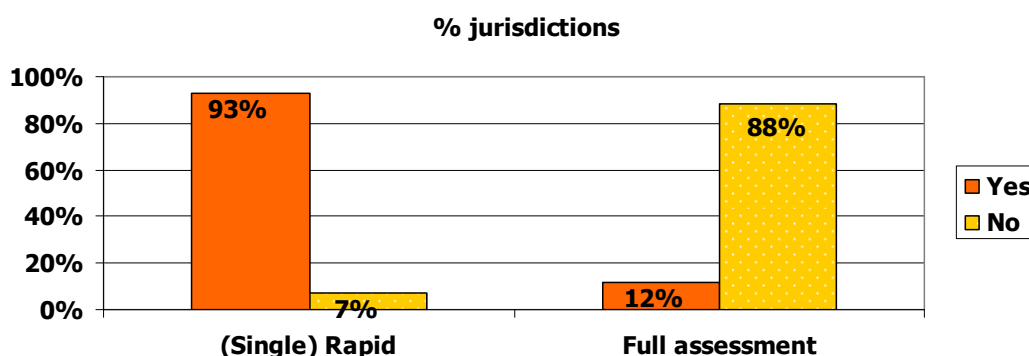
<sup>25</sup> With the exception of England and Wales for which the assessments are performed by NICE, Scotland for which assessments are performed by SMC and Canada for which the assessment is done nationally by the CADTH but the decision on reimbursement (based on the national assessment) is a regional responsibility.

are applicable in all Member States of the EU where decisions are made for the inclusion of pharmaceutical products in lists for pricing and reimbursement.

The timeframe for a rapid assessment in England/Wales is approximately 39 weeks and in Scotland 18 weeks from the date of submission. In Australia, submissions for rapid assessments are considered by the PBAC within 17 weeks. In Canada, the timeframe for rapid assessments is 19 to 25 weeks. In New Zealand and Switzerland there is no specific timeframe.

Specific timeframes for full assessments are not common. Only 12% (2/17) of the jurisdictions that perform full assessment have indicated specific timeframes.

**Figure 8. Jurisdictions in which the assessment to support reimbursement decisions of pharmaceuticals is subject to a specific timeframe (%)**



Number of jurisdictions: 30.

A detailed overview of the results per jurisdiction is provided in Appendix I, Result table 7.

### 2.2.4.3 Organisation of the evaluations

#### Initiation of the reimbursement evaluation

In most jurisdictions reimbursement evaluations are in general initiated by a reimbursement application of the manufacturer. Exemptions to this mechanism are Spain, Germany and England/Wales. In the first two jurisdictions they are only initiated by manufacturers in case of a re-evaluation. Alternative mechanisms of initiation are by the evaluating agency itself or other agencies or institutions such as the Ministry of Health. In Ireland and Spain all pharmaceuticals that receive marketing authorisation will automatically undergo a reimbursement evaluation. Since 1 January 2011 this is also applicable in Germany for all newly approved pharmaceuticals (i.e. pharmaceuticals with new active ingredients) and all new indications of drugs approved after 1 January 2011. The SMC (Scotland) tracks all pharmaceuticals that receive marketing authorisation. Subsequently, marketing authorisation holders are actively approached to submit an application for a product assessment. If the marketing authorisation holder refuses to submit an application the product will automatically receive a negative recommendation. In Ireland, all new pharmaceuticals are subjected to a preliminary rapid review. The term 'preliminary rapid review' as used describes a preliminary process whereby a quick review (4 weeks) of the new pharmaceutical is undertaken. The manufacturers submit initial briefing information which is reviewed and based on this information a decision is made to a) reimburse the product or b) subject the pharmaceutical to a full pharmacoeconomic evaluation.

In England/Wales there is a specified selection procedure based on published criteria in which NICE operates together with the Department of Health, also involving the national horizon scanning centre and condition specific expert panels.

Although in most jurisdictions manufacturers are in general the initiators of the assessment this does not mean that an evaluation cannot be initiated by a different party in these jurisdictions, such as the organisation that performs the assessment, a Ministry or (national organisations of) health insurers.

A detailed overview of the results per jurisdiction is provided in Appendix I, Result table 8.

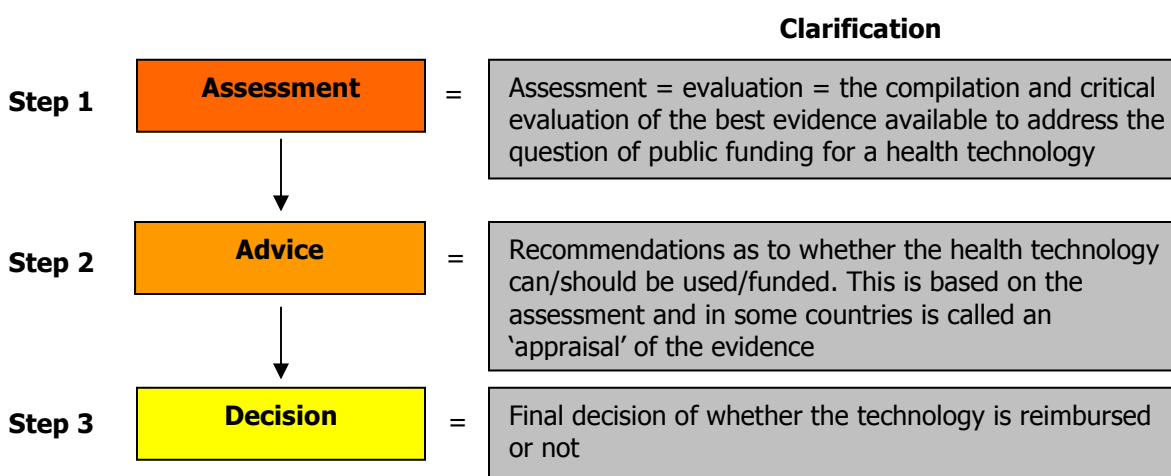
### Agencies

In most jurisdictions several agencies/organisations are involved in preparing and making a reimbursement decision for pharmaceuticals. We have identified the three steps in a reimbursement process that can include different organisations: 1) Assessment, 2) Advice, 3) Decision (Figure 9).

It should be noted that the first step (the assessment) can vary in content, approach and size. For a rapid Assessment the assessment is often based on a submitted dossier by the marketing authorisation holder. If, and the extent in which a separate document is produced by the agency/organisation based on the submitted file as a basis for the advice (step 2) varies between jurisdictions.

It should be noted that the third step, the decision, is based on a variety of criteria. The advice based on the assessment is only one of these.

**Figure 9. Schematic overview of steps in a reimbursement process of pharmaceuticals**



In some jurisdictions the three steps are all conducted by the same organisation. This is applicable to Czech Republic, Denmark, Finland<sup>26</sup>, Italy, Latvia, Malta, New Zealand, Norway<sup>27</sup>, Slovakia, Slovenia, Spain<sup>28</sup>, Sweden<sup>29</sup> and Turkey (illustrated in Figure 10 for Czech Republic).

<sup>26</sup> Step 2 is a joint effort of HILA and the Social Insurance Institution of Finland (Kela)

<sup>27</sup> In case of (single) rapid assessment all steps are conducted by the Norwegian Medicines Agency. For Full assessments Step 1 is performed by NOKC. In addition, the decision can only be made by the Norwegian Medicines Agency if the pharmaceutical is 1) a generic product, new strength, formulation or package size and no more costly than already reimbursed product 2) a new chemical entity, new combination or new indication and if the annual incremental fiscal impact does not exceed Norwegian kroner 5 million 5 years after approval. Otherwise the decision is made by the Ministry of Health and Care Services

<sup>28</sup> Negative decisions by the Ministry of Health are not obligatory to be adopted by regions.

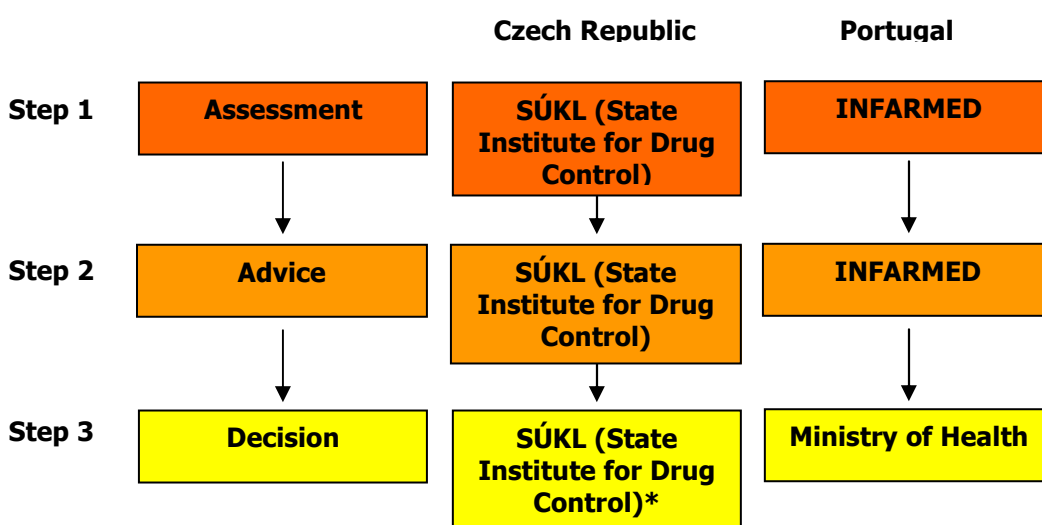
However, different committees within the same organisation may be involved for different steps. For example, in Malta all steps are under the responsibility of the Ministry for Health, the Elderly and Community Care, however the assessment is performed by the pharmacists at the Directorate of Pharmaceutical Policy and Monitoring, the advice is issued by the Government Formulary List Advisory Committee (GFLAC) and the decision is made by the Superintendent of Public Health.

Also common is that the assessment and advice are under the responsibility of one organisation, whereas the decision is made by another organisation. For example, in the Netherlands the assessment and advice are prepared by the CVZ whereas the final decision is made by the Ministry of Health, Welfare and Sports. Similar processes are applicable in Australia, Austria, Belgium, Canada, France, Germany, Luxembourg, Poland, Portugal, Scotland and Switzerland (illustrated in Figure 9 for Portugal). In Poland step 2 is conducted by the same agency as step 1, however step 2 is a joint collaboration with the National Health Fund.

Step 2 (formulating the advice) in many jurisdictions involves an (independent) committee.

A detailed overview of the results per jurisdiction is provided in Appendix I, Result table 9.

**Figure 10. Schematic overview of steps in a reimbursement evaluation of pharmaceuticals: examples**



\* After an appeal by the Marketing Authorisation Holder (in case of a negative decision by SÚKL) the Ministry of Health will make the decision.

### Other stakeholder involvement

At the beginning of this section it was indicated that various stakeholders can have the role of initiator of the assessment (manufacturer, organisation who performs the reimbursement evaluation, Ministry of Health). In the previous section the role of agencies/organisations in the assessment/advice and decision phases were discussed. This section focuses on other roles that stakeholders can have.

<sup>29</sup> In case of (single) rapid assessment. For Full technology assessments Step 1 is performed by SBU. In addition, step 2 is a joint effort of Dental and Pharmaceuticals Benefits Board and the National Board of Health and Welfare.

Various stakeholders are involved in the reimbursement evaluation process. In all jurisdictions industry is involved as provider of data. In more than half of the jurisdictions industry has the opportunity to participate in a general consultation. Industry is less likely to be involved as an expert, however their expertise might be taken into account in case there is a general consultation.

Medical doctors and pharmacists are mainly involved as experts. They can be consulted on an individual basis, through their medical organisations or as part of a decision making committee. In about 40% (12/29) of jurisdictions medical doctors are involved in the general consultation and in about 30% (9/29) of jurisdictions pharmacists are involved in the general consultation. Examples of patient involvement, are letters provided by patient organisations that are submitted on occasion which are then discussed by the decision making committee (Belgium) or optional hearings of patients association at the Transparency Committee in France. The CADTH has developed a formal approach for incorporating patients' perspectives into its Common Drug Review (CDR) process by inviting patient organisations and individuals to submit information via a standardised form<sup>30</sup>.

A detailed overview of the results per jurisdiction is provided in Appendix I, Result table 10.

### **Assessment vs. appraisal phase**

An assessment has been defined as the compilation and critical evaluation of the best evidence available to address the question of public funding for a health technology. An appraisal is a judgment of the value of a given technology. The appraisal is part of step 2 (Figure 8) which is 'providing recommendations as to whether the health technology can/should be used/funded'. The assessment and appraisal phase are always separated in 46% (13/28) of the jurisdictions. They are never separated in less than 40% (11/28) of the jurisdictions and they are sometimes separated in less than 15% (4/28) of the jurisdictions.

A detailed overview of the results per jurisdiction is provided in Appendix I, Result table 11.

### **Appeal**

In almost 90% (25/28) of the jurisdictions there is a process by which the marketing authorisation holders or other stakeholders can appeal a decision by the government entity. In some jurisdictions such as Denmark the procedure can be appealed, but not the actual decision.

A detailed overview of the results per jurisdiction is provided in Appendix I, Result table 11.

### **Review of previous reimbursement evaluations**

A dedicated formal process for reviewing previous reimbursement evaluations is in place in about 30% (9/28) of the jurisdictions. In Belgium for example the Royal Decree of 21 December 2001 imposes an individual review of pharmaceuticals of class 1 (innovative pharmaceuticals) within a period of 18 months to 3 years after the initial reimbursement decision. Previous reimbursement evaluations are reviewed occasionally in approximately 30% (8/28) of the jurisdictions whereas they are never reviewed in almost 40% (11/28) of the jurisdictions. In Spain for example only selected pharmaceuticals are reviewed like orphan pharmaceuticals and innovations with high impact on the budget. In Canada, no national reimbursement decisions are made as this is the responsibility of the regions. There is however a process by which product sponsors can submit a 'request for reconsideration' (similar to appealing a recommendation) for the Common Drug Review programme.

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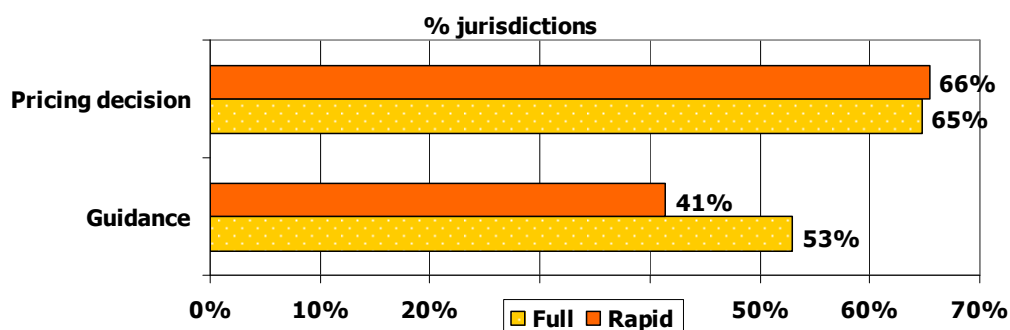
<sup>30</sup> [http://www.cadth.ca/media/cdr/cdr-pdf/Guide-Patient\\_Group\\_Input\\_to\\_CDR\\_final\\_e.pdf](http://www.cadth.ca/media/cdr/cdr-pdf/Guide-Patient_Group_Input_to_CDR_final_e.pdf) (accessed May 2011)

A detailed overview of the results per jurisdiction is provided in Appendix I, Result table 11.

#### 2.2.4.4 Purpose, status and scope

The survey focused on assessment of pharmaceuticals for the purpose of feeding reimbursement decisions. However, this assessments may suit also another purpose. In the graph below it is shown that for rapid and full assessments a frequently stated purpose was supporting pricing decisions (sometimes or always in about 65% of the jurisdictions). Providing guidance is stated to be a purpose for the rapid and full assessments sometimes or always in respectively 41% (12/29) and 51% (9/17) of the jurisdictions. In most jurisdictions guidance consists of prescribing recommendations. For example in Belgium and the Netherlands, a Pharmacotherapeutic Compass (*Gecommendatieerd geneesmiddelen repertorium* in Belgium and *Farmacotherapeutisch Kompas* in the Netherlands) is a booklet/website that provides information for pharmacists and physicians about pharmaceuticals available in the jurisdiction. For each pharmaceutical prescription advice is provided based on pharmacotherapeutic and economic grounds.

**Figure 11. Jurisdictions that use assessments for other purposes always or sometimes (% of jurisdictions)**



Number of jurisdictions for rapid assessment: 30; As US does not perform a rapid assessment, the average is based on n=29.

Number of jurisdictions for full assessment: 30; As CH, CZ, EE, FI, HU, LU, MA, NL, PT, SC, SI, SK and USA do not perform a full assessment the average is based on n=17.

A detailed overview of the results per jurisdiction is provided in Appendix I, Result table 12.

The status of the recommendation based on the assessment varies across jurisdictions (see Table 4). In the majority of jurisdictions the recommendation based on the assessment is an advice to a decision making body (e.g. advice to the Ministry of Health) for both the rapid as well as the full assessment. In fewer jurisdictions the recommendation itself is legislative (binding by law). In this case Step 2 and Step 3 of Figure 8 are the responsibility of the same agency. For the rapid assessment the percentage of jurisdictions in which the recommendation is always or sometimes legislative is 45%. For the full assessment this is applicable in 30% of the jurisdictions. The percentage of jurisdictions in which the recommendations are used for (clinical) guidelines (always or sometimes) is about 30% for the rapid assessment and about 50% for the full assessment.

In some jurisdictions the nature of the status depends on the outcome of the advice. For example, in Australia each Pharmaceutical Benefits Advisory Committee (PBAC) decision to recommend a pharmaceutical is an advice to government which makes the final decision about whether to add the pharmaceutical to the positive list. However, each PBAC decision not to recommend is binding by law: government cannot add the pharmaceutical to the positive list. In England/Wales only the positive decisions are mandatory (legislative): if NICE recommends the

use of a product, it becomes mandatory for primary care trusts to provide and fund it. However, in case of a negative advice it is up to the primary care trusts to decide whether they want to fund the pharmaceutical.

**Table 4. Status of the advice based on the assessment (% of jurisdictions)**

Status of advice	Rapid assessment			Full assessment		
	Always	Sometimes	Never	Always	Sometimes	Never
Advice to decision making body	69%	10%	21%	65%	18%	18%
Legislative*	31%	14%	55%	24%	6%	71%
(Clinical) guidance	10%	21%	69%	12%	35%	53%

\* binding by law

Number of jurisdictions for rapid assessment: 30; As US does not perform a rapid assessment, the average is based on n=29

Number of jurisdictions for full assessment: 30; As CH, CZ, EE, FI, HU, LU, MA, NL, PT, SC, SI, SK and USA do not perform a full assessment the average is based on n=17.

A detailed overview of the results per jurisdiction is provided in Appendix I, Result table 13.

### Publication

The assessment reports are publicly available always or sometimes (complete or in summary form) in about 60% of the jurisdictions for rapid assessments and in about 75% for full assessments. The advice to the decision maker, is publicly available in more than 75% of jurisdictions for rapid assessments and more than 85% of jurisdictions for full assessments. The percentage of jurisdictions that publish the text in English is higher for the document containing the assessment as compared to the document containing the advice.

**Table 5. Jurisdictions in which the assessment/advice\* is publicly available (%)**

Publication	Rapid assessment			Full assessment		
	N	Always or sometimes	Never	N	Always or sometimes	Never
Assessment*	29	62%	38%	17	76%	24%
In English	15	61%	39%	13	77%	23%
Advice*	29	76%	24%	17	88%	12%
In English	19	45%	55%	15	53%	47%

\* complete or in summary form

Number of jurisdictions for rapid assessment: 30; As US does not perform a rapid assessment, the average is based on n=29

Number of jurisdictions for full assessment: 30; As CH, CZ, EE, FI, HU, LU, MA, NL, PT, SC, SI, SK and USA do not perform a full assessment the average is based on n=17.

A detailed overview of the results per jurisdiction is provided in Appendix I, Result table 13.



## Scope

Except for the USA all of the jurisdictions included in the survey perform some form of comparison of clinical data (efficacy or effectiveness) between the pharmaceutical to be evaluated compared with an alternative intervention as part of an evaluation to support the national decision making on reimbursement. This assessment is referred to with a variety of terms such as 'comparative (clinical) effectiveness', 'evaluation of (medical-)therapeutic value', 'clinical added value', 'clinical or therapeutic evaluation' or 'benefit assessment'.

A detailed overview of the results per jurisdiction is provided in Appendix I, Result table 14.

In the survey the jurisdictions were asked to state whether their assessment includes:

- a) Clinical efficacy assessment of pharmaceutical A vs. intervention B (relative efficacy assessment)
- b) Clinical effectiveness assessment of pharmaceutical A vs. intervention B (relative effectiveness assessment)
- c) Benefit/risk assessment of pharmaceutical A vs. intervention B
- d) Cost-effectiveness of pharmaceutical A vs. intervention B

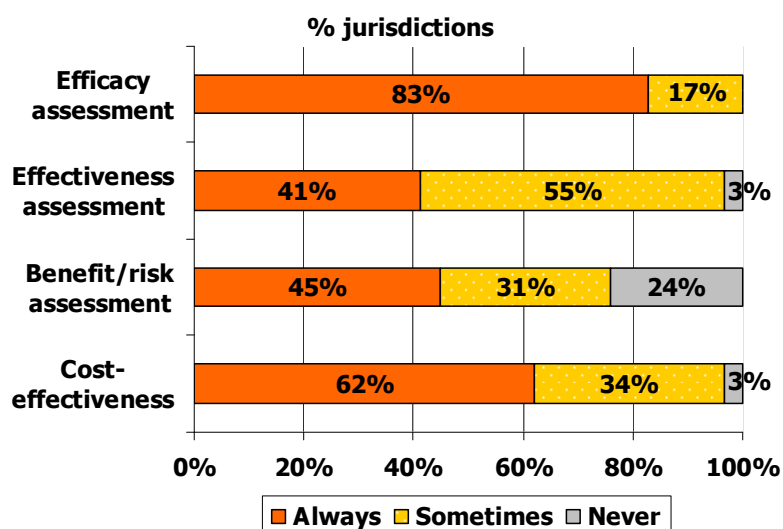
No definitions were provided for the terms clinical efficacy assessment, clinical effectiveness assessment, benefit/risk assessment and cost-effectiveness assessment. The results are presented in Figure 12.

Efficacy of pharmaceutical A versus intervention B is stated to be assessed in more than 80% (24/29) of the jurisdictions always and in less than 20% (5/29) sometimes (Australia, Czech Republic, Luxembourg, Malta, and Turkey). Except for Norway, all jurisdictions state they sometimes or always look at the effectiveness of pharmaceutical A versus intervention B. Of these, about 40% (12/29) to do so always and 55% (16/29) state to do so sometimes. In the latter group, it was stated by some of the jurisdictions that effectiveness is only assessed in case data on effectiveness are available. More than 95% (28/29) of the jurisdictions state they sometimes or always assess the cost-effectiveness. The only jurisdiction which never includes cost-effectiveness is France. However, it should be noted that they have separate price negotiations. Less than half of the jurisdictions state that they always include a benefit/risk assessment. In some jurisdictions the 'relative' effectiveness assessment is integrated in the cost-effectiveness assessment whereas in most jurisdictions these are separate evaluations.

It should be noted that as no predefined definitions were provided for the terms used, the results are susceptible to individual interpretation of interviewees. Further investigation would be required to provide a more precise overview.



**Figure 12. Scope of the reimbursement evaluation of pharmaceutical A vs. intervention B for rapid assessment (% of jurisdictions)**



Number of jurisdictions for rapid assessment: 30; As US does not perform a rapid assessment, the average is based on n=29.

The results for the full assessment were rather similar. However, the percentage of jurisdictions that states to always include a clinical effectiveness assessment of pharmaceutical A vs. intervention B is higher than indicated for the rapid assessment (59% vs. 41%).

A detailed overview of the results per jurisdiction is provided in Appendix I, Result table 15.

## 2.3 Methodology for 'relative effectiveness assessment' of pharmaceuticals

### 2.3.1 Guidelines

In the survey it was asked whether the jurisdictions have some form of document/guideline in which the methodology that is used for the comparative analysis in the rapid assessment is described. More than 80% (24/29) of the jurisdictions state that such a document is available. Of the jurisdictions that have such a document, about 60% (15/24) indicate to have it available in English. Not in all jurisdictions the document is publicly available (e.g. in Denmark, Malta and Spain).

The content of the guidelines varies substantially across jurisdictions in the level of detail on methodology. Some of the documents mainly focus on the procedure of a reimbursement submission or general reimbursement criteria, others use the national guideline for pharmacoconomics as guidance (e.g. Czech Republic and Portugal) and other jurisdictions such as Australia, Germany and England/Wales have a more elaborate guideline with more detailed sections on the methodology used.

The results for the full assessment were similar to those for rapid assessments.

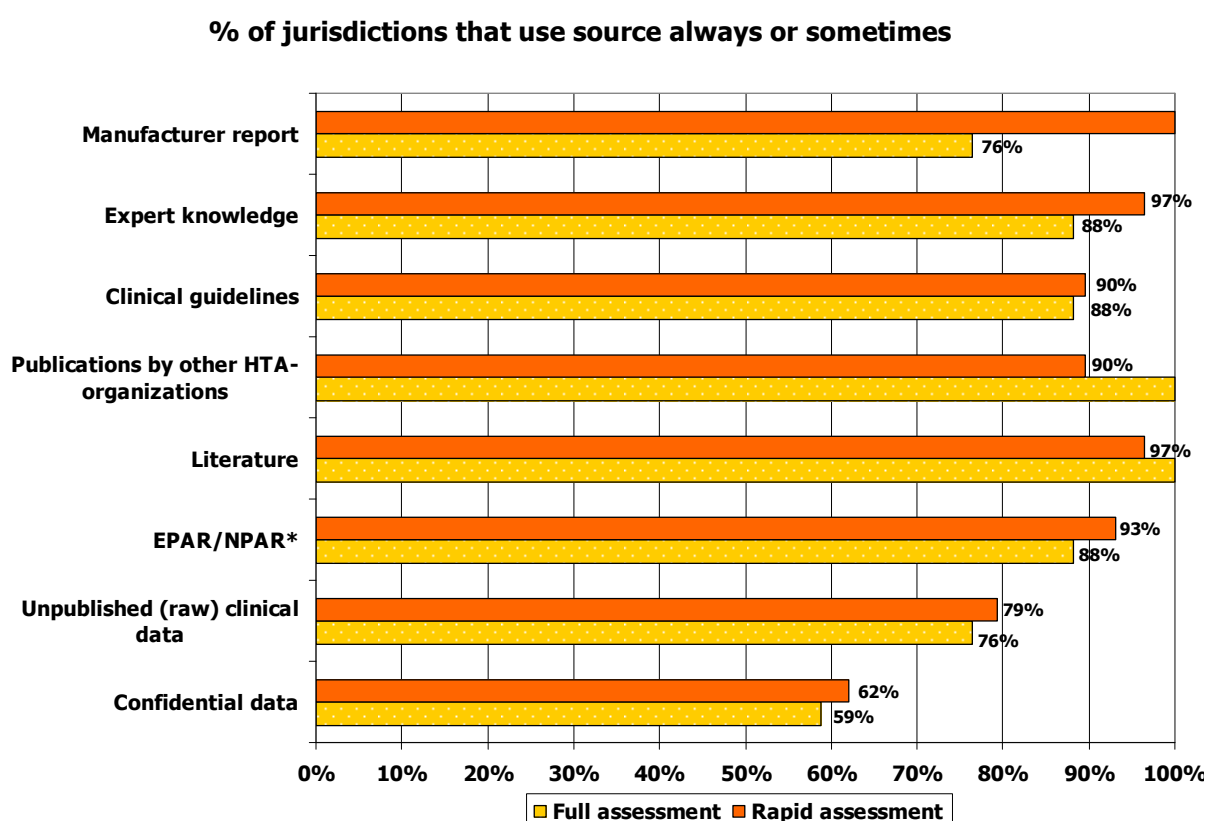
A detailed overview of the results per jurisdiction is provided in Appendix I, Result table 15.

### 2.3.2 Sources

All jurisdictions use multiple sources for their assessment (Figure 13). For a rapid assessment, all jurisdictions use (either always or at least sometimes) a report that is provided by the manufacturer. For a full assessment, this happens in more than 75% (13/17) of the jurisdictions. Expert knowledge, guidelines, other health technology assessment reports, literature and the European Public Assessment Reports (EPAR)/ National Public Assessment Report (NPAR)<sup>31</sup> are all very frequently used for assessments.

Unpublished (raw) clinical data are at least sometimes used in almost 80% of the jurisdictions and confidential data are at least sometimes used in about 60% of the jurisdictions for rapid and full assessment. In some jurisdictions, e.g. Austria, unpublished data are only accepted if it is allowed to quote the data. Other sources mentioned to be used are national pharmaceutical consumption statistics, external expert reports and web based study registries.

**Figure 13. Jurisdictions that use specific sources for relative effectiveness assessment (%)**



\* EPAR= European Public Assessment Report; NPAR=National Public Assessment Report. These also include the summary of product characteristics (SPC).

Number of jurisdictions for rapid assessment: 30; As US does not perform a rapid assessment, the average is based on n=29.

Number of jurisdictions for full assessment: 30; As CH, CZ, EE, FI, HU, LU, MA, NL, PT, SC, SI, SK and USA do not perform a full assessment the average is based on n=17.

A detailed overview of the results per jurisdiction is provided in Appendix I, Result table 16.

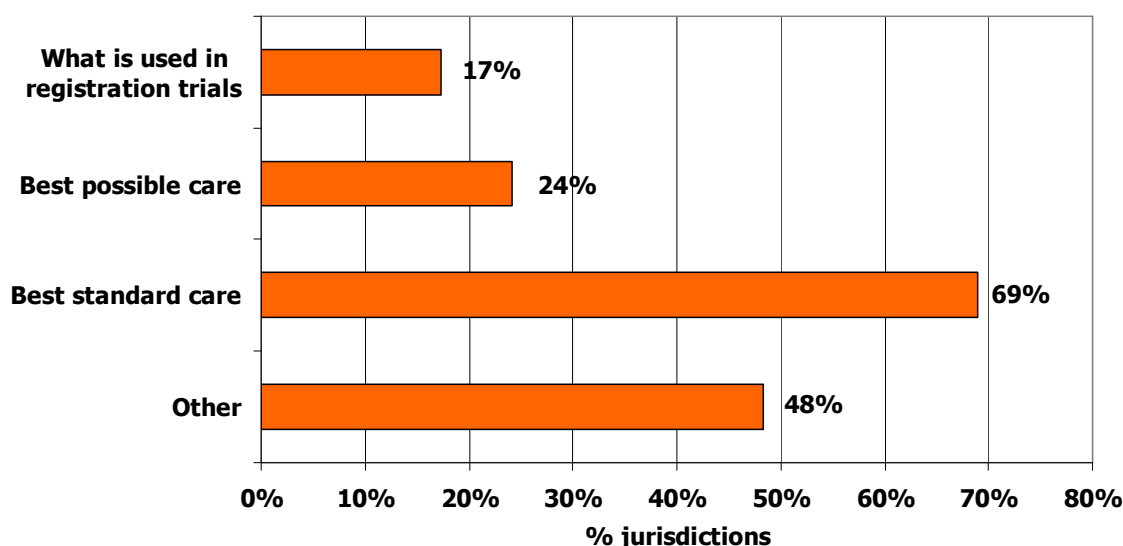
<sup>31</sup> Including the summary of product characteristics

### 2.3.3 Comparator/comparison

The choice of comparator varies across jurisdictions although when looking closely at the definitions of what is to be understood as comparators they are rather similar. The results of the survey are presented in Figure 14. In all jurisdictions several options can exist for the choice of comparator. For example, in Poland the primary comparator for the assessed intervention must be the so-called existing practice. However, it is also recommended to perform a comparison with other comparators, i.e. the following technologies: the most frequently used, the cheapest, the most efficient and compliant with the standards and guidelines for clinical management. Five jurisdictions state that 'whatever is used in the registration trials' can be used as a choice option (Belgium, Slovakia, Slovenia, Spain and Switzerland). For these jurisdictions it was indicated that this would not be the only option for the choice of a comparator. Seven jurisdictions (24%) indicate that 'best possible care' is used as comparator, but again this is never the only option considered. The majority of jurisdictions stated 'best standard care' and/or 'other' as the comparator. In general, for both options it is referred to definitions that are similar to 'usual care'. Examples of definitions mentioned are 'the treatment(s) used in current clinical practice', 'most frequently (or widely) used therapy', 'the validated care in the field', 'the therapy that prescribers would most replace with the proposed pharmaceutical in practice'.

In Austria, the first choice for a comparator is the most similar comparator according to Anatomical Therapeutic Chemical (ATC) level as long as this is reasonable. A sequence in choice of comparator is not uncommon. For example, the Dutch guideline states that standard care is preferred, which is defined as first line treatment according to clinical guidelines and for which the effectiveness is proven. If there is no standard care (according to the definition), the most frequently used care is used for comparison.

**Figure 14. Choice of comparator for a (single) rapid assessment (% of jurisdictions)**



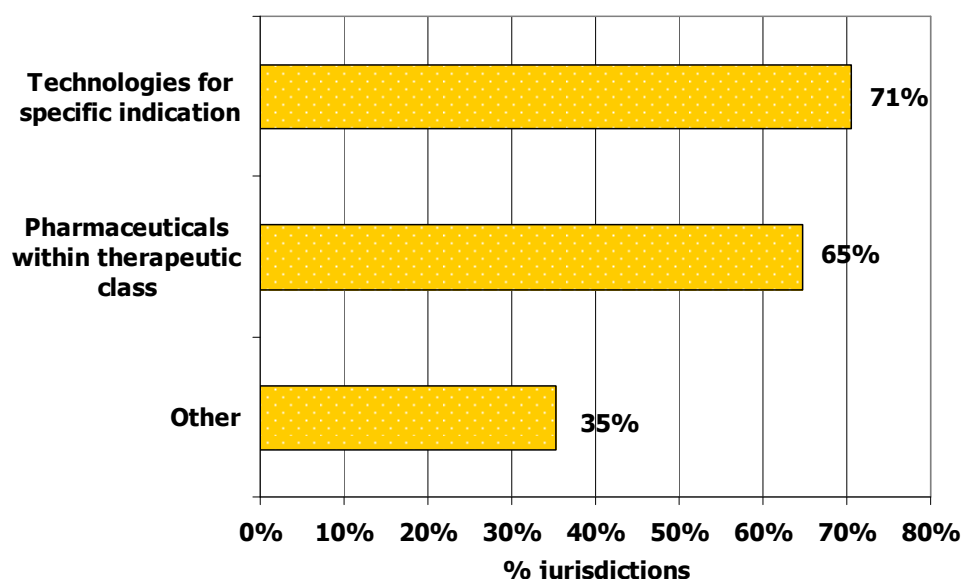
Number of jurisdictions for rapid assessment: 30; As US does not perform a rapid assessment, the average is based on n=29.

A detailed overview of the results per jurisdiction is provided in Appendix I, Result table 17.

For full assessments also often several options can be applicable in a jurisdiction as indicated in Figure 15. In most jurisdictions it can be either 'all technologies for a specific indication' or

'pharmaceuticals within a therapeutic class'. 'Other' answers that were provided are 'determined by the scope of the review' and 'selected on a case by case basis'.

**Figure 15. Choice of comparator for a full assessment (% of jurisdictions)**



Number of jurisdictions for full assessment: 30; As CH, CZ, EE, FI, HU, LU, MA, NL, PT, SC, SI, SK and USA do not perform a full assessment the average is based on n=17.

A detailed overview of the results per jurisdiction is provided in Appendix I, Result table 17.

### **Non-pharmaceuticals as comparator**

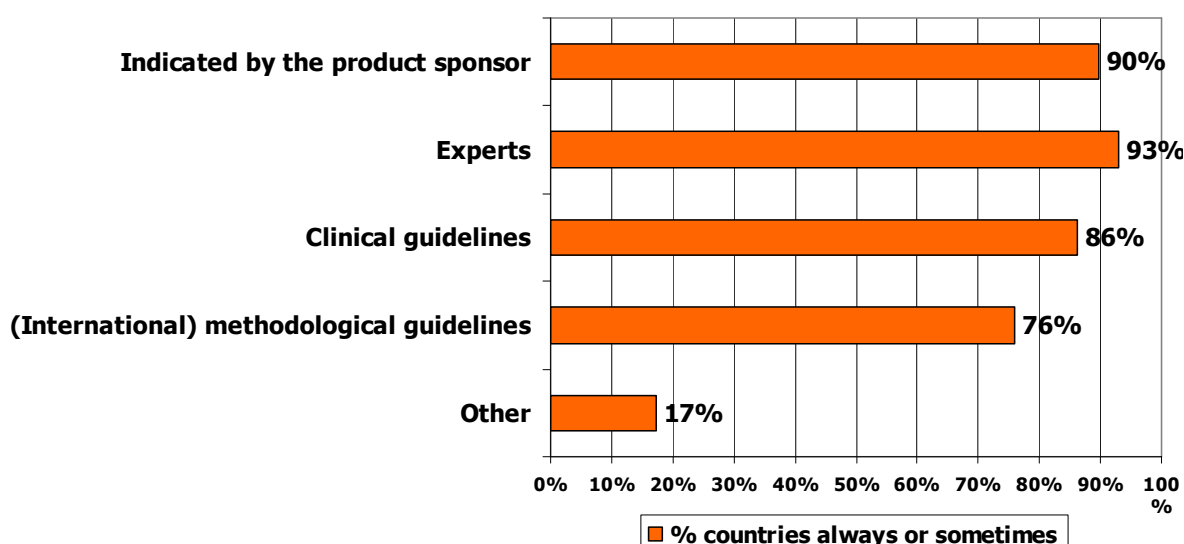
For both rapid and full assessments, in more than 80% of the jurisdictions the choice of the comparator(s) for the assessment can also be a non-pharmaceutical intervention and is thus not limited to pharmaceuticals. However, some of these jurisdictions such as Hungary have indicated that comparison with non-pharmaceuticals is mostly an exception.

A detailed overview of the results per jurisdiction are provided in Appendix I, Result table 17.

### **Sources used to determine the comparator**

Often the assessment body identifies the appropriate comparator(s). As presented in Figure 16, in most jurisdictions multiple sources are used for the identification. In practice often the assessment body checks if the comparator indicated by the marketing authorisation holder is appropriate and may change the comparator or include another comparator based on input from for example experts, clinical guidelines and/or methodological guidelines. Other sources that were mentioned were epidemiological data about treatments, list with reference groups, published literature and assessments by other health technology assessment agencies. In England/Wales all stakeholders are asked to contribute to the identification of the technologies to be included.

**Figure 16. Jurisdictions that use specific sources to identify appropriate comparator for rapid assessment (%)**



Number of jurisdictions for rapid assessment: 30; As US does not perform a rapid assessment, the average is based on n=29.

The sources used for a full assessment are similar to the sources for the rapid assessment.

### Indirect comparisons

Indirect comparisons can be used to determine the relative effectiveness of two treatments in the absence of direct head-to-head evidence. All jurisdictions except for Turkey (97%, 28/29) may use indirect comparisons in case no direct comparisons are available in a rapid assessment. Only a few jurisdictions have clear preferences for the type of analysis used when comparing indirectly. For Australia, it is stated specifically that the comparators should preferably be compared with frequentist method after exchangeability assessment and determination of most appropriate metric of comparative treatment effect of the pharmaceuticals of interest against the common reference. For New Zealand, it was indicated that the frequentist method is preferred as well. For Scotland, bayesian analysis is preferred, naive indirect comparisons are not preferred. The SMC is developing a section on indirect comparison to be implemented in the manufacturer's guideline in the summer of 2011. For Poland, it was stated that the recommended method for performing indirect comparisons of studies with a common comparator depends on the outcome measures used. In the case of odd ratios, it is recommended to use logical regression or metaregression, and in the case of measures such as relative risks, risk difference, difference of mean values or hazard ratios. The recommended methods include adjusted indirect comparison and Bucher or metaregression. In justified cases, network meta-analysis can be used.

For a full assessment, indirect comparisons are not used in Germany, Sweden and Turkey.

A detailed overview of the results per jurisdiction is provided in Appendix I, Result table 17.

### 2.3.4 Outcomes

In general, all clinically relevant outcomes are accepted for the assessment. Often outcomes related to mortality and/or morbidity and/or quality of life are preferred. Final outcomes (preferably patient-oriented clinically significant endpoints) are preferred over intermediate

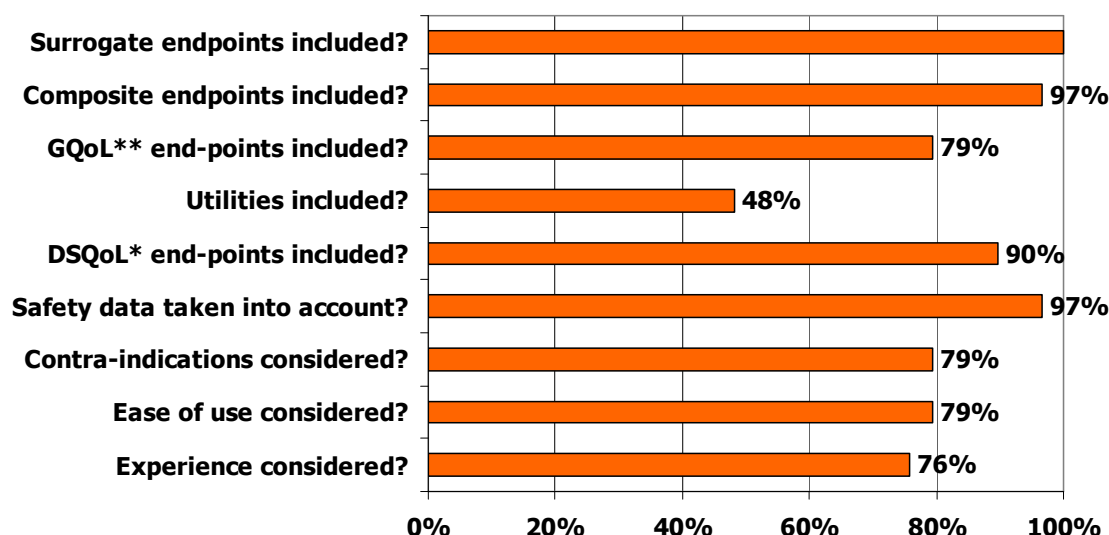
endpoints. In Ireland, quality-adjusted life years (QALYs) is the preferred measure of outcome. In England/Wales, the clinical outcome measures would usually be expected to have an impact on survival or health-related quality of life (HRQL) and be able to be translated into QALYs for the evaluation of cost effectiveness.

In all jurisdictions surrogate outcomes are accepted for the assessment. However many jurisdictions state that they are not preferred, they are considered less relevant for the final advice than clinical outcomes, and they are only included if they are considered clinically relevant and/or are validated. There may be situations in which exemptions are made. For example, the German guidelines state that<sup>32</sup>:

*'In the case of extremely serious diseases in terms of morbidity and mortality without treatment alternatives, surrogate outcomes of unclear validity may have to be accepted as outcomes that potentially indicate a benefit of an intervention.'*

The Australian guidelines state that surrogate outcomes are accepted if they form the primary outcome in the primary analysis of the relevant direct randomised trial<sup>33</sup>.

**Figure 17. Jurisdictions that use specific outcomes for rapid assessment (%)**



\*DSQoL=Disease specific quality of life; \*\*GQoL= generic quality of life data

Number of jurisdictions for rapid assessment: 30; As US does not perform a rapid assessment, the average is based on n=29.

Composite outcomes are in general also not preferred but accepted (see Figure 17). It is stated for example that composite outcomes are only included if clinical trials reporting single outcomes are not available. In Germany, composite outcomes are only included if all components are patient relevant endpoints and all components are also reported separately. For Malta, it is not known whether they will be accepted as such a situation has not occurred yet.

Most jurisdictions include quality of life data (see Figure 17) with the premise that the instrument used should be validated. Disease specific quality of life data are accepted slightly more often than generic quality of life data (90% [26/29] vs. 79% [23/29]). Some jurisdictions have

<sup>32</sup> General Methods Version 3.0. Cologne: Institute for Quality and Efficiency in Health Care (IQWiG); 2008.

<sup>33</sup> Guidelines for Preparing Submissions to the Pharmaceutical Benefits Advisory Committee. Version 4.3. Canberra: Pharmaceutical Benefits Advisory Committee (PBAC); 2008.

standard requirements before quality of life data can be included. For example, Australia stated that they are only included if they are reported in the relevant direct randomised trials and are considered relevant. For England/Wales, it is stated that measurement of changes in health related quality of life should be reported directly from patients and the value of changes in patients' health related quality of life (that is, utilities) should be based on public preferences using a choice-based method. For France it is stated that generic quality of life data are only included as complementary data, disease specific quality of life data scales are included if they are appropriate for the specific disease.

Jurisdictions who do not accept any quality of life outcomes for the relative effectiveness assessment are Latvia, Luxembourg and Turkey.

Almost half of the jurisdictions state that utilities<sup>34</sup> can be used for determining the relative effectiveness.

The only jurisdiction which does not include safety data is Norway. They are only included in Norway if they are provided by the marketing authorisation holder. In order to be granted reimbursement in Norway, the marketing authorization holder has to demonstrate the seriousness of the disease/condition, that long-term treatment is necessary (more than 3 months) and the efficacy and cost-effectiveness.

Various outcomes such as drop-out from study due to side effects, deaths due to side-effects, major side-effects and irreversible side-effects are mentioned as relevant safety outcomes.

If a new pharmaceutical is limited in its usage because of contra-indications that are not applicable to the comparator (or the other way around) this may influence the advice. Most jurisdictions also take into account contra-indication in the assessment (except for Czech Republic, Hungary, Norway, Poland and Scotland) compared to the alternative (see Figure 17). Although the relevance of this aspect in the overall assessment varies between jurisdictions and some only consider the contra-indications on a case by case basis.

Ease of use of the technology (patient friendliness) is considered in almost 80%(23/29) of the jurisdictions (see Figure 17). In England/Wales it is considered to be included in the HRQL. Australia, Austria, France, Germany, Latvia and Portugal do not include the ease of use.

Experience with the use of the technology (e.g. whether the pharmaceutical has already been prescribed in many patients) is considered in the assessment in more than 75% (22/29) of the jurisdictions. In England/Wales this is considered relevant if experience (as in surgical procedures) affects the efficacy/effectiveness.

The survey responses for the full assessment are similar to those received for the rapid assessment.

A detailed overview of the results per jurisdiction is provided in Appendix I, Result table 18.

### **2.3.5 Quality assessment of available evidence**

Almost 40% (11/29) of jurisdictions never use a classification system to indicate the level of evidence of the included studies in a rapid assessment. It is used in about 60% (18/29) of jurisdictions (in 31% always and 31% sometimes). Such classification systems are more frequently used for a full assessment. Except for France and Latvia, all jurisdictions who perform a full assessment use a classification system always (almost 53%) or sometimes (over 35%). International classification systems mentioned to be used are for example Grading of

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<sup>34</sup> Valuations of changes in patients' health related quality of life.

Recommendations Assessment, Development and Evaluation (GRADE), Scottish Intercollegiate Guidelines Network (SIGN) and the JADAD scale. Some jurisdictions use self-developed systems.

A detailed overview of the results per jurisdiction is provided in Appendix I, Result table 19.

### 2.3.6 Generalisability (applicability) of trial data

All jurisdictions consider at least sometimes if the clinical trial data that are part of the assessment are also applicable to the general patient population (see Table 6). The percentage of jurisdictions in which this is always considered is higher for the full assessments than for the rapid assessments.

**Table 6. Jurisdictions that consider the generalisability of clinical trials data (%)**

	<b>Always</b>	<b>Sometimes</b>	<b>Never</b>
Rapid assessment	66%	34%	0%
Full assessment	82%	18%	0%

Number of jurisdictions for rapid assessment: 30; As US does not perform a rapid assessment, the average is based on n=29.

Number of jurisdictions for full assessment: 30; As CH, CZ, EE, FI, HU, LU, MA, NL, PT, SC, SI, SK and USA do not perform a full assessment the average is based on n=17.

A detailed overview of the results per jurisdiction is provided in Appendix I, Result table 19.

### 2.3.7 Effectiveness and extrapolation of results

As shown in Table 7 the effectiveness is stated to be assessed always in half of the jurisdictions and sometimes in the other half for a rapid assessment. For a full assessment the percentage of jurisdictions in which this is always considered is slightly higher than for rapid assessments. For Norway it is only considered if data are available and as part of cost-effectiveness analysis. In Spain it is only considered for the comparator (for which more data may already be available), but not for the new pharmaceutical.

**Table 7. Jurisdictions that assess the effectiveness (%)**

	<b>Always</b>	<b>Sometimes</b>	<b>Never</b>
Rapid assessment	48%	52%	0%
Full assessment	59%	41%	0%

Number of jurisdictions for rapid assessment: 30; As US does not perform a rapid assessment, the average is based on n=29.

Number of jurisdictions for full assessment: 30; As CH, CZ, EE, FI, HU, LU, MA, NL, PT, SC, SI, SK and USA do not perform a full assessment the average is based on n=17.

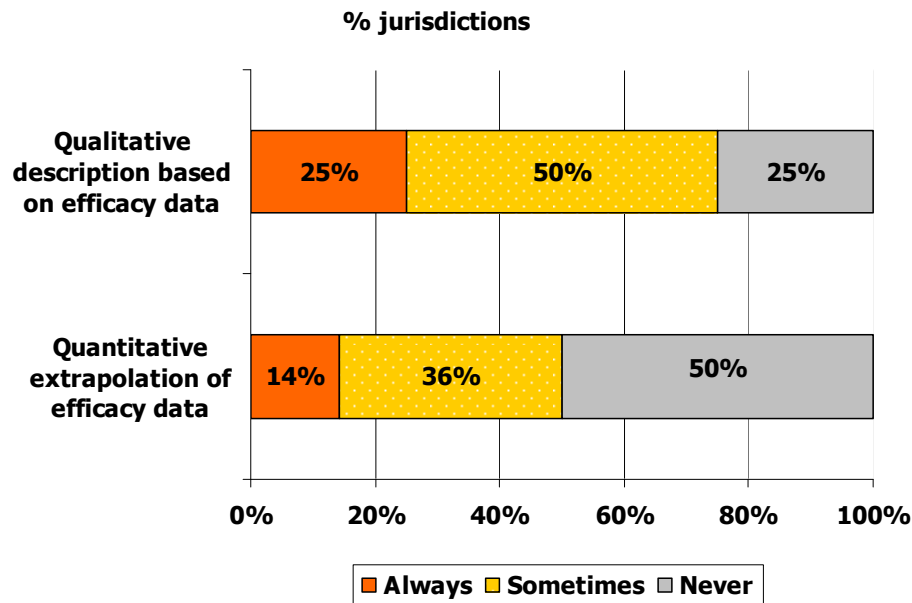
In the case where no effectiveness data are available from clinical studies, efficacy data are extrapolated qualitatively (a qualitative interpretation of the data) sometimes or always in 75% (21/28<sup>35</sup>) of the jurisdictions. Quantitative exercise (e.g. modelling) is done sometimes or always in 50% (14/28<sup>35</sup>) of the jurisdictions (see Figure 18). For a full assessment a quantitative exercise is done at least sometimes in more than 60% (11/17) of the jurisdictions. Often, the quantitative analysis is part of a cost-effectiveness analysis.

For Italy it was indicated that there can be a request for a registry if AIFA feels a clear need for effectiveness data that are not available yet.

<sup>35</sup> N=28 as these data are missing for Spain.



**Figure 18. Jurisdictions that extrapolate efficacy data to effectiveness data if effectiveness data are not available through clinical trial data for a rapid assessment (% of jurisdictions)**

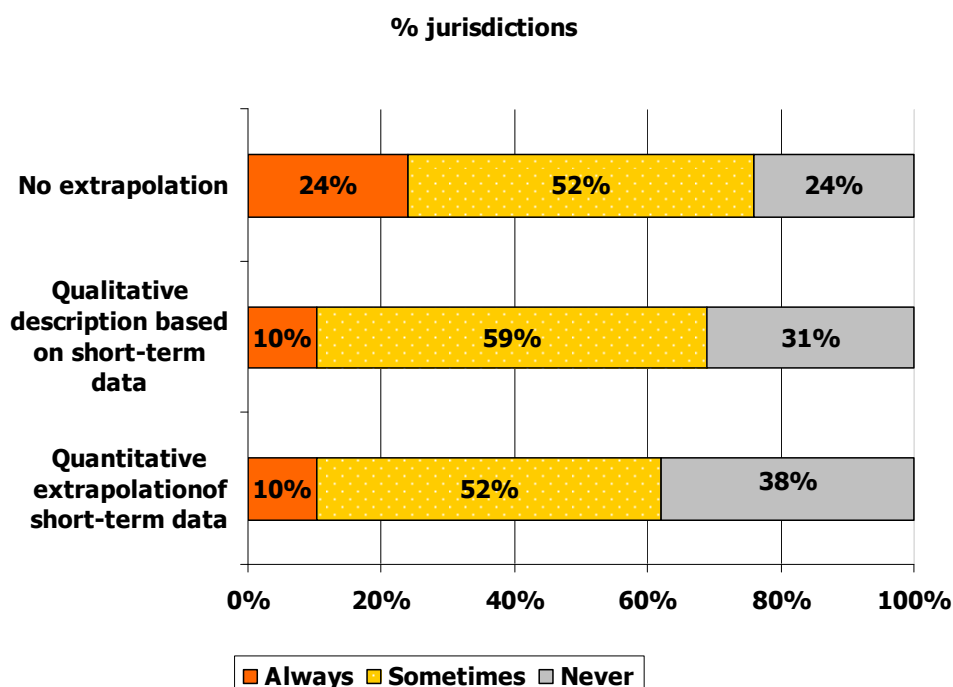


Number of jurisdictions for rapid assessment: 30; As US does not perform a rapid assessment, the average is based on n=29.

A detailed overview of the results per jurisdiction is provided in Appendix I, Result table 19.

In absence of long-term data, short-term data are extrapolated qualitatively sometimes to always in almost 70% (20/29) of the jurisdictions and quantitatively in more than 60% (18/29) of the jurisdictions (see Figure 19). The quantitative analysis is mostly part of a cost-effectiveness analysis.

**Figure 19. Jurisdictions that extrapolate short-term data in absence of long-term data for a rapid assessment (% of jurisdictions)**



Number of jurisdictions for rapid assessment: 30; As US does not perform a rapid assessment, the average is based on n=29.

Results for a full assessment are similar.

A detailed overview of the results per jurisdiction is provided in Appendix I, Result table 19.

The Australian interviewee indicated that concepts seem to be combined in these questions: extrapolation and transformation which are separated explicitly in their guidelines. The Australian guidelines indicate a clear separation of three entities<sup>36</sup>:

- The **applicability** is under discussion in case the participants and circumstances of use in the trial might not be the same as the intended population for treatment in Australia. This can be evaluated through premodelling studies of applicability in for example subgroup analyses and surveys of the patterns of health care resource provision in Australia corresponding to one or more health states included in a modelled economic evaluation.
- The length of follow-up (time horizon) of participants in the trial might be less than the expected duration of therapy or expected duration of overall health and health care resource impacts. In this case, the clinical evaluation would need to be **extrapolated** to the intended duration of therapy or expected health and resource impacts. Examples of premodelling studies of extrapolation include extrapolating integrals of time-to-event analyses and a review of the literature for single-arm follow-up studies of the natural history of the condition to estimate rates of disease progression.

<sup>36</sup> Australian Government Department of Health and Ageing. 2008. Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee. Version 4.3. Available at <http://www.health.gov.au/internet/main/publishing.nsf/content/pbacguidelines-index> (Accessed 16 December 2010).

- The outcomes measured in the trial might not be the patient-relevant final outcomes of treatment. In this case, the clinical evaluation would need to be **transformed** to take account of the patient-relevant final outcomes (in terms of quality-adjusted life-years gained). Examples of premodelling studies of transformation include transforming comparative treatment effects measured on surrogate outcomes to final outcomes and scenario-based studies to value health outcomes using utilities.



### **3 International activities related to relative effectiveness assessment**

The websites of the following organisations were searched for activities related to relative effectiveness assessment:

The Agency for Healthcare Research and Quality (AHRQ), CADTH, The Cochrane Collaboration, European Medicines Agency (EMA), Health Technology Assessment International (HTAi), Institute for Clinical and Economic Review (ICER), International Network of Agencies for Health Technology Assessment (INAHTA), International Society for Pharmacoepidemiology (ISPE), International Society for Pharmacoeconomics and Outcomes Research (ISPOR), Oregon Health & Science University (OHSU) Drug Effectiveness Review Project (DERP), The Medical Services Advisory Committee (MSAC), PHARMAC, PCORI, PBAC, Pharmaceutical Health Information System (PHIS), The Pharmaceutical Pricing and Reimbursement Information (PPRI), The Medicine Evaluation Committee (MEDEV), Supporting policy-relevant reviews and trials (SUPPORT), Vancouver Group/ International Committee of Medical Journal Editors, World Health Organization (WHO).

The agencies listed above that are involved in reimbursement decisions of pharmaceuticals (CADTH, PBAC and PHARMAC) were screened for specific activities on the development of methodology for relative effectiveness assessment. Databases with assessment reports of pharmaceuticals are not listed. For their currently used methodology on relative effectiveness assessments we refer to chapter 2.

If relevant activities were identified they are listed per agency in the sections below, grouped into European activities (3.1) and international activities (3.2) and national activities outside of Europe (3.3).

#### ***3.1 European activities***

##### **3.1.1 EMA**

The European Medicines Agency (EMA) is a decentralised body of the EU. EMA is notably responsible for the scientific evaluation of applications for European marketing authorisations for human and veterinary medicines for preventive, diagnosis and treatment purpose (centralised procedure).

The Committee for Medicinal Products for Human Use (CHMP) carries out scientific evaluation on applications from pharmaceutical companies. It is responsible for preparing the Agency's opinions on all questions concerning medicines for human use. Concerning the centralised procedure, the CHMP is responsible for conducting the initial assessment of medicines for which an EU-wide marketing authorisation is sought. Assessments conducted by the CHMP are based on purely scientific criteria and determine whether or not the medicines concerned meet the necessary quality, safety and efficacy requirements. These processes ensure that medicines have a positive benefit-risk balance.

The CHMP also plays an important role in this EU-wide 'pharmacovigilance' activity by closely monitoring reports of potential safety concerns and, when necessary, making recommendations to the European Commission regarding changes to a medicine's marketing authorisation, or its suspension/withdrawal from the market.

The CHMP publishes a European public assessment report (EPAR) for every centrally authorised medicine, setting out the scientific grounds for the Committee's opinion in favour of granting the authorisation. EPARs are published on the Agency's website.

Current activities of the EMA related to the subject relative effectiveness assessment are presented in the table below.

<b>EMA (<a href="http://www.ema.europa.eu">http://www.ema.europa.eu</a> accessed on 9 December 2010)</b>
<p>The EMA has produced numerous guidelines that may be useful for conducting relative effectiveness assessment of pharmaceuticals on clinical efficacy and safety. The guidelines are intended to provide a basis for practical harmonisation of the manner in which the EU Member States and the Agency interpret and apply the detailed requirements for the demonstration of quality, safety and efficacy contained in the Community directives. They also help to ensure that applications for marketing authorisation are prepared in a manner that will be recognised as valid by the Agency.</p> <p>Clinical efficacy and safety guidelines are provided for<sup>37</sup>:</p> <ul style="list-style-type: none"> <li>• Clinical pharmacology and pharmacokinetics</li> <li>• Alimentary tract and metabolism</li> <li>• Blood and blood forming organs</li> <li>• Blood products (including biotech alternatives)</li> <li>• Cardiovascular system</li> <li>• Dermatologicals</li> <li>• Genito-urinary system and sex hormones</li> <li>• Anti-infectives for systemic use</li> <li>• Antineoplastic and immunomodulating agents</li> <li>• Musculo-skeletal system</li> <li>• Nervous system</li> <li>• Respiratory system</li> <li>• General</li> <li>• Herbal medicinal products</li> <li>• Information on medicinal products</li> <li>• Radiopharmaceuticals and Diagnostic Agents</li> </ul> <p><a href="http://www.ema.europa.eu/htms/human/humanguidelines/efficacy.htm">http://www.ema.europa.eu/htms/human/humanguidelines/efficacy.htm</a></p>
<p>EMA began a three-year project on benefit-risk methodology in early 2009. The project aims to identify decision-making models that can be used in the Agency's work, to make the assessment of the benefits and risks of medicines more consistent, more transparent and easier to audit. The project included 5 steps of which the first 2 have already been completed.</p> <ol style="list-style-type: none"> <li>1. Describing the benefit-risk assessment models already being used in the European Union's regulatory network</li> <li>2. Assessing the suitability of the current tools and processes used in benefit-risk assessments Completed</li> <li>3. Field-testing the most appropriate models in five European medicine regulatory agencies Started</li> <li>4. Refining the most suitable models for use in medicines regulation to create a new benefit-risk tool</li> <li>5. Training European assessors to use the final tool</li> </ol>

<sup>37</sup> European Medicines Agency. Clinical efficacy and safety guidelines introduction. Available at [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000085.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580027549](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000085.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580027549) (accessed January 2011)

**EMA (<http://www.ema.europa.eu> accessed on 9 December 2010)**

In collaboration with EUnetHTA partners, the EMA is considering how the EPAR could make a better contribution to the assessment of relative efficacy by health technology assessment bodies in the EU Member States. Based on comments by WP5 (based on a letter by MEDEV) and two face-to-face meetings in 2010 EMA has implemented an adapted EPAR template from November 2010 onwards. Collaboration in 2011 will continue by means of an evaluation of the adapted EPARs.

### 3.1.2 MEDEV

The Medicine Evaluation Committee (MEDEV) is an informal cooperation between the competent authorities for the assessment and pricing of medicines in Europe. The secretariat and the coordination of the work of the committee is organised by the office of the European Social Insurance Platform ([www.esip.org](http://www.esip.org)). The main focus of MEDEV is the timely provision and exchange of information on all topics relating to the assessment of pharmaceuticals, assessment methodologies, decisions on pricing and reimbursement, national pharmaceutical policies and the national and European regulations governing these issues."

Current activities of the MEDEV related to the subject relative effectiveness assessment of pharmaceuticals are presented in the table below.

**MEDEV ([www.esip.org](http://www.esip.org))**

Prompt face-to-face exchanges of information between members on the therapeutic value and relative effectiveness of new pharmaceuticals, taking into consideration pharmacoeconomic aspects, take place five times a year. Further exchanges are supported by a dedicated website and e-mail.

MEDEV produces common assessment reports based on the results of assessments completed by one or more of its members.

MEDEV aims to provide definitions of parameters for cost-benefit analyses and international price analyses.

MEDEV performs comparisons of countries and systems with regard to pharmaceutical benefits (evaluation of previously taken measures and development of new strategies).

MEDEV aims at building up trans-national cooperation with other competent authorities in assessment and/or pricing.

MEDEV engages representatives of other European governmental and non-governmental organisations (NGOs) and with other international associations of health insurance agencies, patient organisations, and pharmaceutical companies to exchange knowledge.

A number of MEDEV participants have engaged together in a pilot to provide early scientific advice (pre phase 3) to the pharmaceutical industry.

In collaboration with EUnetHTA partners, the MEDEV is providing input on how the EPAR could

<b>MEDEV (<a href="http://www.esip.org">www.esip.org</a>)</b>
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make a better contribution to the assessment of relative efficacy by health technology assessment bodies in the EU Member States.
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### 3.1.3 PPRI

The Pharmaceutical Pricing and Reimbursement Information (PPRI), is a networking and information-sharing initiative on issues of pharmaceutical policies from a public health perspective. It involves PPRI Members of almost 60 institutions (mainly competent authorities and third party payers) from all countries of the EU, plus Albania, Canada, Croatia, Iceland, Norway, Republic of Serbia, Switzerland, South Africa, South Korea and Turkey.

Current activities of the PPRI initiative related to the subject relative effectiveness assessment are presented in the table below.

<b>PPRI (<a href="http://ppri.oebig.at">http://ppri.oebig.at</a>)</b>
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PPRI report: comprehensive analysis on the underlying health care and pharmaceutical systems, on pharmaceutical pricing and reimbursement policies as well as rational use of pharmaceuticals in countries included in the comparative analysis, based on the country reports. This document is available at: <a href="http://ppri.oebig.at/Downloads/Publications/PPRI_Report_final.pdf">http://ppri.oebig.at/Downloads/Publications/PPRI_Report_final.pdf</a>
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PPRI Pharma Profiles: country specific reports on health and pharmaceutical systems, with a special focus on pricing, reimbursement and rational use of pharmaceuticals. The PPRI Pharma Profiles are intended to be regularly updated, and are available at: <a href="http://ppri.oebig.at/index.aspx?Navigation=r 2 1-">http://ppri.oebig.at/index.aspx?Navigation=r 2 1-</a>
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### 3.1.4 PHIS

Pharmaceutical Health Information System (PHIS) is an European Commission funded project and is a network comprising national representatives (competent authorities, Third Party Payers, hospital associations) and European stakeholders in the field of pharmaceuticals. The PHIS project runs from September 2008 to April 2011 (32 months). The PHIS project aims at increasing knowledge and exchange of information on pharmaceutical policies, in particular on pricing and reimbursement, in the EU Member States, covering both the outpatient and the inpatient sector.

Current activities of PHIS related to the subject relative effectiveness assessment of pharmaceuticals are presented in the table below.

<b>PHIS (<a href="http://phis.goeg.at/">http://phis.goeg.at/</a>)</b>
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A glossary with key terms related to pharmaceuticals
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A Library, offering country specific information on out-patient and in-patient pharmaceutical pricing and reimbursement for the EU Member States
--

The PHIS Hospital Pharma Report with information on pharmaceutical policies in the inpatient sector in the EU Member States, including a price survey.
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## 3.2 International activities

### 3.2.1 ISPOR

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) is an international, educational, scientific and non-for-profit member-driven organisation formed to promote the practice and science of pharmacoeconomics and health outcomes assessment. The mission of ISPOR is to promote research on the economic, clinical, and quality-of-life outcomes of health care interventions and to promote the translation of this research into information that health care decision-makers find useful.

ISPOR embraces health care researchers, health care regulators & technology assessors, health care payers, health care providers and patients.

Current activities of ISPOR related to the subject relative effectiveness assessment of pharmaceuticals are presented in the table below.

<b>ISPOR (<a href="http://www.ispor.org">www.ispor.org</a>)</b>
<p>ISPOR published a variety of articles, books, information and tools. Publication related to the subject relative effectiveness assessment are listed below:</p> <p><b>Books</b>  Health Care Cost, Quality And Outcomes: ISPOR Book Of Terms  Economic, Clinical, and Patient Reported Outcomes Research: Good Research Practices</p> <p><b>Journal</b>  ISPOR publishes the scientific journal "Value in Health". This journal contains original research articles in the areas of pharmacoeconomics (health economics), outcomes research (clinical, economic, and patient-reported outcomes research), and conceptual and health policy articles.</p> <p><b>Tools For Health Outcomes Researchers</b>  ISPOR Good Outcomes Research Practices</p> <p><b>Tools for Health Care Decision Makers</b>  ISPOR Global Health Care Systems Road Map  Pharmacoeconomic Guidelines Around The World</p> <p><b>Good Outcomes Research Practices &amp; Issues</b>  ISPOR Good Outcomes Research Practices are consensus documents on key outcomes research methods. The following subjects seem relevant for relative effectiveness assessment:</p> <ul style="list-style-type: none"> <li>• <i>Comparative Effectiveness Research</i> (Defining, Reporting and Interpreting Non-randomized Studies of Treatment Effects Using Secondary Databases, Approaches to Mitigate Bias And Confounding in The Design of Non-randomized Studies of Treatment Effects Using Secondary Databases, Analytic Methods to Improve Causal Inference From Non-randomized Studies of Treatment Effects Using Secondary Databases, Prospective Observational Clinical Studies Good Research Practices);</li> <li>• <i>Patient Reported Outcomes Methods</i> (ISPOR Patient Reported Outcomes /Quality of Life Initiatives, PRO / QoL Regulatory Issues, PRO Methods and Concepts, PRO Cultural Adaptation, Translation &amp; Linguistic Validation of an Application, PRO: Changing Mode of</li> </ul>

- Administration of Instruments/ePRO, PRO: Use of Existing Instruments & their Modification, Conjoint Analysis in Health Good Research Practices<sup>38</sup>);
- *Real World Data Methods and Studies* (Real World Data, Checklist for Retrospective Database Studies, Retrospective Database Analysis, Medication Compliance and Persistence: Terminology and Definitions, Checklist for Medication Compliance and Persistence Studies Using Retrospective Databases, Methods for Integrating Medication Compliance and Persistence in Pharmacoeconomic Evaluations, Medication Compliance and Persistence Issues, Disease-specific Systematic Reviews of Medication Compliance and Persistence Studies, Medication Compliance and Persistence in Breast Cancer Treatment, Medication and Persistence in Rheumatoid Arthritis, Patient Registry Data Management and Analysis, Metrics & Methodologies to Quantify Risks & Benefits);
  - *Use of Outcomes Research in Health Care Decisions* (Outcomes Research & Health Care Decisions, Health Technology Assessment & Health Care Policies, Risk Benefit & Health Care Decisions);
  - *Special Interest Groups* (Patient Registry, Patient Reported Outcomes, Preference-based Methods, Risk Benefit Management)
  - *ISPOR Task Forces* (Conjoint Analysis in Health<sup>38</sup>, Indirect Treatment Comparisons, PRO: Assessment in Children and Adolescents, PRO: Establishing and Reporting Evidence of the Content Validity of Patient-Reported Outcomes Instruments, Prospective Observational Clinical Studies Good Research Practices Task Force).

### 3.2.2 ISPE

The International Society for Pharmacoepidemiology (ISPE) is an international organization dedicated to advancing the health of the public by providing a forum for the open exchange of scientific information and for the development of policy, education, and advocacy for the field of pharmacoepidemiology, including such areas as pharmacovigilance, pharmaceutical utilisation research, comparative effectiveness research, and therapeutic risk management.

ISPE is a non-profit international professional membership organisation dedicated to promoting pharmacoepidemiology, the science which applies epidemiologic approaches to studying the use, effectiveness, value and safety of pharmaceuticals.

ISPE sponsors conferences and seminars, a quarterly newsletter, and an official journal — *Pharmacoepidemiology and Drug Safety* — published by Wiley.

Current activities of ISPE related to the subject relative effectiveness assessment are presented in the table below.

**ISPE (<http://www.pharmacoepi.org/aboutISPE/index.cfm> accessed on 2 December 2010)**

There is a special Interest Groups at ISPE that focuses on comparative effectiveness research:

#### **ISPE Comparative Effectiveness Research (CER)**

The objectives of the interest group is to support educational programs on comparative effectiveness research; to foster development of methods for improved confounding adjustment that is particularly pertinent in non-randomized studies of intended treatment effects; to foster the development of methods for improved benefit-risk assessment; to foster discussions and

<sup>38</sup> It should be noted that such methods are typically called 'Discrete Choice Experiments' in most of the world outside of North America.

developments in designing randomized and nonrandomized prospective effectiveness studies; to develop and revise guidance documents for good comparative effectiveness research.

### ***3.3 National activities outside of Europe***

#### **3.3.1 AHRQ**

The Agency for Healthcare Research and Quality (AHRQ) is a USA Federal agency charged with improving the quality, safety, efficiency, and effectiveness of health care for all Americans. AHRQ sponsors and conducts research that provides evidence-based information on health care outcomes, quality, cost, use and access. The information helps health care decision makers, patients and clinicians, health system leaders, purchasers, and policymakers to make more informed decisions and improve the quality of health care services.

Current activities of the AHRQ related to the subject relative effectiveness assessment are presented in the table below.

<b>AHRQ (<a href="http://www.ahrq.gov/">http://www.ahrq.gov/</a>)</b>
<p><b>Effective Health Care Program</b></p> <p>The Effective Health Care Program funds individual researchers, research centers, and academic organisations to work together with the AHRQ to provide effectiveness and comparative effectiveness data for clinicians, consumers, and policymakers.</p> <p>The Effective Health Care Program produces three primary products:</p> <ul style="list-style-type: none"> <li>• <u>Research reviews</u>: These comprehensive reports draw on completed scientific studies to make head-to-head comparisons of different health care interventions. They also show where more research is needed. There are two types of research reviews: <ol style="list-style-type: none"> <li>1. Comparative effectiveness and effectiveness reviews outline the effectiveness — or benefits and harms — of treatment options.</li> <li>2. Technical briefs explain what is known — and what is not known — about new or emerging health-care tests or treatments.</li> </ol> </li> <li>• <u>Original research reports</u>: These reports are based on clinical research and studies that use health-care databases and other scientific resources and approaches to explore practical questions about the effectiveness — or benefits and harms — of treatments.</li> <li>• <u>Summary guides</u>: These short, plain-language guides — tailored to clinicians, consumers, or policymakers — summarize the findings of research reviews on the benefits and harms of different treatment options. Consumer guides provide useful background information on health conditions. Clinician and policymaker guides rate the strength of evidence behind a report's conclusions. The guides on medications also contain basic wholesale price information.</li> </ul> <p>The Effective Health Care Program, the AHRQ, the Scientific Resource Center, and the Evidence-</p>

based Practice Centers (EPCs) have also developed a “Methods Guide for Comparative Effectiveness Reviews”<sup>39</sup>, intending to support researchers who are conducting effectiveness and comparative effectiveness reviews, systematic reviews of existing research on the effectiveness, comparative effectiveness, and comparative harms of different health care interventions. The draft guidelines (published in 2007) contains chapters on:

- *topic development* (topic nomination, formulation and refinement of key questions, analytic frameworks, modifying key questions);
- *selecting evidence: controlled trials* (effectiveness trials, efficacy trials, applicability of efficacy trials);
- *selecting evidence: observational studies of beneficial effects* (decision framework);
- *finding evidence* (previously published systematic reviews, bibliographic databases, other web sites and databases, scientific information packets, miscellaneous resources);
- *assessing the quality and applicability of included studies* (stages in rating quality of studies, rating applicability);
- *harms* (terminology, sources of evidence on harms, assessing risk of bias of harms, reporting instruments for assessing risk of bias in studies on harms, synthesizing evidence on harms, reporting evidence on harms);
- *quantitative synthesis* (when to combine individual studies, choice of effect measures, choice of model for combining studies, exploring heterogeneity, indirect comparison, combining studies of mixed designs, sensitivity analysis, interpretation and translation of results of meta-analysis, reporting the quantitative synthesis of studies);
- *rating a body of evidence* (domains of strength of evidence, required domains, optional domains, other pertinent issues, overall strength of evidence, incorporating multiple domains into overall grade, reporting strength of evidence)

This guideline has set an important standard for the conduct of comparative effectiveness research in the USA. The guideline was published with ongoing revisions for which updates of chapters and expansions will be published. This is the current working table of content<sup>39</sup>:

- Foreword: Comparing Medical Interventions: AHRQ and the Effective Health Care Program (published);
- Principles in Developing and Applying Guidance for Comparing Medical Interventions (published);
- Identifying, Selecting and Refining Topics for Comparative Effectiveness Systematic Reviews (published);
- Finding Evidence for Comparing Medical Interventions (published);
- Selecting Observational Studies for Comparing Medical Interventions (published);
- Assessing the Quality of Studies when Comparing Medical Interventions (AHRQ Manuscript under review);
- Assessing the Applicability of Studies when Comparing Medical Interventions (published);
- Assessing Harms when Comparing Medical Interventions (published);
- Conducting Quantitative Synthesis When Comparing Medical Interventions (published);
- Grading the Strength of a Body of Evidence when Comparing Medical Interventions (published);

<sup>39</sup> Agency for Healthcare Research and Quality. Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews, Version 1.0 [Draft posted Oct. 2007]. Rockville, MD. Available at: [http://effectivehealthcare.ahrq.gov/repFiles/2007\\_10DraftMethodsGuide.pdf](http://effectivehealthcare.ahrq.gov/repFiles/2007_10DraftMethodsGuide.pdf) (accessed January 2011)

- Avoiding Potential Biases when Comparing Medical Interventions (work in progress — draft due winter 2011)
- Using Existing Systematic Reviews to Replace de Novo Processes in CERs (published);
- Updating Reports Comparing Medical Interventions (work in progress — draft due winter 2011).

The AHRQ in conjunction with the Centers for Medicare and Medicaid Services, commissioned a guide to provide practical, scientific advice on the design, operation, analysis, and evaluation of patient registries, entitled "Registries for Evaluating Patient Outcomes: A User's Guide". This document supports researchers who are developing and supporting a registry to conduct observational studies to seek objective information to increase what is known from clinical trials and other research studies. A registry that is appropriately designed, conducted, and analysed will provide unique scientific information about the effectiveness, safety, and quality of the health-care service or intervention that is being studied.

### **Evidence-based Practice Center (EPC)**

The EPCs are 14 institutions that critically examine existing scientific evidence on a clinical topic and summarize what is known and not known from the current science base.

The EPCs review all relevant scientific literature on clinical, behavioural, and organisation and financing topics to produce evidence reports, technical reviews (covering nonclinical methodological topics), and technology assessments.

The resulting evidence reports and technology assessments are used by Federal and State agencies, private sector professional societies, health delivery systems, providers, payers, and others committed to evidence-based health care.

Reports are available at:

<http://www.ahrq.gov/clinic/epcindex.htm>

<http://www.ahrq.gov/clinic/epc/epcseries.htm>

The **American Recovery and Reinvestment Act of 2009** (Recovery Act) appropriated \$1.1 billion for comparative effectiveness research. The Agency for Healthcare Research and Quality (AHRQ) received \$300 million and agreed to manage the \$400 million allocated to the Secretary of the Department of Health and Human Services.

AHRQ is using the Recovery Act funds to expand and broaden a variety of existing activities through its Effective Health Care (EHC) program.

The AHRQ has organised **invitational symposiums on comparative effectiveness research methodology** in 2006 (Emerging Methods in Comparative Effectiveness and Safety) and 2009 (Clinical and Comparative Effectiveness Research Methods II), 2010 (Research Methods for Clinical and Comparative Effectiveness Studies – Part II).

Individuals at the AHRQ have produced a number of **peer-reviewed methodological papers** on comparative effectiveness research.

### 3.3.2 ICER

The Institute for Clinical and Economic Review (ICER), based at the Institute for Technology Assessment at Massachusetts General Hospital, provides independent evaluation of the clinical effectiveness and comparative value of health care interventions.

ICER's mission is to lead innovation in comparative effectiveness research through methods that integrate considerations of clinical benefit and economic value. Through collaboration with patients, clinicians, manufacturers, insurers and other healthcare stakeholders, ICER develops tools to support patient decisions and medical policy that share the goal of achieving maximum value for money.

Current activities of the ICER related to the subject relative effectiveness assessment are presented in the table below.

<b>ICER (<a href="http://www.icer-review.org/index.php">http://www.icer-review.org/index.php</a>)</b>
ICER reviews are made publicly available.
ICER has a paper entitled 'The ICER Appraisal Process: Comparisons with AHRQ's Methodology' <sup>40</sup> , which discusses key similarities and differences in its methodology and the methodology that is presented in the AHRQ's Methods Guide for Comparative Effectiveness Reviews <sup>39</sup> . The following topics are discussed: <ul style="list-style-type: none"><li>• topic development;</li><li>• finding &amp; selecting evidence;</li><li>• evidence synthesis;</li><li>• grading strength of evidence;</li><li>• comparative value;</li></ul>

### 3.3.3 Oregon Health & Science University (OHSU) Drug Effectiveness Review Project (DERP)

Drug Effectiveness Review Project (DERP) is a collaboration of public entities (the Center for Evidence-based Policy and the Oregon Evidence-based Practice Center) that have joined together to produce systematic, evidence-based reviews of the comparative effectiveness and safety of pharmaceuticals in many widely used pharmaceutical classes, and to apply the findings to inform public policy and related activities in local settings.

Current activities of the DERP related to the subject relative effectiveness assessment are presented in the table below.

<b>Oregon Health &amp; Science University (OHSU) Drug Effectiveness Review Project (DERP) (<a href="http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/index.cfm">http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/index.cfm</a>)</b>
The DERP project produces systematic literature reviews of drug classes. Components of these

<sup>40</sup> The Institute for Clinical and Economic Review (ICER). The ICER Appraisal Process: Comparisons with AHRQ's Methodology. Available at <http://www.icer-review.org/index.php/icer-vs-ahrq-processes-1252010.html> (accessed January 2011).

**Oregon Health & Science University (OHSU) Drug Effectiveness Review Project (DERP) (<http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/index.cfm>)**

reviews include: key questions, draft documents and evidence tables, and final documents and evidence tables. The following areas of research' are ongoing:

- asthma;
- antidepressants;
- diabetes;
- fibromyalgia drugs;
- neuropathic pain;
- antiplatelets;
- opioids;
- multiple sclerosis;
- attention deficit disorder;
- targeted immune modulators

### 3.3.4 PBAC

The Pharmaceutical Benefits Advisory Committee (PBAC) is an independent Australian statutory body that makes recommendations and gives advice to the Minister about which pharmaceuticals and medicinal preparations should be made available as pharmaceutical benefits. The Committee considers the effectiveness and cost of a proposed benefit compared to alternative therapies. The methodology of PBAC for relative effectiveness assessment is included in chapter 2.

Further activities of the PBAC related to the subject relative effectiveness assessment are presented in the table below.

**PBAC (<http://www.health.gov.au/internet/main/publishing.nsf/content/health-pbs-general-listing-committee3.htm>)**

The PBAC has technical working groups that issue reports on methodological challenges. The following reports have been published:

- A framework for evaluating proposed surrogate measures and their use in submissions to PBAC<sup>41</sup>;
- Pharmaceutical Benefits Advisory Committee, Indirect Comparisons Working Group. Assessing indirect comparisons<sup>42</sup>

### 3.3.5 PCORI

The Patient-Centered Outcomes Research Institute (PCORI) is a newly established institute in the USA that focuses on prioritising and funding comparative effectiveness research using a largely

<sup>41</sup> Pharmaceutical Benefits Advisory Committee, Surrogate to Final Outcome Working Group. a framework for evaluating proposed surrogate measures and their use in submissions to PBAC. Available at [http://www.eunetha.net/WR\\_Documents\\_Secure/JA%20WP5%20Relative%20Effectiveness%20Assessment%20\(REA\)%20of%20Pharmaceuticals/4\\_Library/Literature%20SG1/Methodology/Surrogate%20endpoints/PBAC\\_surrogate%20measures.pdf](http://www.eunetha.net/WR_Documents_Secure/JA%20WP5%20Relative%20Effectiveness%20Assessment%20(REA)%20of%20Pharmaceuticals/4_Library/Literature%20SG1/Methodology/Surrogate%20endpoints/PBAC_surrogate%20measures.pdf) (accessed January 2011).

<sup>42</sup> Pharmaceutical Benefits Advisory Committee, Indirect Comparisons Working Group to the. Assessing indirect comparisons. Available at [http://www.health.gov.au/internet/main/publishing.nsf/Content/B11E8EF19B358E39CA25754B000A9C07/\\$File/ICWG%20Report%20FINAL2.pdf](http://www.health.gov.au/internet/main/publishing.nsf/Content/B11E8EF19B358E39CA25754B000A9C07/$File/ICWG%20Report%20FINAL2.pdf) (Accessed January 2011).



stakeholder-driven process. This initiative builds upon the strong foundation laid in 2009 by the \$1.1 billion in funding for comparative effectiveness research in the American Recovery and Recovery Act. The Institute is going to establish and execute a national comparative effectiveness research agenda by identifying research priorities and funding and facilitating new comparative effectiveness research studies. These studies will consist of both systematic reviews of existing evidence and new prospective research, including clinical trials and observational studies.

The specific duties of the Institute are to:

- Establish an objective research agenda;
- Develop research methodological standards;
- Contract with eligible entities to conduct the research;
- Ensure transparency by requesting public input; and,
- Disseminate the results to patients and healthcare providers.

A standing methodology committee will lead efforts to identify and refine methodological standards for different types of comparative effectiveness research study designs, such as pragmatic clinical trials, randomized controlled trials, and patient registries. A 15-member committee will be composed of experts in comparative effectiveness methods, biostatisticians, epidemiologists, health services researchers, and other experts. The committee must begin releasing methodological standards for conducting comparative effectiveness research within 18 months of the establishment of the Institute. These standards will be used to select proposed studies for funding and to guide researchers as they design trials. In addition, the committee will develop tools to help researchers determine which methods are most appropriate for a particular research question.

No specific activities of the PCORI related to relative effectiveness assessment have been identified as the institute is still in development at the time of writing this report.



## 4 Discussion

The remit of WP5 is to develop methodology for relative effectiveness assessment of pharmaceuticals based on the existing tools within EUnetHTA. The aim of this background review is to provide an overview of the processes, the scope and the scientific methods used for relative effectiveness assessment in current national practice, as a starting point for the development of models and guidelines that have the best chance of acceptance/usage across the Member States. In addition, an overview is provided of current activities that have been identified in relation to relative effectiveness assessment of pharmaceuticals.

### 4.1 *The concept of relative effectiveness assessment*

In Europe the term relative effectiveness is commonly referred to, and has been defined by the High Level Pharmaceutical forum as: *'the extent to which an intervention does more good than harm compared to one or more intervention alternatives for achieving the desired results when provided under the usual circumstances of health care practice'*.

In the USA the term comparative effectiveness research is very popular, which has been defined as following: *"the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of comparative effectiveness research is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels."*

For both definitions questions pop-up. There are discussions whether something defined as effectiveness should include unintended (harms) in addition to intended effects (goods). It is also considered disputable whether establishing how an intervention performs under usual circumstances of health care practice is at all feasible. Additionally, it has been indicated that the word 'relative' can have a mathematical meaning referring to a ratio, for example like in a relative risk calculation, whereas a net therapeutic benefit could also be described as added life expectancy. The latter would be expressed as a difference in months, rather than a ratio.

Both relative effectiveness and comparative effectiveness seem to be rather concepts or basket terms, instead of being scientifically well defined. However both definitions indicate that there is a need to establish the net clinical benefit of interventions beyond the boundaries of a strictly controlled setting (e.g. randomised controlled clinical trials).

The purpose of a relative effectiveness assessment is to inform health care professionals, patients and decision makers about the net therapeutic benefit<sup>43</sup> of an intervention compared to alternative interventions. Therefore it can be seen as a specific element of a health technology assessment that focuses on the clinical implications of the intervention, whereas the concept of health technology assessment is broader and can also include for example social, ethical and cost aspects. However, boundaries are difficult to define as some social, organisational, legal and/or ethical aspects may be relevant input for the relative effectiveness as well.

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<sup>43</sup> This is also sometimes referred to as the therapeutic or clinical (added) value. However, within WP5 'net clinical benefit' it is chosen as the preferred term as it is up to the Member States to decide on the value.

## **4.2 National approaches to and use of relative effectiveness assessment and other activities**

This report provides an overview of the processes and methodologies used for relative effectiveness assessment by health technology assessment organisations in European jurisdictions, Australia, Canada, the USA and New Zealand. The analysis is limited to assessments that provide input for national reimbursement decisions<sup>44</sup>. In order not to exclude evaluations of pharmaceuticals of jurisdictions based on the definition of the High Level Pharmaceutical Forum of relative effectiveness the following type of assessments were included: all 'comparative analysis' assessing the efficacy and/or effectiveness of pharmaceutical(s) in comparison to alternatives that provide input for national reimbursement decisions.

Most jurisdictions work with either a national positive or a national negative reimbursement list for pharmaceuticals for outpatient use. For pharmaceuticals for inpatient use it is much less common to have a positive/negative list<sup>45</sup>. In general, in jurisdictions with a positive list, pharmaceuticals must be evaluated before they can enter the list (e.g. France, Netherlands). In jurisdictions with a negative list (and no positive list) in general pharmaceuticals are only evaluated in case there is a specific need (e.g. high costs, doubts about the relative effectiveness).

Most jurisdictions have defined a list with criteria that a product should adhere to in order to be reimbursed. The most commonly used criteria are effectiveness, safety and cost-effectiveness (applicable in more than 80% of the jurisdictions).

The reimbursement evaluations of pharmaceuticals can be divided in the following three steps: 1) assessment, 2) advice, 3) decision. In 13 out of 30 jurisdictions these three steps are conducted by the same agency, whereas in the other jurisdictions at least two agencies/organisations are involved.

Except for the USA, all jurisdictions included perform analysis of efficacy and/or effectiveness of pharmaceutical(s) in comparison to alternatives to feed national reimbursement decisions on pharmaceuticals<sup>46</sup>. This assessment is referred to with a variety of terms such as 'comparative (clinical) effectiveness', 'evaluation of (medical-)therapeutic value', 'clinical added value', 'clinical or therapeutic evaluation' or 'benefit assessment'. In some jurisdictions it is part of a pharmacoeconomic evaluation whereas in other jurisdictions clinical assessment is separate from the pharmacoeconomic assessment.

In general, these evaluations can be divided into (single) rapid assessment<sup>47</sup> and full assessments of pharmaceuticals<sup>48</sup>. Rapid assessments often have to be carried out within a specific timeframe

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<sup>44</sup> With the exception of England/Wales, Scotland and Canada. For England/Wales the assessments are performed by NICE and they are used as input for regional reimbursement/funding decisions by regional health authorities. Similar for Scotland the assessments are performed by SMC and they are used as input for regional reimbursement/funding decisions by regional health authorities. In Canada the assessment is done nationally by the CADTH but the decision on reimbursement (based on the national assessment) is a regional responsibility.

<sup>45</sup> Inclusion on a positive list is often based on a reimbursement evaluation (which among other information often is based on input from some kind of health technology assessment) whereas negative lists (e.g. Germany and England/Wales) are often exclusions of specific types of pharmaceuticals such as non-prescription or life style pharmaceuticals which are not per definition subject to a reimbursement evaluation before being placed on the negative list.

<sup>46</sup> As already mentioned for the UK evaluations by NICE as well as evaluations by the SMC are included which means they feed regional reimbursement decisions. For Canada the assessment is done nationally by the Canadian Agency for Drugs and Technologies in Health (CADTH) but the decision on reimbursement (based on the national assessment) is a regional responsibility.

<sup>47</sup> (Single) rapid assessments are assessments of a new pharmaceutical at the time of introduction to the market in comparison to one or more alternative interventions.

whereas for a full assessment a pre-specified timeframe is only applicable in a minority of jurisdictions.

All jurisdictions state that they almost always assess the relative efficacy of the pharmaceutical and less than half of the jurisdictions state that they always look at relative effectiveness. In addition, almost half of the jurisdictions state that they always include a benefit/risk assessment and more than 60% of the jurisdictions state they always look at the cost-effectiveness. It should be noted that as no predefined definitions were provided in the survey for the terms relative efficacy, relative effectiveness, benefit/risk assessment and cost-effectiveness, these results are very susceptible to individual interpretation. Further investigation would be required to provide a more precise overview.

Most jurisdictions have some form of document/guideline available in which the methodology that is used for the comparative analysis is described. The document is not publicly available in some countries and in general, the content of the guidelines (level of detail on methodology) is not very detailed. The Australian guideline, which is a guideline for market authorisation holders on how to present data, can be considered as the most detailed on methodology. For transparency reasons as well as collaborative purposes it would be advisable that more jurisdictions invest in a written and publicly available protocol, in English, on methodology.

All jurisdictions use multiple sources for their assessment often including a report that is provided by the manufacturer, expert knowledge, guidelines, other health technology assessment reports, literature and European or National Assessment Reports. There is some divergence between jurisdictions whether unpublished clinical data and/or confidential data are used.

The choice of comparator varies across jurisdictions although when looking closely at the definitions of what is to be understood as comparator they are rather similar with definitions that are similar to 'usual care'. For both rapid and full assessments, in the majority of the jurisdictions the choice of the comparator(s) for the assessment can also be a non-pharmaceutical intervention and is thus not limited to pharmaceuticals.

The type of outcomes that is included in the analysis is similar for the included jurisdictions for a rapid as well as for a full assessment. In general, all clinically relevant outcomes are accepted for the assessment. Often outcomes related to mortality and/or morbidity and/or quality of life are preferred. In general, surrogate outcomes are not preferred, however they are accepted for the assessment if they are considered clinically relevant or are validated (this often depends on the indication/therapeutic area). Composite outcomes are in general also accepted but not preferred. Most jurisdictions include quality of life data with the premise that the instrument used should be validated. The use of utilities diverges (half of the countries would include them in the analysis). Safety data are included in almost all jurisdictions. Contra-indications, the ease of use of the technology (patient friendliness) and experience with the technology (e.g. whether the pharmaceutical has already been prescribed in many patients) are also considered in the majority of jurisdictions.

All jurisdictions consider sometimes or always the external validity of the pivotal clinical trial data for the general patient population. In the absence of effectiveness data or long-term data, efficacy data or short-term data are extrapolated qualitatively (a qualitative interpretation of the data) sometimes or always in about three-quarter of the jurisdictions, however a quantitative

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<sup>48</sup> Full assessments of pharmaceuticals are assessments (non-rapid) of (all) available technolog(y)(ies) for a particular step in a treatment pathway or a specific condition.

exercise (e.g. modelling) is only done sometimes or always in 50-60% of the jurisdictions. The quantitative analysis is often part of a cost-effectiveness analysis.

The methodological approaches used for rapid and full assessments do not differ a lot. The main difference seem to be the number of comparators (more comparators for a full assessment) and the timing of the assessment (rapid is usually performed soon after market authorisation whereas full assessment is usually performed several years later when more effectiveness data may be available).

There are various agencies all over the world that are involved in relative effectiveness or comparative effectiveness research/assessments. We have tried to identify key institutes that work in this field, especially with a focus on methodological guidelines. Guidelines on methodological issues that are relevant to relative effectiveness assessment are developed or are in development by the AHRQ, PBAC, EMA and ISPOR. In the future the PCORI Institute (USA) will probably have a relevant role in guideline development as well.

The European MEDEV is an informal working group of the European Social Insurance Platform which among others focuses on daily exchange of information on relative effectiveness assessment. Whereas the focus of WP5 is to create common methodology for future cooperation the MEDEV focuses on exchange of information on ongoing assessments.

In collaboration with WP5, the EMA is considering how the EPAR could make a better contribution to the assessment of relative efficacy/effectiveness by health technology assessment bodies in the EU Member States. Written input from WP5 (based on a letter by MEDEV) and two face-to-face meetings in 2010 have resulted in adaptation of the EPAR template by EMA. The revised template was implemented from November 2010 onwards. Collaboration in 2011 will continue by means of an evaluation of the adapted EPARs.

### ***4.3 Relevance for the development of common methodology on relative effectiveness assessment***

National reimbursement decisions on pharmaceuticals are based on multiple criteria. In addition to other information the decisions are always based on input from an analysis of efficacy and/or effectiveness of pharmaceutical(s) in comparison to alternatives. This indicates that there is an element, this comparative analysis, which can be shared between jurisdictions. This review has indicated that although the reimbursement processes differ between jurisdictions, the methodology that is used for the comparative analysis is rather similar. If the EUnetHTA HTA Core Model is taken into account, the elements of such a comparative analysis can mainly be found in the first 4 domains. However, it may be possible that there are some elements within the domains of ethical analysis, organisational aspects, social and legal aspects that are also relevant for the comparative analysis.

In line with the recommendation of the High Level Pharmaceutical Forum that relative effectiveness and cost-effectiveness should be considered as two separate entities, the domain of cost-effectiveness is excluded from the scope of WP5. Hence all items/sections of the HTA Core Model related to costs are not included in the models developed by WP5.

It is the remit of WP5 to develop methodology for relative effectiveness assessment of pharmaceuticals based on the existing tools within EUnetHTA. In addition, the tools should be close to what is already happening in daily practice. In general, the assessment of pharmaceuticals can be divided into (single) rapid assessment<sup>47</sup> and full assessments of pharmaceuticals<sup>48</sup>. The first type of assessment is performed in almost all jurisdictions included in the survey and full assessment are performed in almost 60% of the jurisdictions. Therefore WP5

will also develop 2 models, a Rapid Model and a Full model. As presented in Figure 20 the scope of the Full model will be all domains of the HTA Core Model except for cost and economic considerations. The scope of the Rapid model will also be all domains of the HTA Core Model except for cost and economic considerations, however only a limited number of elements<sup>49</sup> of the ethical analysis, the organisational analysis, the social aspects and the legal aspects will be included.

**Figure 20. Models to be developed within WP5**

HTA Core Model	WP5	
	Full Model	Rapid Model
Health problem and current use of technology	Health problem and current use of technology	Health problem and current use of technology
Description and technical characteristics of the technology	Description and technical characteristics of the technology	Description and technical characteristics of the technology
Safety	Safety	Safety
Effectiveness	Effectiveness	Effectiveness
Cost and economic considerations	<del>Cost and economic considerations</del>	<del>Cost and economic considerations</del>
Ethical analysis	Ethical analysis	<del>Ethical analysis</del>
Organisational analysis	Organisational analysis	<del>Organisational analysis</del>
Social aspects	Social aspects	<del>Social aspects</del>
Legal aspects	Legal aspects	<del>Legal aspects</del>
	<ul style="list-style-type: none"> <li>• Multiple comparators</li> <li>• Years after market authorisation</li> <li>• Indication based</li> </ul>	<ul style="list-style-type: none"> <li>• Limited number of comparators</li> <li>• Soon after market authorisation</li> </ul>

One important element to notice is that there seems to be variation between jurisdictions in the terminology and definitions that are used for similar processes. This may lead to confusion on whether jurisdictions are actually doing the same thing. This may be driven by language barriers, but also by variation in interpretation due to cultural and legislative differences. As already indicated by the High Level Pharmaceutical Forum shared terminology and definitions would create a common basis. In order to develop common methodology it will be essential to be clear about the wording and the content of definitions for WP5. Guidelines can play a relevant role in this process.

<sup>49</sup> A domain within the core model can be divided in individual topics which subsequently can be divided into issues. Example: in *Health Problem and Current Use of the Technology* there is a topic *Target condition*. Within this topic target condition there is an issue *Which disease/health problem/potential health problem will the technology be used for?* These issues are called elements.

Moreover, the analysis of jurisdictions identified that methods to do the assessment are in general not explicitly reported. Hence, there is a clear need for guidelines on methodological issues as methodological approaches are not well described in guidelines in Europe yet. The guidelines that are being developed by WP5 can play an important role in making it more explicit. Currently, within WP5, guidelines are in development for the following topics:

- 1) Endpoints used in the context of a relative effectiveness assessment (including clinical endpoints, surrogate endpoints, composite endpoints, quality of life and safety);
- 2) Criteria for choice of the most appropriate comparator(s);
- 3) Direct comparison & indirect comparisons;
- 4) Level of evidence (including internal validity, external validity and extrapolation from efficacy results to real life situation);

For the specific topics of guidelines under development in WP5, guidelines developed by organisations such as the AHRQ, PBAC, EMA and ISPOR should be considered as well as existing guidelines of the national organisations.

As mentioned, the methodological approaches used for rapid and full assessments are similar, especially in terms of relevant outcomes. Probably the main difference, also presented in Figure 20, is the number of comparators (more comparators for a full assessment) and the timing of the assessment (rapid is usually performed soon after market authorisation whereas full assessment is usually performed several years later when more clinical effectiveness data may be available).. This affects the possibilities to look at effectiveness data for a rapid assessment and there is divergence between jurisdictions in how this is tackled. Some jurisdictions only take efficacy data into account in their comparative analysis if no effectiveness data are available for the rapid assessment. Other jurisdictions may extrapolate the data of the efficacy trials qualitatively or quantitatively. It is relevant that all methodological options are identified and presented within WP5 and guidance should be provided for direct and indirect comparisons as well as for qualitative and quantitative extrapolation.

One of the issues where there is confusion about terminology is benefit/risk assessment. There is a debate ongoing on whether a benefit/risk assessment (the balance between doing more good than harm) is part of a relative effectiveness assessment. Some consider a benefit/risk assessment<sup>50</sup> strictly the remit of registration authorities, whereas others feel this should also be part of the relative effectiveness assessment. We feel that the confusion (or disagreement) seems to be caused mainly by the word, benefit/risk assessment, which is strongly associated with drug regulatory agencies as there seems to be agreement that in a net therapeutic benefit assessment (relative effectiveness assessment) that is used for a reimbursement decision the intended as well as the unintended effects are included with an emphasis on the size of these effects relative to the comparator.

Although there is agreement regarding the fact that a relative effectiveness assessment should include intended as well as the unintended effects, there is variance in whether the weighting of the intended and unintended effects is part of the assessment or if this is explicitly limited to the appraisal phase. This is also illustrated by the fact that less than half of the jurisdictions always split the assessment and appraisal phase. In the traditional HTA Core Model there is no section in which the intended and unintended effects are combined (e.g. there is a clear split between the safety and effectiveness domain). However, if we believe within WP5 that relative effectiveness assessment must lead to the estimation of the net therapeutic benefit for a certain pharmaceutical, a combination of the intended and unintended effects within our model is relevant. The actual weighting of the outcomes of such a combination, to determine the 'value' must remain the remit of national decision makers, however a transparent presentation of the

<sup>50</sup> Drug regulatory agencies have traditionally assessed the quality, safety and efficacy of drugs, and the current paradigm dictates that a new drug should be licensed when the benefits outweigh the risks (Eichler et al. 2010).



results can only be helpful for consistent weighting. Therefore, the pilot of WP5 with the Rapid Model will also be used to see if it is possible to generate a section that aggregates the intended and unintended effects (a synthesis document).

Although our review shows that in many jurisdictions the definition for the choice of comparator is similar to 'usual care' the choice of comparator may differ between jurisdictions as usual care can differ between jurisdictions. This may affect shared assessments. However, in various jurisdictions the same pivotal trials are used in the assessments (hence using the same comparator). In case of difference in usual care between jurisdictions, different methodologies for direct and indirect comparison may be used to come to adjusted interpretations for jurisdictions. Adequate justification of the reason for choice of comparator will be relevant for shared or adjusted assessments.

A summary of most relevant challenges for a common methodology on relative effectiveness assessment as discussed above and how these will be addressed in WP5 is presented in Table 8.

**Table 8. Summary of most relevant challenges for a common methodology on relative effectiveness assessment and how these will be addressed in WP5**

Challenge	WP5 activity
Methodology to do assessments is often not explicitly reported	<ul style="list-style-type: none"> <li>• Production of guidelines on important methodological issues</li> <li>• Standardisation of reporting for assessments through using the Rapid/Full model</li> </ul>
Variation between jurisdictions in terminology and definitions	<ul style="list-style-type: none"> <li>• Production of guidelines on important methodological issues</li> </ul>
How to handle lack of effectiveness data	<ul style="list-style-type: none"> <li>• Production of guidelines on external validity and extrapolation of efficacy results</li> <li>• Standardisation of reporting in Rapid/Full model</li> </ul>
How to present unintended and intended effects	<ul style="list-style-type: none"> <li>• Inclusion of section in Rapid/Full model that aggregates intended and unintended effects</li> </ul>
Variance in usual care between jurisdictions	<ul style="list-style-type: none"> <li>• Production of guideline on 'Criteria for the choice of the most appropriate comparator(s)' as well as a guideline that provides methodology on direct and indirect comparisons in order to come to adjusted interpretations for jurisdictions with different forms of care</li> </ul>

WP5 considers it relevant that stakeholders are involved in the production of the products (the relative effectiveness assessment models as well as the guidelines). Therefore, input on draft products is asked from the Stakeholder Advisory Group<sup>51</sup>. In addition, all products will be placed on the public EUnetHTA website for public consultation.

<sup>51</sup> Whose members can be nominated by the EUnetHTA Joint Action Stakeholder Forum participants. For more details on the Stakeholder Forum see: [http://www.eunetha.net/en/Public/About\\_EUnetHTA/Organisation2/Stakeholder-Forum/](http://www.eunetha.net/en/Public/About_EUnetHTA/Organisation2/Stakeholder-Forum/)

It may be concluded on the basis of the results of our review that there is a common ground for the development of a shared methodology for relative effectiveness assessment of pharmaceuticals. Our results also show that there are still a number of issues to be dealt with in the development stage before such a shared methodology may be used in Europe. Especially questions on how to deal with relative efficacy data in relation to the assessment of relative effectiveness and aggregation of intended and unintended effects should be discussed thoroughly. Finally, our review seems to indicate that the EUnetHTA HTA Core Model, especially the first four domains, can be used as a model for this relative effectiveness assessment of pharmaceuticals. However, there are no clear boundaries. Therefore a broad approach, in which all domains of the HTA Core Model, except the domain 'Cost and economic considerations', are included, is preferred in WP5. A further adaptation of the HTA Core Model and a simultaneous development of guidelines will help us to realise the aim of WP5 in the coming two years.



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## Appendix I. Results of the survey per jurisdiction

### Result table 1. Type of healthcare system

<b>Result table 1. Type of healthcare system (jurisdictions 1-15)</b>														
X=applicable	1. Australia	2. Austria	3. Belgium	4. Canada	5. Czech Republic	6. Denmark	7. England & Wales	8. Estonia	9. Finland	10. France	11. Germany	12. Hungary	13. Ireland	14. Italy
<b>Is the health care system primarily?</b>														
A tax-based national health service				X <sup>1</sup>		X	X		X				X	X
An insurance-based health system (social or private health insurance)	X <sup>2</sup>	X	X		X			X		X	X	X		
A privately financed health system (direct/out-of-pocket payments)														

Result table 1. Type of healthcare system (jurisdictions 16-31)																
X=applicable	15.	Latvia														
	16.	Luxembourg														
	17.	Malta														
	18.	Netherlands														
	19.	New Zealand														
	20.	Norway														
	21.	Poland														
	22.	Portugal														
	23.	Scotland														
	24.	Slovakia														
25.	Slovenia															
26.	Spain															
27.	Sweden															
28.	Switzerland															
29.	Turkey															
30.	USA															
Is the health care system primarily?																
A tax-based national health service	X		X <sup>3</sup>		x			X <sup>4</sup>	X			X	X		X <sup>5</sup>	

<sup>1</sup> Canada's publicly funded health care system is best described as an interlocking set of ten provincial and three territorial health insurance plans. The system provides access to universal, comprehensive coverage for medically necessary hospital and physician services

<sup>2</sup> Medicare is a composite of Federal programs with the primary function of financing the delivery of health care, mostly as a third party payer, not actually to deliver it

[illegible]

Result table 1. Summary table: Type of healthcare system		Number of jurisdictions included
X=applicable	%	
Is the health care system primarily?		
A tax-based national health service	50%*	30
An insurance-based health system (social of private health insurance)	53%*	
A privately financed health system (direct/out-of-pocket payments)	0%	

\* the sum is more than 100% as The Turkish health care system is equally both a National Health Service and a Social Health Insurance System.

<sup>3</sup> Healthcare is free for everyone in and Malta and therefore, there is no mandatory system of contribution. Employees and employers pay weekly national insurance contributions, which fund the healthcare service as well as other social services like pensions

<sup>4</sup> The Portuguese health care system is characterized by three co-existing systems: the national health service, special public and private insurance schemes for certain professions (health subsystems) and voluntary private health insurance

<sup>5</sup> The Turkish health care system is both a National Health Service and a Social Health Insurance System

<sup>6</sup> Health insurance is primarily provided by the private sector, with the exception of programs such as Medicare, Medicaid, TRICARE, the Children's Health Insurance Program and the Veterans Health Administration

**Result table 2. Characteristics of health insurance**

<b>Result table 2. Characteristics of health insurance (jurisdictions 1-15)</b>	1. Australia	2. Austria	3. Belgium	4. Canada	5. Czech Republic	6. Denmark	7. England& Wales	8. Estonia	9. Finland	10. France	11. Germany	12. Hungary	13. Ireland	14. Italy
Y=yes N=no														
<b>Are the following characteristics applicable to the insurance system?</b>														
Participation in health insurance is mandatory (everyone is obliged by law to be insured)	Y	Y	Y	N	Y	NA	NA	Y	Y	Y	Y	Y	N	NA
Social insurance	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	N	N
Private health insurance as primary insurance (e.g. as main type of health insurance)	N	N	N	N	N	N	N	N	N	N	Y	N	N	N
Private health insurance as complementary health insurance (e.g. additional insurance to cover extra services and/or co-payment)	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y

<b>Result table 2. Characteristics of health insurance (jurisdictions 16-31)</b>	15. Latvia	16. Luxembourg	17. Malta	18. Netherlands	19. New Zealand	20. Norway	21. Poland	22. Portugal	23. Scotland	24. Slovakia	25. Slovenia	26. Spain	27. Sweden	28. Switzerland	29. Turkey	30. USA
Y=yes N=no																
<b>Are the following characteristics applicable to the insurance system?</b>																
Participation in health insurance is mandatory (everyone is	Y	Y	N	Y	N	Y	Y	N <sup>7</sup>	NA	Y	Y	NA	NA	Y	Y	N <sup>8</sup>

<sup>7</sup> Part of the population, approximately 20–25%, are also covered by a health subsystem, which means that they have a third option for the choice of care, although financing of the health subsystem is compulsory for certain beneficiaries (as it is occupation-based health insurance)

<b>Result table 2. Characteristics of health insurance (jurisdictions 16-31)</b>  Y=yes N=no	15. Latvia	16. Luxembourg	17. Malta	18. Netherlands	19. New Zealand	20. Norway	21. Poland	22. Portugal	23. Scotland	24. Slovakia	25. Slovenia	26. Spain	27. Sweden	28. Switzerland	29. Turkey	30. USA
obliged by law to be insured)																
Social insurance	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	N	Y <sup>9</sup>	N	Y	Y <sup>10</sup>
Private health insurance as primary insurance (e.g. as main type of health insurance)	N	N	N	Y	N	N	N	N	N	N	N	N	N	Y	Y	Y
Private health insurance as complementary health insurance (e.g. additional insurance to cover extra services and/or co-payment)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y <sup>11</sup>

<sup>8</sup> Massachusetts has adopted a universal health care system through the Massachusetts 2006 Health Reform Statute. Which requires all residents to purchase health insurance who can afford to do so, and provides subsidised insurance plans for those that can not afford insurance. In addition, with the introduction of the Health Care Reform Bill, from 2014 and onwards, everyone in the USA must purchase health insurance or face a \$695 annual fine. There are some exceptions for low-income people

<sup>9</sup> Swedish social insurance compensates loss of income when a person is unable to support him/herself by working as a result, for example, of an illness or caring for a child

<sup>10</sup> Medicare for people who are aged 65 and over, or who meet other special criteria. Medicaid for Medicaid for eligible individuals and families with low incomes and resources

<sup>11</sup> Some people elect to purchase a type of supplemental coverage, called a Medigap plan, to help fill in the holes in Original Medicare (Part A and B). These Medigap insurance policies are standardized by Centers for Medicare & Medicaid Services, but are sold and administered by private companies

<b>Result table 2. Summary table: . Characteristics of health insurance</b>							
	<b>Y</b>	<b>N</b>	<b>%Y</b>	<b>%N</b>	<b>Total</b>	<b>Total number of jurisdictions</b>	<b>Entries 'not applicable'</b>
<b>Are the following characteristics applicable to the insurance system?</b>							
Participation in health insurance is mandatory (everyone is obliged by law to be insured)	18	6	75%	25%	100%	30	6
Social insurance	22	8	73%	27%	100%	30	0
Private health insurance as primary insurance (e.g. as main type of health insurance)	5	25	17%	83%	100%	30	0
Private health insurance as complementary health insurance (e.g. additional insurance to cover extra services and/or co-payment)	29	1	97%	3%	100%	30	0

### Result table 3. Reimbursement list

<b>Result table 3. Reimbursement list (jurisdictions 1-15)</b>															
Y=yes N=no	1. Australia	2. Austria	3. Belgium	4. Canada	5. Czech Republic	6. Denmark	7. England& Wales	8. Estonia	9. Finland	10. France	11. Germany	12. Hungary	13. Ireland	14. Italy	
<b>Is a national positive or negative list used for reimbursement purposes for pharmaceuticals?</b>															
<b>Pharmaceuticals for outpatient use</b>															
	National positive list	y	y	y	n <sup>12</sup>	y <sup>13</sup>	y	n	y	y	y	n	y	y	y <sup>14</sup>
	National negative list	n	n	n	n	n	y	n	n <sup>15</sup>	n	y	n	n	n	y <sup>14</sup>
<b>Pharmaceuticals for inpatient use</b>															
	National positive list	y <sup>16</sup>	n	y	n	y	n	n	n	y	n	y	n	n	y <sup>14</sup>
	National negative list	n	n	n	n	n	y	n	n	n	n	n	n	n	y <sup>14</sup>

<sup>12</sup> No national, however regions do have their lists. Governments fund approximately half of prescription pharmaceutical purchases in Canada through a patchwork of federal, provincial, and territorial pharmaceutical plans. All of these pharmaceutical plans operate their own positive formularies

<sup>13</sup> The outpatient and inpatient lists are to separated lists with some overlap

<sup>14</sup> The system groups pharmaceuticals into two main reimbursement categories according to a combination of relevance in terms of effectiveness and cost: Class A (fully reimbursed) and Class C (not reimbursed)

<sup>15</sup> Since 2006 the HILA has had the power to make a negative list, but as of 2011 no such list has been made

<sup>16</sup> Inpatients in public hospitals are reimbursed from sources other than the PBS. Hence the positive list for inpatient care is only applicable to private hospitals

Result table 3. Reimbursement list (jurisdictions 16-31)		15. Latvia	16. Luxembourg	17. Malta	18. Netherlands	19. New Zealand	20. Norway	21. Poland	22. Portugal	23. Scotland	24. Slovakia	25. Slovenia	26. Spain	27. Sweden	28. Switzerland	29. Turkey	30. USA
Y=yes N=no																	
Is a national positive or negative list used for reimbursement purposes for pharmaceuticals?																	
Pharmaceuticals for outpatient use																	
National positive list		y	y	y	y	y	y	y	y	n <sup>17</sup>	y	y	n	y	y	y <sup>18</sup>	n
National negative list		n	n	n	n	n	n	n	n	y <sup>19</sup>	y	n	y	n	n	n	n
Pharmaceuticals for inpatient use																	
National positive list		y	n	y	n <sup>20</sup>	n	n	y <sup>21</sup>	y <sup>22</sup>	n	n	y <sup>23</sup>	n	n	n	y <sup>18</sup>	n
National negative list		n	n	n	n	n	n	n	y <sup>22</sup>	y <sup>19</sup>	n	n	n	n	n	n	n

<sup>17</sup> The regional health authorities decide on funding of pharmaceuticals

<sup>18</sup> There are two separate positive lists for outpatient and inpatient pharmaceuticals

<sup>19</sup> UK NHS blacklist

<sup>20</sup> There is a list for expensive hospital pharmaceuticals (*beleidsregel dure geneermiddelen*) for which hospitals receive separate funding (normally the costs of pharmaceuticals have to be funded by the *DBC* (DRG) fee)

<sup>21</sup> Several pharmaceuticals (very expensive e.g. in cancer or rare diseases) are listed in the NHF catalogues. Other pharmaceuticals are not included in the list

<sup>22</sup> Since 2007 positive and negative lists have been set up. Only for new launched pharmaceuticals and new indications of pharmaceuticals

<sup>23</sup> Since January 2011 there is a positive list for expensive pharmaceuticals for inpatient use



<b>Result table 3. Summary table: Reimbursement list</b>							
	<b>Y</b>	<b>N</b>	<b>Total</b>	<b>%Y</b>	<b>%N</b>	<b>Number of jurisdictions included</b>	<b>Total</b>
<b>Is a national positive or negative list used for reimbursement purposes for pharmaceuticals?</b>							
<b>Pharmaceuticals for outpatient use</b>							
National positive list	24	6	30	80%	20%	30	100%
National negative list	6	24	30	20%	80%	30	100%
<b>Pharmaceuticals for inpatient use</b>							
National positive list	12	18	30	40%	60%	30	100%
National negative list	4	26	30	13%	87%	30	100%

## Result table 4. Co-payment of pharmaceuticals

Result table 4. Co-payment of pharmaceuticals (jurisdictions 1-15)		1. Australia	2. Austria	3. Belgium	4. Canada	5. Czech Republic	6. Denmark	7. England& Wales	8. Estonia	9. Finland	10. France	11. Germany	12. Hungary	13. Ireland	14. Italy
X=applicable															
<b>Can the following co-financing options for reimbursed pharmaceuticals be applicable?</b>															
<b>Pharmaceuticals for outpatient use</b>															
	% of price			X <sup>24</sup>			X <sup>25</sup>		X <sup>26</sup>	X <sup>27</sup>	X <sup>28</sup>	X <sup>29</sup>	X <sup>30</sup>		
	Fixed fee	X <sup>31</sup>								X <sup>32</sup>			X <sup>33</sup>		X <sup>34</sup>

<sup>24</sup> Percentage co-payment of 0% (Cat A: vital pharmaceuticals, for example: treatment of diabetes or cancer) 15 or 25% (Cat B: Therapeutically important pharmaceuticals, for example: antibiotics, cardiovascular pharmaceuticals), 50% (Cat C: Pharmaceuticals for symptomatic treatment, for example: mucolytic agents to treat chronic bronchitis, PPI), 60%(Cat Cs: Influenza vaccines and antihistamines) or 80% (Cat Cx: Contraceptive pharmaceuticals). Maximum co-payment per prescription of € 6.70 to € 26.10 in specific reimbursement categories

<sup>25</sup> The needs-based system is constructed around a rather large out-of-pocket payment (OPP) at the beginning of the patient's personal reimbursement period (100%), and gradually higher reimbursement rates and corresponding lower out-of-pocket payments (OPP) by the end of the personal reimbursement period (15%). Reduced co-payments are applicable to children, chronically and terminally ill. The reimbursement period is one year

<sup>26</sup> all pharmaceuticals on the positive list are, based on the underlying diseases, reimbursed at a rate of 100%, 75% (or 90% for vulnerable groups) and 50%. In the 75%/90% reimbursement category, the patient has to pay 25%/10% of the price of the pharmaceutical. In the 50% category, if the price of a pharmaceutical exceeds € 3.20, 50% is covered by the Estonian Health Insurance Fund (EHIF) to an upper limit of € 12.80 (2008). The remaining part of the product's price has to be paid by the patient

<sup>27</sup> Based on Health Insurance Act 3 different reimbursement categories are 42 % (Basic Refund Category), 72 % (Lower Special Refund Category, pharmaceuticals for ten chronic conditions such as hypertension, asthma, coronary heart disease and rheumatoid arthritis) or 100% (Higher Special Refund Category, 34 severe chronic conditions and life-threatening diseases)

<sup>28</sup> different percentages are applied according to appraisal: important corresponds to 65% moderate : 35% and weak : 15% of reimbursement

<sup>29</sup> Prescription fee as percentage of price, with absolute minimum and maximum

<sup>30</sup> Co-payment rates vary between are 25%, 55%, 80% of the PRP. Pharmaceuticals with approved special indications are reimbursed at 100%, 90%, 70% and 50%. Approval special indications means that the pharmaceutical is prescribed by a specialist or a GP acting on advice of a specialist; otherwise they fall in the category of normative reimbursement at a higher co-payment rate

<sup>31</sup> Prescription pharmaceuticals covered by the Pharmaceutical Benefits Scheme (PBS) have a standard co-payment: AUS\$33.30 (2010) in general with a reduced rate of AUS\$5.40 per item dispensed for individuals with concession cards. After a total co-payment of AUS\$1281.30, subsequent prescription fees are AU\$5.40 for the remainder of the calendar year. The co-payment ceiling (AU\$324) and prescription fee (AU\$5.40, then nil after AU\$324) is lower for concession card holders

<sup>32</sup> 3 Euro per pharmaceutical if 100% reimbursed, after exceeding annual ceiling (Euro 675.39 in 2011) it is 1,50 euro per pharmaceutical

<sup>33</sup> For fully reimbursed pharmaceuticals there is a fixed charge (~1eur) to be paid

<b>Result table 4. Co-payment of pharmaceuticals (jurisdictions 1-15)</b>														
X=applicable	1. Australia	2. Austria	3. Belgium	4. Canada	5. Czech Republic	6. Denmark	7. England & Wales	8. Estonia	9. Finland	10. France	11. Germany	12. Hungary	13. Ireland	14. Italy
Payment of difference between reference price and retail price	X <sup>35</sup>		X		X	X		X	X		X	X		X <sup>36</sup>
Prescription fee		X <sup>37</sup>			X <sup>38</sup>	X <sup>39</sup>	X <sup>40</sup>	X <sup>41</sup>					X <sup>42</sup>	
Deductible*													X <sup>43</sup>	
Annual co-payment ceiling**	X	X <sup>44</sup>	X <sup>45</sup>		X <sup>46</sup>	X			X <sup>47</sup>		X <sup>48</sup>		X <sup>49</sup>	
Other	X <sup>50</sup>		X <sup>51</sup>	X <sup>52</sup>		X <sup>53</sup>		X <sup>54</sup>	X <sup>55</sup>	X <sup>56</sup>		X <sup>57</sup>		

<sup>34</sup> Prescription fees (named "ticket") – a fixed amount per prescription and/or per pack, (decided at regional level)

<sup>35</sup> Any extra charge for a higher priced benefit than the benchmark price is paid by the patient, together with their usual patient contribution. Under the brand premium arrangements, reimbursement to pharmacists is based on the lowest-priced brand. Any extra charge for a higher priced brand is paid by the patient, together with their usual patient contribution

<sup>36</sup> A co-payment for pharmaceuticals in the form of payment of the difference between the price of a more expensive pharmaceutical compared to the cheaper product containing the same active ingredient (reference price)

<sup>37</sup> € 4.90

<sup>38</sup> Only if the price is fully reimbursed (30 Czech koruna in 2010)

<sup>39</sup> DKK 10.0 in 2010

<sup>40</sup> £7.20 in 2010

<sup>41</sup> Patients have to pay a fixed co-payment (prescription fee) of € 1.28 in the 100% and 75%/90% reimbursement categories and of € 3.20 in the 50% reimbursement category (2008)

<sup>42</sup> only applicable to Medical card holders which you receive below a certain income level. In that case you pay 50 cent charge per prescription item, subject to a monthly ceiling of €10 per family. (From 1 October 2010)

<sup>43</sup> Non-medical card holders who are subject to the drug payment schedule (DPS) pay a maximum of €120 a month (from January 2010) for approved prescribed pharmaceuticals, pharmaceuticals and certain appliances for use by yourself and your family in that month. In order to qualify for this scheme, you must be ordinarily resident in Ireland.

<sup>44</sup> 2% of the annual income of the insured patient

<sup>45</sup> Annual threshold for vulnerable groups (criteria: income, age, social status)

<sup>46</sup> 5000 Czech koruna and 2500 Czech koruna (2010) for pensioned and children

<sup>47</sup> Annual ceiling of Euro 675.39 (2011)

<sup>48</sup> There is an out of pocket maximum of 2% of gross income per year. This co-payment is charged supplementary to any amount payable above the reference price

<sup>49</sup> Medical card holders (which you receive below a certain income level) are subject to a monthly ceiling of €10 per family (From 1 October 2010)

<sup>50</sup> The co-payment ceiling (AU\$324, 2010) and fixed fee (AU\$5.40, then nil after AU\$324) is lower for concession card holders

<sup>51</sup> Reduced co-payment rates of 15% instead of 25% for patients with so-called preferential reimbursement status (widows, orphans, retired persons, disabled people, low income, etc.)

<sup>52</sup> Outpatient pharmaceuticals finance differs across provinces

<sup>53</sup> Supplementary reimbursement schemes exist for the disabled, pensioners and low income groups (outpatient pharmaceuticals)

<b>Result table 4. Co-payment of pharmaceuticals (jurisdictions 1-15)</b>	1. Australia	2. Austria	3. Belgium	4. Canada	5. Czech Republic	6. Denmark	7. England& Wales	8. Estonia	9. Finland	10. France	11. Germany	12. Hungary	13. Ireland	14. Italy
X=applicable														
<b>Pharmaceuticals for inpatient use</b>														
% of price														
Fixed fee		X <sup>58</sup>	X <sup>59</sup>							X <sup>60</sup>	X <sup>61</sup>			
Payment of difference between reference price and retail price														
Prescription fee														
Deductible*														
Annual co-payment ceiling**														
Other	X <sup>62</sup>													

<sup>54</sup> 1) Reduced co-payment rates of 10% instead of 25% for vulnerable groups 2) Patients with private expenses for reimbursable pharmaceuticals between € 384.- and € 1,278.- per year qualify for supplementary benefits from the EHIF (if the overall sum of private pharmaceutical expenditure lies between € 384.- and € 639.- per year, the EHIF reimburses 50% of the sum above € 384.-, if the private pharmaceutical expenditure lies between € 639.- and € 1,278.- per year, the EHIF reimburses 75% of the sum above € 639.-. If pharmaceutical expenditure is above € 1,278.-, the additional benefit is limited to € 607.- per year)

Patients have to apply for this benefit only once in their lifetime and from then on the EHIF calculates and pays the benefits automatically on a quarterly basis. However, private expenses considered neither include the prescription fees and the sums paid above the reference price of the pharmaceuticals nor any self-medication (2008).

<sup>55</sup> Social assistance by the local municipal authorities covering the cost of pharmaceuticals is available to people with low incomes, pensioners receiving support, children and people with disabilities

<sup>56</sup> Co-payment exemptions for socially disadvantaged people (income less than € 7,083 - annually)

<sup>57</sup> there is special reimbursement for people with low income (reimbursement for socially disadvantaged persons). Approximately 5% of the population are eligible to pharmaceuticals reimbursed at 100% according to a separate list, revised each year by a committee with representatives of the OEP, the NEFMI, the MOK and the MGYK. This list also comprises about 100 OTC products

<sup>58</sup> co-payment for inpatient care: 7,50 euro per day (not pharmaceutical specific)

<sup>59</sup> a fixed daily amount of € 0.62 for dispensed reimbursed pharmaceutical. Ad 5) only applicable pharmaceuticals dispensed inside the hospital, otherwise outpatient rules are applicable

<sup>60</sup> for each day spent at hospital the patient pays a fixed amount including all expenditure

<sup>61</sup> 10 euro per inpatient day with a max of 28 days (not specific for pharmaceuticals)

<sup>62</sup> In general in private hospitals the co-payment rules of the PBS are applicable. In public hospitals no co-payment is requested

<b>Result table 4. Co-payment of pharmaceuticals (jurisdictions 16-31)</b>																
X=applicable	15. Latvia	16. Luxembourg	17. Malta	18. Netherlands	19. New Zealand	20. Norway	21. Poland	22. Portugal	23. Scotland	24. Slovakia	25. Slovenia	26. Spain	27. Sweden	28. Switzerland	29. Turkey	30. USA
<b>Can the following co-financing options for reimbursed pharmaceuticals be applicable?</b>																
<b>Pharmaceuticals for outpatient use</b>																
% of price	X	X <sup>63</sup>				X <sup>64</sup>	X	X <sup>65</sup>		X	X <sup>66</sup>	X <sup>67</sup>	X <sup>68</sup>	X <sup>69</sup>	X <sup>70</sup>	
Fixed fee	X				X <sup>71</sup>											
Payment of difference between reference price and retail price				X <sup>72</sup>		X <sup>73</sup>		X		X	X <sup>74</sup>				X	
Prescription fee										X				X	X <sup>75</sup>	
Deductible*				X <sup>76</sup>									X <sup>77</sup>	X <sup>78</sup>		

<sup>63</sup> 20% for most pharmaceuticals, 60% for pharmaceuticals which are considered of minor interest in the course of treatment, e.g. minor painkillers. There is no co-payment on pharmaceuticals for certain chronic or severe diseases, e.g. cancer

<sup>64</sup> In 2008 63% of pharmaceutical price was reimbursed for pharmaceuticals on schedule 2, 3a and 3b. The limit of co-payment was NOK 510 (€63) per prescription

<sup>65</sup> For the general regime the % co-payment varies from 5-85%. For the special regime (pensioners with income below the national minimum wage) the % co-payment varies from 0-70%

<sup>66</sup> 100% reimbursement for pharmaceuticals on the positive pharmaceutical list applied in prevention and in therapy of the specified groups of insured persons and of the diseases and health states defined in paragraph 1 of Article 23 of the Law on Health Care and Health Insurance (see above); 75% reimbursement for all other pharmaceuticals on the positive pharmaceutical list; 25% reimbursement for the pharmaceuticals on the intermediate pharmaceutical list

<sup>67</sup> 40% for active workers; 10% (with a ceiling of 2.64 € per package) for chronic or severe diseases; Free for retired people

<sup>68</sup> Percentage co-payment rates, decreasing with rising pharmaceutical expenditure and no co-payment above a maximum limit. 0% reimb (€0-€96,96 euro), 50% reimb (€96,96-€183,15), 75% reimb (€183,15-€355,52), 90% reimb (€355,52-€463,25), 100% reimb (>€463,25). (defined in Act on Pharmaceutical Benefits)

<sup>69</sup> 10% co-payment; In order to encourage the use of generic pharmaceuticals, the co-payment increases from 10% to 20% if the patient asks for the brand-name pharmaceutical

<sup>70</sup> 20% co-payment

<sup>71</sup> \$3

<sup>72</sup> For pharmaceuticals on list 1A there is a maximum reimbursement price

<sup>73</sup> There is no reference price system however, patient has to pay difference between cheapest pharmaceutical and the one consumed unless exemption is indicated by physician

<sup>74</sup> In 2003 a new reimbursement measure has been implemented: a maximum allowable cost for similar pharmaceuticals (so called reference pricing on generic level). If the price of any product is higher than the reference price, the difference will have to be paid by the patient (co-payment). In 2005, 42 INN have been included with 256 presentations. Included pharmaceuticals represent 41% of pharmaceutical consumption in DDD's and 32% of expenditures

<sup>75</sup> About 8 Turkish Lira

<sup>76</sup> Ceiling in 2011 is €170

<sup>77</sup> €96,96

<b>Result table 4. Co-payment of pharmaceuticals (jurisdictions 16-31)</b>																
X=applicable																
	15. Latvia	16. Luxembourg	17. Malta	18. Netherlands	19. New Zealand	20. Norway	21. Poland	22. Portugal	23. Scotland	24. Slovakia	25. Slovenia	26. Spain	27. Sweden	28. Switzerland	29. Turkey	30. USA
Annual co-payment ceiling**		X <sup>79</sup>				X <sup>80</sup>							X <sup>81</sup>	X <sup>82</sup>		
Other						X <sup>83</sup>			X <sup>84</sup>							X <sup>85</sup>
<b>Pharmaceuticals for inpatient use</b>																
% of price																
Fixed fee													X <sup>86</sup>	X <sup>87</sup>		
Payment of difference between reference price and retail price																
Prescription fee																
Deductible*				X <sup>88</sup>												
Annual co-payment ceiling**																
Other									X <sup>89</sup>							X <sup>85</sup>

\* **Deductible:** is a fixed amount which the patient has to pay for a defined period before the cost is fully or partially reimbursed

\*\* **Annual co-payment ceiling:** a limitation of the annual maximum amount of co-payment to be borne by a patient (e.g. a maximum co-payment per prescription like in Belgium, or annual ceilings of private expenses on pharmaceuticals and/or on health care in Germany and Luxembourg).

<sup>78</sup> There is a minimum (depending upon the insurance tariff one has to pay it can be higher) "deductible" of 300 Swiss Francs per year

<sup>79</sup> The expenses may not exceed 2.5% of the net income. Patients list their co-payment for the previous year and submit the list to the sickness fund, so they get the amount above the threshold reimbursed

<sup>80</sup> Annual ceiling of NOK 1740 (€216) per patient

<sup>81</sup> Co-payment ceiling of Euro 194 per 12-month period in primary care - except insulin which is totally free of charge

<sup>82</sup> There is a ceiling of 700 Swiss francs per year for the 10% participation of the patients to the care costs on addition to the minimum deductible of 300 per annum

<sup>83</sup> exemption rule on co-payment: reimbursement is 100% for children <12 years and low-income pensioners

<sup>84</sup> In Scotland all prescription charges were abolished on 1st April 2011

<sup>85</sup> Every health plan has a separate co-financing scheme. The medicare Part D is a federal programme to subsidise the cost of pharmaceuticals for medicare beneficiaries. For Medicaid, there are federally-imposed upper limits and specific restrictions, each State generally has broad discretion in determining the payment methodology and payment rate for services

<sup>86</sup> Daily fee of Euro 8,6 per day in hospital covering both pharmaceuticals and other treatments

<sup>87</sup> There is a daily co-payment fee for hospital care

<sup>88</sup> Ceiling in 2011 is €170

<sup>89</sup> There is an option for co-payment if a pharmaceutical is not funded by the NHS. However this is very rarely used

Result table 4. Summary table: Co-payment of pharmaceuticals	Number jurisdictions	%	Number of jurisdictions included
Can the following co-financing options for reimbursed pharmaceuticals be applicable?			
Pharmaceuticals for outpatient use			30
% of price	18	60%	
Fixed fee	5	17%	
Payment of difference between reference price and retail price	16	53%	
Prescription fee	9	30%	
Deductible*	4	13%	
Annual co-payment ceiling**	12	40%	
Other	10	33%	
Pharmaceuticals for inpatient use			
% of price	0	0%	
Fixed fee	6	20%	
Payment of difference between reference price and retail price	0	0%	
Prescription fee	0	0%	
Deductible*	1	3%	
Annual co-payment ceiling**	0	0%	
Other	3	10%	

**Result table 5. Pharmaceuticals that are subject to reimbursement evaluations**

Result table 5. Pharmaceuticals that are subject to reimbursement evaluations (jurisdictions 1-15)															
A=always S=sometimes N=never															
	1. Australia	2. Austria	3. Belgium	4. Canada	5. Czech Republic	6. Denmark	7. England& Wales	8. Estonia	9. Finland	10. France	11. Germany	12. Hungary	13. Ireland	14. Italy	
<b>Are the following groups of (reimbursed) prescription pharmaceuticals subject to reimbursement evaluations?</b>															
<b>Pharmaceuticals for outpatient use</b>															
Generics	N	A	A	N	A	S	S	A	A	S	N	A	A <sup>90</sup>	A <sup>91</sup>	
Branded	A	A	A	S	A	A	A	A	A	A	S	A	A <sup>90</sup>	A	
Oncology	A	A	A	S	A	S	A	A	A	A	S	A	A <sup>90</sup>	A	
Autoimmune diseases (RA, MS, etc)	A	A	A	S	A	S	A	A	A	A	S	A	A <sup>90</sup>	A	
Orphan	A	A	A	S	A	N	S	A	A	A	S	A	A <sup>90</sup>	A	
<b>Pharmaceuticals for inpatient use</b>															
Generics	N	N	A	N <sup>92</sup>	A <sup>93</sup>	N	S	S	N	S	N	A	A <sup>90</sup>	A <sup>91</sup>	
Branded	A	N	A	N <sup>92</sup>	A <sup>93</sup>	N	A	S	N	A	N	A	A <sup>90</sup>	A	
Oncology	A	N	A	N <sup>92</sup>	A <sup>93</sup>	N	A	S	N	A	N	A	A <sup>90</sup>	A	
Autoimmune diseases (RA, MS, etc)	A	N	A	N <sup>92</sup>	A <sup>93</sup>	N	A	S	N	A	N	A	A <sup>90</sup>	A	
Orphan	A	N	A	N <sup>92</sup>	A <sup>93</sup>	N	S	S	N	A	N	A	A <sup>90</sup>	A	

<sup>90</sup> All new pharmaceuticals are subject to a reimbursement evaluation since September 2009. This evaluation takes the form of an initial preliminary rapid review (4 weeks) that examines the cost and effectiveness of the pharmaceutical relative to existing products that are reimbursed in the Irish healthcare setting and the potential budget impact of the new medicine. Following this review, a decision is made to reimburse the drug or to proceed with a full rapid assessment (90 days)

<sup>91</sup> Limited assessment

<sup>92</sup> No national assessments are performed however hospitals may have their own mechanisms to do such reviews

<sup>93</sup> The evaluation is limited to a maximum price evaluation



Result table 5. Pharmaceuticals that are subject to reimbursement evaluations (jurisdictions 16-31)																	
A=always S=sometimes N=never																	
	15. Latvia	16. Luxembourg	17. Malta	18. Netherlands	19. New Zealand	20. Norway	21. Poland	22. Portugal	23. Scotland	24. Slovakia	25. Slovenia	26. Spain	27. Sweden	28. Switzerland	29. Turkey	30. USA	
Are the following groups of (reimbursed) prescription pharmaceuticals subject to reimbursement evaluations?																	
<i>Pharmaceuticals for outpatient use</i>																	
Generics	A	A	S	N	A	A	A <sup>94</sup>	A	N	A	A	S	A	A	N	S	
Branded	A	A	S	A	A	A	A <sup>94</sup>	A	S	A	A	A	A	A	A	S	
Oncology	A	A	S	A	A	A	A <sup>94</sup>	A	A	A	A	A	A	A	A	S	
Autoimmune diseases (RA, MS, etc)	A	A	S	A	A	A	A <sup>94</sup>	A	A	A	A	A	A	A	A	S	
Orphan	A	A	A	A	A	A	A <sup>94</sup>	A	A	A	A	A	A	A	A	S	
<i>Pharmaceuticals for inpatient use</i>																	
Generics	A	N	S	N	S	N	S	A	N	A	N	S <sup>95</sup>	N	N	N	S	
Branded	A	N	S	S	S	N	S	A	S	A	S <sup>96</sup>	A	N	N	A	S	
Oncology	A	N	S	S	S	N	S	A	A	S	S <sup>96</sup>	A	N	N	A	S	
Autoimmune diseases (RA, MS, etc)	A	N	S	S	S	N	S	A	A	S	S <sup>96</sup>	A	N	N	A	S	
Orphan	A	N	A	S	S	N	S	A	A	S	S <sup>96</sup>	A	N	N	A	S	

<sup>94</sup> Mandatory procedure of reimbursement (HTA) evaluation refers to pharmaceuticals which are included in the list for the past 2 years. Pharmaceuticals that have been placed on the list earlier hadn't undergone full procedure (only a kind of budget impact analysis)

<sup>95</sup> All new pharmaceuticals approved or with new indications obtained after January 2007 are subject to reimbursement evaluation except generics approved for hospital use before January 2007

<sup>96</sup> Expensive hospital pharmaceuticals (with a threshold of > €5.000 per patient per year) are subject to a reimbursement evaluation

Result table 5. Summary table: Pharmaceuticals that are subject to reimbursement evaluations									
	A	S	N	Total	%A	%S	%N	Total	
Pharmaceuticals for outpatient use									
Generics	18	6	6	30	60%	20%	20%	100%	
Branded	25	5	0	30	83%	17%	0%	100%	
Oncology	25	5	0	30	83%	17%	0%	100%	
Autoimmune diseases (RA, MS, etc)	25	5	0	30	83%	17%	0%	100%	
Orphan	25	4	1	30	83%	13%	3%	100%	
Pharmaceuticals for inpatient use									
Generics	8	8	14	30	27%	27%	47%	100%	
Branded	13	8	9	30	43%	27%	30%	100%	
Oncology	13	8	9	30	43%	27%	30%	100%	
Autoimmune diseases (RA, MS, etc)	13	8	9	30	43%	27%	30%	100%	
Orphan	13	8	9	30	43%	27%	30%	100%	

## Result table 6. Criteria used for reimbursement decisions

Result table 6. Criteria used for reimbursement decisions (jurisdictions 1-15)														
NA=not applicable X=applicable														
	1. Australia	2. Austria	3. Belgium	4. Canada	5. Czech Republic	6. Denmark	7. England & Wales <sup>97</sup>	8. Estonia	9. Finland	10. France	11. Germany	12. Hungary	13. Ireland	14. Italy
<b>Which criteria are used for reimbursement decisions of pharmaceuticals?</b>														
<b>Pharmaceuticals for outpatient use</b>														
Efficacy/effectiveness	X <sup>98</sup>	X	X <sup>99</sup>	NA <sup>100</sup>	X	X	X	X	X	X	X	x	x	X
Safety	X <sup>98</sup>	X	X <sup>99</sup>	NA <sup>100</sup>	X	X	X <sup>101</sup>	X	X	X	X	x	x	X
Severity of disease	X <sup>102</sup>			NA <sup>100</sup>	X			X	X	X		x	x	X
Cost-effectiveness	X <sup>103</sup>	X	X <sup>104</sup>	NA <sup>100</sup>	X	X	X	X	X		X <sup>105</sup>	x	x	X
Cost containment				NA <sup>100</sup>				X				x	x	
Value for money	X <sup>103</sup>			NA <sup>100</sup>		X <sup>106</sup>	X <sup>107</sup>	X	X			x	x	
Budget impact	X	X	X	NA <sup>100</sup>	X			X	X			x	x	X
Ease of use (patient friendliness)		X <sup>108</sup>	X <sup>99</sup>	NA <sup>100</sup>	X		X <sup>109</sup>					x	x	
Other, ...	X <sup>102</sup>	X <sup>110</sup>	X <sup>111</sup>	NA <sup>100</sup>	X <sup>112</sup>			X <sup>113</sup>		X <sup>114</sup>	X <sup>115</sup>	X <sup>116</sup>		
<b>Pharmaceuticals for inpatient use</b>														
Efficacy/effectiveness	X <sup>98</sup>	NA	X <sup>99</sup>	NA <sup>117</sup>	X	NA	X <sup>109</sup>	X	NA	X	NA	x	x	X
Safety	X <sup>98</sup>	NA	X <sup>99</sup>	NA <sup>117</sup>	X	NA		X	NA	X	NA	x	x	X

<sup>97</sup> The criteria presented are criteria for health technology assessment as reimbursement decisions are a regional responsibility

<sup>98</sup> The conditions in which use has been demonstrated to be effective and safe compared to other therapies and considering comparative costs

<sup>99</sup> As part of the therapeutic value (efficacy, effectiveness, side-effects, applicability and ease of use)

<sup>100</sup> Criteria differ according to province

<sup>101</sup> Is included as part of the relative effectiveness assessment in that adverse events with the new pharmaceutical compared with its comparator are included in the overall benefit modeling

<sup>102</sup> A range of other factors, costs and health benefits are relevant. These factors may include, for example, costs of hospitalization or other alternative medical treatment that may be required, as well as less tangible factors such as patients' quality of life

<sup>103</sup> The PBAC is required to ensure that the money that the community spends in subsidising the PBS represents cost-effective expenditure of taxpayers' funds

<sup>104</sup> Only applicable for list 1: pharmaceuticals with added value

<sup>105</sup> Wirtschaftlichkeit

<sup>106</sup> The price of the product must be proportionate to its therapeutic value

<b>Result table 6. Criteria used for reimbursement decisions (jurisdictions 1-15)</b>  <b>NA=not applicable</b> <b>X=applicable</b>	1. Australia	2. Austria	3. Belgium	4. Canada	5. Czech Republic	6. Denmark	7. England& Wales <sup>97</sup>	8. Estonia	9. Finland	10. France	11. Germany	12. Hungary	13. Ireland	14. Italy
Severity of disease	X <sup>102</sup>	NA		NA <sup>117</sup>	X	NA		X	NA	X	NA	x	x	X
Cost-effectiveness	X <sup>103</sup>	NA	X <sup>104</sup>	NA <sup>117</sup>	X	NA	X	X	NA		NA	x	x	X
Cost containment		NA		NA <sup>117</sup>	X	NA		X	NA		NA	x	x	
Value for money	X <sup>103</sup>	NA		NA <sup>117</sup>		NA	X <sup>107</sup>	X	NA		NA	x	x	
Budget impact	X	NA	X	NA <sup>117</sup>	X	NA		X	NA		NA	x	x	X
Ease of use (patient friendliness)		NA	X <sup>99</sup>	NA <sup>117</sup>		NA			NA		NA	x	x	
Other, ...	X <sup>102</sup>	NA	X <sup>111</sup>	NA <sup>117</sup>	X <sup>118</sup>	NA		X <sup>119</sup>	NA	X <sup>114</sup>	NA	X <sup>116</sup>		

<sup>107</sup> Considered the same as cost-effectiveness

<sup>108</sup> Expected duration and treatment frequency

<sup>109</sup> If ease of use has a proven impact on quality of life it would be included

<sup>110</sup> Perceived degree of innovation

<sup>111</sup> 1) Applicability 2) price 3) medical need (included in legal act: therapeutic value, price, medical need, budget impact, cost-effectiveness)

<sup>112</sup> 1) If the impact is positive on the SHI system 2) Quality

<sup>113</sup> Need for alternatives

<sup>114</sup> 1) Existence of therapeutic alternatives 2) Impact in terms of public health (burden of disease, health impact at the community level, transposability of clinical trial results) 3)

Characteristics of the drug: preventive, symptomatic or curative'

<sup>115</sup> Necessity and efficiency

<sup>116</sup> 1) lack of alternative therapies, 2) prescription status

<sup>117</sup> Criteria may differ according to province, region and/or hospital

<sup>118</sup> 1) if the impact is positive on the SHI system 2) Quality

<sup>119</sup> Need for alternatives

<b>Result table 6. Criteria used for reimbursement decisions (jurisdictions 16-31)</b>																
<b>X=applicable</b>																
	15. Latvia	16. Luxembourg	17. Malta	18. Netherlands	19. New Zealand	20. Norway	21. Poland	22. Portugal	23. Scotland <sup>120</sup>	24. Slovakia	25. Slovenia	26. Spain	27. Sweden	28. Switzerland	29. Turkey	30. USA
<b>Which criteria are used for reimbursement decisions of pharmaceuticals?</b>																
<b>Pharmaceuticals for outpatient use</b>																
Effectiveness	X	X	X	X <sup>121</sup>	X	X	X	X	X <sup>122</sup>	X	X	X	x	X	X	NA <sup>123</sup>
Safety	X	X	X	X <sup>121</sup>	X	<sup>124</sup>	X	X	X <sup>122</sup>	X	X	X	x	X	X	NA <sup>123</sup>
Severity of disease	X	X	X		X	X	X	X	X <sup>125</sup>	X		X	x	X	X	NA <sup>123</sup>
Cost-effectiveness	X	X	X	X	X	X	X	X	X	X	X		x	X	X <sup>126</sup>	NA <sup>123</sup>
Cost containment	X		X		X							X <sup>127</sup>				NA <sup>123</sup>
Value for money	X	X	X		X			X <sup>128</sup>	X <sup>128</sup>	X						NA <sup>123</sup>
Budget impact	X		X	X	X		X	X		X	X	X			X	NA <sup>123</sup>
Ease of use (patient friendliness)		X	X	X <sup>129</sup>	X				X	X	X	X	(x) <sup>130</sup>	X		NA <sup>123</sup>
Other, ...		X <sup>131</sup>	X <sup>132</sup>	X <sup>133</sup>	X <sup>134</sup>						X <sup>135</sup>	X <sup>136</sup>	X <sup>137</sup>	X <sup>138</sup>		NA <sup>123</sup>

<sup>120</sup> The criteria presented are criteria for health technology assessment as reimbursement decisions are a regional responsibility

<sup>121</sup> Effectiveness and safety are expressed as positive effects and negative effects

<sup>122</sup> The relative effectiveness/safety is considered

<sup>123</sup> Criteria differ according to health plan, although many health plans adhere to the guidelines for formulary submission dossiers by the Academy of Managed Care Pharmacy (AMCP).

<sup>124</sup> Safety can be assessed within the cost-effectiveness analysis, but not on a regular/systematical basis (depends on whether data were provided by the marketing authorization holder. The marketing authorization holder has to demonstrate seriousness of disease/condition, that long-term treatment is necessary (more than 3 months), efficacy and cost-effectiveness to be granted reimbursement

<sup>125</sup> Only in some cases and it is not a major criterion

<sup>126</sup> Sometimes, in combination with budget impact

<sup>127</sup> The price of the product must be proportionate to that of the available alternatives when comparing the therapeutic usefulness

<sup>128</sup> Considered the same as cost-effectiveness

<sup>129</sup> However, it is not a major criterion

<sup>130</sup> Sometimes

<sup>131</sup> Patient need

<sup>132</sup> 1) Innovation (included in legal act) 2) availability and versatility of medicinal product (included in legal act) 3) Value of the medicine as indicated by the Medical Experts 4)

Recommendations given by organizations providing national guidance 5) Situation in other countries

<sup>133</sup> Experience and suitability

<sup>134</sup> a) health need of people, b) availability of alternatives, c) direct cost to health service users, d) government priorities, e) "such other criteria as PHARMAC thinks fit"

<b>Result table 6. Criteria used for reimbursement decisions (jurisdictions 16-31)</b>																
<b>X=applicable</b>	15. Latvia	16. Luxembourg	17. Malta	18. Netherlands	19. New Zealand	20. Norway	21. Poland	22. Portugal	23. Scotland <sup>120</sup>	24. Slovakia	25. Slovenia	26. Spain	27. Sweden	28. Switzerland	29. Turkey	30. USA
<b>Pharmaceuticals for inpatient use</b>																
Effectiveness	X	NA	X	X <sup>121, 139</sup>	X	NA	X	X	X <sup>140</sup>	X	X	X	x	NA	X	NA <sup>123</sup>
Safety	X	NA	X	X <sup>121, 139</sup>	X	NA	X	X	X <sup>140</sup>	X	X	X	x	NA	X	NA <sup>123</sup>
Severity of disease	X	NA	X	X <sup>141, 139</sup>	X	NA	X	X	X <sup>142</sup>	X		X	x	NA	X	NA <sup>123</sup>
Cost-effectiveness	X	NA	X	X	X	NA	X	X	X	X	X		x	NA	X	NA <sup>123</sup>
Cost containment	X	NA	X		X	NA						X <sup>143</sup>		NA		NA <sup>123</sup>
Value for money	X	NA	X		X	NA		X <sup>144</sup>	X <sup>144</sup>	X				NA		NA <sup>123</sup>
Budget impact	X	NA	X	X	X	NA	X	X		X	X	X		NA	X <sup>126</sup>	NA <sup>123</sup>
Ease of use (patient friendliness)		NA	X	X <sup>129</sup>	X	NA			X	X	X	X	(x) <sup>145</sup>	NA		NA <sup>123</sup>
Other, ...			X <sup>132</sup>	X <sup>133, 139</sup>	X <sup>146</sup>						X <sup>147</sup>	X <sup>136</sup>	X <sup>148</sup>			NA <sup>123</sup>

<sup>135</sup> 1) ethical aspects, 2) public priorities, 3) therapeutic value (if no comparison is available, 4) recommendations of reference sources (nice, CVZ etc)

<sup>136</sup> 1) the specific necessities of certain groups of people 2) the degree of innovation of the pharmaceutical 3) Existence of pharmaceuticals or other alternatives for the same diseases

<sup>137</sup> Marginal utility, which means that there are no other available pharmaceuticals or methods of treatment deemed considerably more suitable. This is generally also referred to as addition patient utility

<sup>138</sup> Daily therapy costs when comparing pharmaceuticals

<sup>139</sup> Only expensive hospital pharmaceuticals are evaluated that require additional funding. After 4 years they are re-evaluated

<sup>140</sup> The relative effectiveness/safety is considered

<sup>141</sup> Severity of disease is only considered at the re-evaluations after 4 years

<sup>142</sup> Only in some cases and it is not a major criterion

<sup>143</sup> The price of the product must be proportionate to that of the available alternatives when comparing the therapeutic usefulness

<sup>144</sup> Considered the same as cost-effectiveness

<sup>145</sup> sometimes

<sup>146</sup> a) health need of people, b) availability of alternatives c) direct cost to health service users d) government priorities e) "such other criteria as PHARMAC thinks fit"

<sup>147</sup> 1) ethical aspects, 2) public priorities, 3) therapeutic value (if no comparison is available, 4) recommendations of reference sources (nice, CVZ etc)

<sup>148</sup> Marginal utility, which means that there are no other available pharmaceuticals or methods of treatment deemed considerably more suitable. This is generally also referred to as addition patient utility

<b>Result table 6. Summary table: Criteria used for reimbursement decisions</b>				
<b>X= applicable</b>				
	<b>Number jurisdictions</b>	<b>Jurisdictions not applicable<sup>149</sup></b>	<b>X</b>	<b>%</b>
<b>Which criteria are used for reimbursement decisions of pharmaceuticals?</b>				
<b><i>Pharmaceuticals for outpatient use</i></b>	<b>30</b>	<b>2</b>		
Effectiveness			28	<b>100%</b>
Safety			27	<b>96%</b>
Severity of disease			21	<b>75%</b>
Cost-effectiveness			26	<b>93%</b>
Cost containment			7	<b>25%</b>
Value for money			14	<b>50%</b>
Budget impact			19	<b>68%</b>
Ease of use (patient friendliness)			17	<b>61%</b>
Other, ...			16	<b>57%</b>
<b><i>Pharmaceuticals for inpatient use</i></b>	<b>30</b>	<b>8</b>		
Effectiveness			22	<b>100%</b>
Safety			22	<b>100%</b>
Severity of disease			18	<b>82%</b>
Cost-effectiveness			20	<b>91%</b>
Cost containment			8	<b>36%</b>
Value for money			11	<b>50%</b>
Budget impact			17	<b>77%</b>
Ease of use (patient friendliness)			13	<b>59%</b>
Other, ...			13	<b>59%</b>

<sup>149</sup> Countries in which no national reimbursement evaluation is performed for pharmaceuticals for inpatient use

## Result table 7. Are (single) rapid and/or full assessments of pharmaceuticals performed and timeframe

<b>Result table 7. Are (single) rapid and/or full assessments of pharmaceuticals performed and timeframe (1-17)</b>	1. Australia	2. Austria	3. Belgium	4. Canada	5. Czech Republic	6. Denmark	7. England& Wales	8. Estonia	9. Finland	10. France	11. Germany	12. Hungary	13. Ireland	14. Italy
NA=not applicable Y=yes N=No														
Are rapid (single) technology* assessments of pharmaceuticals carried out in the jurisdiction to support decision making on reimbursement?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y <sup>150</sup>	Y	Y	Y
Are these subject to the timeframe of the Transparency Directive 89/105/EEC (e.g. a timeframe of 90/180 days)?	N	Y	Y	N	Y	Y	N	Y	Y	Y	N	Y	Y	Y
Are these subject to a different timeframe than the Transparency Directive?	Y <sup>151</sup>	NA	NA	Y <sup>152</sup>	Y <sup>153</sup>	NA	Y <sup>154</sup>	NA	NA	NA	Y <sup>150</sup>	NA	NA	NA
Are full assessments** of pharmaceuticals carried out in the jurisdiction to support decision making on reimbursement?	Y	Y	Y	Y	N	Y	Y	N	N	Y	Y	N	Y	Y <sup>155</sup>
Are these subject to a specific timeframe?	N	N	N	N	NA	N	Y <sup>156</sup>	NA	NA	N	N	NA	N	N

\* (Single) rapid assessment are assessments of a new pharmaceutical at the time of introduction to the market in comparison to one or more alternative interventions.

\*\* Full assessments of pharmaceuticals are assessments (non-rapid) of (all) available technology(ies) for a particular step in a treatment pathway or a specific condition.

<sup>150</sup> As of 1 January 2011 a new law was introduced, the *Arzneimittel marktneuordnungsgesetz* (law for pharmaceuticals that are introduced on the market). The law implies that for all new pharmaceuticals are assessed compared to an appropriate comparator within 3 months after introduction to the market

<sup>151</sup> All submissions lodged by the PBAC's due date are considered by PBAC within 17 weeks

<sup>152</sup> 19 to 25 weeks

<sup>153</sup> According to the Czech Law - approx. 75 and 160 days

<sup>154</sup> Approx 39 weeks

<sup>155</sup> This is a new initiative: the first assessment is currently ongoing

<sup>156</sup> Approx 54 weeks



<b>Result table 7. Are (single) rapid and/or full assessments of pharmaceuticals performed and timeframe (jurisdictions 16-31)</b>	15. Latvia	16. Luxembourg	17. Malta	18. Netherlands	19. New Zealand	20. Norway	21. Poland	22. Portugal	23. Scotland	24. Slovakia	25. Slovenia	26. Spain	27. Sweden	28. Switzerland	29. Turkey	30. USA
X=applicable																
Are rapid (single) technology* assessments of pharmaceuticals carried out in the jurisdiction to support decision making on reimbursement?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Are these subject to the timeframe of the Transparency Directive 89/105/EEC (e.g. a timeframe of 90/180 days)?	Y	Y	Y	Y	N	Y <sup>157</sup>	Y	Y	N	Y	Y	Y	Y	N	N	NA
If not subject to the Transparency Directive 89/105/EEC, are these subject to a different timeframe?	NA	NA	NA	NA	N	Y <sup>157</sup>	NA	NA	Y <sup>158</sup>	NA	NA	NA	NA	N	Y <sup>159</sup>	NA
Are full assessments** of pharmaceuticals carried out in the jurisdiction to support decision making on reimbursement?	Y	N	N	N <sup>160</sup>	Y	Y	Y	N <sup>161</sup>	N	N	Y	N <sup>162</sup>	Y	N <sup>163</sup>	Y	N
Are these subject to a specific timeframe?	N	NA	NA	NA	N	N	N	NA	NA	NA	N	NA	N	NA	Y <sup>159</sup>	NA

\* (Single) rapid assessment are assessments of a new pharmaceutical at the time of introduction to the market in comparison to one or more alternative interventions.

\*\* Full assessments of pharmaceuticals are assessments (non-rapid) of (all) available technology(y)(ies) for a particular step in a treatment pathway or a specific condition.n

<sup>157</sup> But not if the decision is passed on to the MoH. In that case there is no timeframe

<sup>158</sup> 18 weeks from the date of submission

<sup>159</sup> 3 months

<sup>160</sup> Full assessments are performed only very occasionally

<sup>161</sup> This will be introduced in 2011

<sup>162</sup> At national level, they are not. At regional level they are performed by agencies and hospitals to support decision making on rational use.

<sup>163</sup> In theory this could be performed, however it never has happened in practice

<b>Result table 7. Summary table: Are (single) rapid and/or full assessments of pharmaceuticals performed and timeframe</b>							
NA=not applicable Y=yes N=No							
	<b>Y</b>	<b>N</b>	<b>NA</b>	<b>Total</b>	<b>%Y</b>	<b>%N</b>	<b>Total</b>
Are rapid (single) technology* assessments of pharmaceuticals carried out in the jurisdiction to support decision making on reimbursement?	29	1	0	30	97%	3%	100%
Are these subject to the timeframe of the Transparency Directive 89/105/EEC (e.g. a timeframe of 90/180 days)?	21	8	1	30	72%	28%	100%
Are these subject to a different timeframe than the Transparency Directive?	8	2	20	30	80%	20%	100%
Are full assessments** of pharmaceuticals carried out in the jurisdiction to support decision making on reimbursement?	17	13	0	30	57%	43%	100%
Are these subject to a specific timeframe?	2	15	13	30	12%	88%	100%

\* (Single) rapid assessment are assessments of a new pharmaceutical at the time of introduction to the market in comparison to one or more alternative interventions.

\*\* Full assessments of pharmaceuticals are assessments (non-rapid) of (all) available technolog(y)(ies) for a particular step in a treatment pathway or a specific condition.

## Result table 8. Initiation of reimbursement assessment

Result table 8. Initiation of reimbursement assessment (jurisdictions 1-15)	1. Australia	2. Austria	3. Belgium	4. Canada <sup>164</sup>	5. Czech Republic	6. Denmark	7. England& Wales	8. Estonia	9. Finland	10. France	11. Germany	12. Hungary	13. Ireland	14. Italy
NA=no national reimbursement evaluation A=always S=sometimes N=never														
How is the reimbursement assessment initiated?														
All pharmaceuticals that receive marketing authorisation will automatically undergo a pricing/reimbursement evaluation:	N	N	N	N	N	N	N	N	N	N	S <sup>165</sup>	N	A <sup>166</sup>	N
Reimbursement application by manufacturer	A	A	A	A	S <sup>167</sup>	A	N	S	S <sup>168</sup>	S <sup>168</sup>	S <sup>169</sup>	S <sup>168</sup>	A	A
Initiated by organisation that performs the assessment	N <sup>170</sup>	S	S	N	S <sup>171</sup>	N	A <sup>172</sup>	S	S <sup>173</sup>	S <sup>174</sup>	S	S	N	N
Initiated by other agency, namely.....:	N <sup>170</sup>	N	S <sup>175</sup>	N	S <sup>176</sup>	N	N	S <sup>177</sup>	N	S <sup>178</sup>	S <sup>179</sup>	S <sup>180</sup>	A <sup>181</sup>	N

<sup>164</sup> Answer is applicable to common drug review programm

<sup>165</sup> This is the general procedure for all newly approved pharmaceuticals (i.e. pharmaceuticals with new active ingredients) after January 1, 2011 and all new indications of pharmaceuticals approved after January 1, 2011

<sup>166</sup> Since September 2009, the NCPE in collaboration with the HSE Corporate Pharmaceutical Unit (HSE-CPU), consider the cost-effectiveness of all new pharmaceuticals. In practice, all new pharmaceuticals are subjected to a preliminary rapid review. The term 'preliminary rapid review' as used describes a preliminary process whereby a quick review (4 weeks) of the new pharmaceutical is undertaken. The manufacturers submit initial briefing information per the following template:

<http://www.ncpe.ie/document.php?cid=26&sid=145&docid=200>

this information is reviewed and a decision made to a) reimburse the product or b) subject the pharmaceutical to a full pharmacoeconomic evaluation

<sup>167</sup> Mostly

<sup>168</sup> This is the general procedure and therefore most often applicable. For rapid assessment, the first assessment is always initiated following a reimbursement application by marketing authorisation holder

<sup>169</sup> In case new clinical data become available, a marketing authorisation holder can apply for a re-evaluation

<sup>170</sup> Since 1990, we have had more than 1500 "major" submissions, and less than 10 would have been not provided by the manufacturer/sponsor. These others would have been lodged by patient or prescriber groups and these usually resulted in pressure on the manufacturer to lodge a submission rather than a recommendation to list. At the very least, there needs to be confirmation from the manufacturer/sponsor that it is prepared to supply the pharmaceutical on the PBS and to propose the prices for listing. In addition, as the section on full assessments indicates, government and PBAC can initiate a review of current PBS listings, and often these are across multiple pharmaceuticals

<sup>171</sup> On a regular basis for reassessments

<sup>172</sup> Topic selection is done by NICE and the Department of Health together, involving the national horizon scanning centre and condition specific expert panels, all based on published criteria. After this, NICE does the scoping after which the Department of Health will refer to NICE of not

<sup>173</sup> The Pharmaceuticals Pricing Board may, on its own initiative, examine the reasonability of a medicinal product's wholesale price and reimbursement status and decide to terminate the confirmed wholesale price and reimbursement status

<b>Result table 8. Initiation of reimbursement assessment (jurisdictions 1-15)</b>															
<b>NA=no national reimbursement evaluation</b> <b>A=always</b> <b>S=sometimes</b> <b>N=never</b>															
	1. Australia	2. Austria	3. Belgium	4. Canada <sup>164</sup>	5. Czech Republic	6. Denmark	7. England& Wales	8. Estonia	9. Finland	10. France	11. Germany	12. Hungary	13. Ireland	14. Italy	
<b>Can the assessment be initiated pre-marketing authorisation?</b>	A	N	S <sup>182</sup>	S <sup>183</sup>	S <sup>184</sup>	A <sup>185</sup>	S <sup>186</sup>	N	N	S <sup>187</sup>	N	N	N	N	S <sup>188</sup>

<sup>174</sup> Re-assessment to maintain inscription on the list of reimbursed pharmaceuticals is every 5 years for pharmaceuticals listed for admission to community pharmacies and at any time for all drugs when significant new information is available. In addition, full assessment of pharmaceuticals (with the same indication and/or within the same pharmaceutical class) can be initiated according to HAS programm

<sup>175</sup> Ministry of Social affairs: they can suggest reclassifications of a group of pharmaceuticals

<sup>176</sup> Health insurers sometimes request reassessments

<sup>177</sup> Professional associations

<sup>178</sup> Full assessment of pharmaceuticals (with the same indication and/or within the same pharmaceutical class) are initiated on specific request from health authorities (disinvestment program, efficiency of therapeutic strategy of hypertension, statins) or according to HAS program (Growth hormones in patients without deficit, hypertension,...).

<sup>179</sup> Ministry of health or G-BA

<sup>180</sup> National Health Insurance Fund Administration of Hungary

<sup>181</sup> Health Service Executive

<sup>182</sup> Since December 2007, pharmaceutical companies are allowed to already submit class 1 reimbursement applications to the Reimbursement Committee, from the moment that they dispose of a positive advice of the CHMP (Committee for Medicinal Products for Human Use). In this case, the evaluation by the expert can start earlier, whilst the actual reimbursement procedure on Reimbursement Committee level can still only be launched after reception of the market authorisation

<sup>183</sup> Manufacturers may file a pre-NOC priority review submission within 60 to 90 days of the anticipated NOC or NOC/c, if the pharmaceutical meets one of the following criteria: 1) the new pharmaceutical is effective for the treatment of an immediately life-threatening disease or other serious disease for which it offers substantial improvements in clinically important outcome measures of effectiveness, safety, tolerability, and/or quality of life compared with other available therapies in Canada, or for which no comparable pharmaceutical is marketed in Canada; 2) or the new pharmaceutical, if listed by all CDR participating drug plans, has the potential to result in combined annual savings to the drug plans of at least \$2.5 million, based on the manufacturer's list price

<sup>184</sup> Only for the special treatment programme (e.g. in case of lack of a vital treatment)

<sup>185</sup> If a positive opinion has been issued by the CHMP or national body

<sup>186</sup> To provide timely guidance

<sup>187</sup> There is a HAS fast-track procedure through reimbursement for innovative health care products: Assessment starts before MA has been granted, and opinion can be issued a few weeks after marketing authorisation

<sup>188</sup> This is however the exemption: only if there is a specific need by the population

<b>Result table 8. Initiation of reimbursement assessment (jurisdictions 16-31)</b>	15. Latvia	16. Luxembourg	17. Malta	18. Netherlands	19. New Zealand	20. Norway	21. Poland	22. Portugal	23. Scotland	24. Slovakia	25. Slovenia	26. Spain	27. Sweden	28. Switzerland	29. Turkey	30. USA
<b>NA=no national reimbursement evaluation</b> <b>A=always</b> <b>S=sometimes</b> <b>N=never</b>																
<b>How is the reimbursement assessment initiated?</b>																
All pharmaceuticals that receive marketing authorisation will automatically undergo a pricing/reimbursement evaluation:	N	N	N	N	N	N	N	N	N <sup>189</sup>	N	N	A	N	N	N	NA
Reimbursement application by manufacturer	S	S	S <sup>190</sup>	S	S	A	S	A	A <sup>189</sup>	A	S	S <sup>191</sup>	S	S	A <sup>192</sup>	NA
Initiated by organisation that performs the assessment	S	S	N	S	S	N	N	N	N <sup>189</sup>	N	S <sup>193</sup>	A <sup>194</sup>	S	S <sup>195</sup>	N	NA
Initiated by other agency, namely.....:	S <sup>196</sup>	S <sup>197</sup>	S <sup>198</sup>	S <sup>199</sup>	S <sup>200</sup>	N	S <sup>201</sup>	N	N	N	S <sup>202</sup>	N	S <sup>203</sup>	N	N	NA
<b>Can the assessment be initiated pre-marketing authorisation?</b>	N	N	N	S <sup>204</sup>	S	N	N	N	S	N	N	S <sup>205</sup>	S <sup>206</sup>	S <sup>207</sup>	N	NA

<sup>189</sup> The SMC tracks all pharmaceuticals that received marketing authorisation. Subsequently marketing authorisation holders are actively approached to submit application for a product assessment. If the marketing authorisation holder refuses to submit an application the product will automatically receive a negative recommendation

<sup>190</sup> Most often

<sup>191</sup> In case of submissions by the marketing authorisation holder for increases of prices or exclusion from reimbursement

<sup>192</sup> Sometimes physicians indicate the need for a evaluation but then they ask the manufacturer to submit the application

<sup>193</sup> Mainly for exclusions from positive list

<sup>194</sup> Directorate-General for Pharmacy and Healthcare Products

<sup>195</sup> Federal Office of Public Health can initiate an assessment of a pharmaceutical if it is important for a treatment and there is no request from the marketing authorisation holder or if the office thinks it should be excluded from the positive list. In practice, initiations of reimbursement evaluations without application of the marketing authorisation holder rarely occurs

<sup>196</sup> Ministry of Health or health professionals' organisations

<sup>197</sup> Division de la Pharmacie et des médicaments

<sup>198</sup> More rarely, however the lead consultant of a specialty (working within the Public Sector) can make a request for a pharmaceutical to be introduced on the Government Formulary List

<sup>199</sup> Health insurer, individual physicians, patient organisations

<sup>200</sup> Health professionals, consumer groups or individuals

<sup>201</sup> MoH, NHF, national consultants in a medical field suitable for a particular health care service

<sup>202</sup> Clinics or hospital

<sup>203</sup> Organisation of county councils

<sup>204</sup> For instance if the EMA has granted fast approval

<sup>205</sup> Sometimes (very few times) the assessment is initiated before the marketing authorisation at request of the applicant as a kind of advise for special pharmaceuticals like radiopharmaceuticals, etc. In such a cases the most frequently item reviewed is the existence of similars

<sup>206</sup> An application can be submitted up to 3 months prior to marketing authorisation

<sup>207</sup> PreMA assessment can only be performed for princeps (not for generics)

<b>Result table 8. Summary table: Initiation of reimbursement assessment</b>										
	<b>A</b>	<b>S</b>	<b>N</b>	<b>Total</b>	<b>%A</b>	<b>%S</b>	<b>%N</b>	<b>Total</b>	<b>Number jurisdictions</b>	<b>Number jurisdictions NA</b>
<b>How is the reimbursement assessment initiated?</b>										
All pharmaceuticals that receive marketing authorisation will automatically undergo a pricing/reimbursement evaluation:	2	1	26	29	<b>7%</b>	<b>3%</b>	<b>90%</b>	<b>100%</b>	30	1
Reimbursement application by manufacturer	12	16	1	29	<b>41%</b>	<b>55%</b>	<b>3%</b>	<b>100%</b>		
Initiated by organisation that performs the assessment	2	15	12	29	<b>7%</b>	<b>52%</b>	<b>41%</b>	<b>100%</b>		
Initiated by other agency, namely.....:	1	14	14	29	<b>3%</b>	<b>48%</b>	<b>48%</b>	<b>100%</b>		
<b>Can the assessment be initiated pre-marketing authorisation?</b>	2	12	15	29	<b>7%</b>	<b>41%</b>	<b>52%</b>	<b>100%</b>		

**Result table 9. Agencies/organisations involved in reimbursement decisions**

	<b>Agency/organisation that performs the (single) rapid assessment*</b>	<b>Agency/organisation that performs the Full assessment</b>	<b>Agency/organisation that provides advice for making a reimbursement decision</b>	<b>Agency/organisation that makes the reimbursement decision</b>	<b>(Independent) committee that is involved in the process</b>
1. Australia	Pharmaceutical Benefits Advisory Committee (PBAC)	PBAC <sup>208</sup>	PBAC	Department of Health and Ageing	Pharmaceutical Benefits Advisory Committee (PBAC), Economics Sub-Committee (ESC) <sup>209</sup> , and Drug Utilisation Sub-Committee (DUSC) <sup>210</sup>
2. Austria	Pharmaceutical Evaluation Board (HEK, Heilmittel-Evaluierungskommission)	HEK	Main Association of Austrian Social Security Institutions (HBV, Hauptverband der österreichischen Sozialversicherungsträger), HEK	HBV	Independent Pharmaceutical Commission (UHK, Unabhängige Heilmittelkommission) >> for appeal procedures
3. Belgium	INAMI (FR)/RIZIV (NL) <sup>211</sup> (Institut national d'assurance maladie-invalidité/ RijksInstituut voor Ziekte- en InvaliditeitsVerzekering)	INAMI/RIZIV	INAMI/RIZIV	Ministry of Social Affairs	Reimbursement Committee (CTG)
4. Canada	Canadian Agency for Drugs and Technologies in Health (CADTH)	CADTH	CADTH	Health care plan for each province/territory (often within a ministry of health)	The Canadian Expert Drug Advisory Committee (CEDAC)
5. Czech Republic	SÚKL (State Institute for Drug Control)	NA	SÚKL (State Institute for Drug Control)	SÚKL (State Institute for Drug Control). In case of an appeal by the Marketing Authorisation Holder the Ministry of Health will make a decision.	NA

<sup>208</sup> A few times there have been "multi-technology assessment" submissions from groups of manufacturers/sponsors in the context of a review of current PBS listings

<sup>209</sup> The Economics Sub-Committee assesses the clinical and economic analyses required of all major applications to the PBS

<sup>210</sup> The Drug Utilisation Sub-Committee assesses forecasts of pharmaceutical use

<sup>211</sup> German abbreviation of the institute: LIKIV: 'Landesinstitut für Kranken- und Invalidenversicherung'. English abbreviation of the institute (NIHDI: 'National Institute for Health) and Disability Insurance'

	<b>Agency/organisation that performs the (single) rapid assessment*</b>	<b>Agency/organisation that performs the Full assessment</b>	<b>Agency/organisation that provides advice for making a reimbursement decision</b>	<b>Agency/organisation that makes the reimbursement decision</b>	<b>(Independent) committee that is involved in the process</b>
6. Denmark	Danish Medicines Agency (DKMA)	DKMA	DKMA (The Reimbursement Committee of the Danish Medicines Agency)	DKMA	The Reimbursement Committee of the Danish Medicines Agency <sup>212213</sup>
7. England& Wales	Product sponsor and academic group	Academic group and stakeholders	National institute of clinical excellence (NICE), HTA agency and experts nominated by stakeholders and selected by Appraisal Committee Chair	NICE, Primary Care Trust <sup>214</sup>	Technology appraisal committee
8. Estonia	Estonian Health Insurance Fund (EHIF)	NA	Pharmaceutical Committee based on input from State Agency of Medicines (SAM) and EHIF	Ministry of Health	Pharmaceutical Committee
9. Finland	The Pharmaceuticals Pricing Board (HILA), which is affiliated to the Ministry of Social Affairs and Health (STM)	NA	HILA, Expert group within HILA, Social Insurance Institution of Finland (Kela)	HILA	Not applicable
10. France	Haute Autorité de Santé (HAS) (French National Authority for Health)	HAS	HAS	Ministry of Health and Social Affairs (Ministère de la Santé et des Affaires Sociales)	Commission de la Transparence (Transparency Committee)
11. Germany	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) or Gemeinsamer Bundesausschuss (G-BA – Federal Joint Committee) or third party	IQWiG or G-BA	IQWiG <sup>215</sup> and G-BA committee (Unterausschuss Arzneimittel)	G-BA plenum	G-BA committee (Unterausschuss Arzneimittel)
12. Hungary	ESKI (National Institute for Strategic Health Research)	NA	National Health Insurance Fund Administration (NHFHA), the Health Technology	NHFHA: The Head of the Pharmaceutical Department for outpatient	TAC

<sup>212</sup> The Committee consists of 6 medical doctors and one representative from The Danish Regions (Payer)

<sup>213</sup> Recommends to the DKMA (step 2)

<sup>214</sup> Decisions of NICE with positive outcome are obliged to be adopted, however negative decisions not

<sup>215</sup> IQWiG provides a recommendation for the interpretation of the evidence. The recommendation as to whether the health technology can/should be funded is made by a G-BA committee (Unterausschuss Arzneimittel). The decision on funding is made by the G-BA plenum



	<b>Agency/organisation that performs the (single) rapid assessment*</b>	<b>Agency/organisation that performs the Full assessment</b>	<b>Agency/organisation that provides advice for making a reimbursement decision</b>	<b>Agency/organisation that makes the reimbursement decision</b>	<b>(Independent) committee that is involved in the process</b>
			Assessment Institute, and the Technology Appraisal Committee (TAC)	pharmaceuticals; the Head of Department of Curative-Preventive Provisions for hospital-only medicine(s)	
13. Ireland	National Centre for Pharmacoeconomics (NCPE)	Stakeholders. Academic Groups, NCPE, Health Information and Quality Authority (HIQA)	NCPE, HIQA	Health Service Executive (HSE), Department of Health and Children	NA
14. Italy	The Technical Scientific Committee (CTS) within the AIFA (Agenzia Italiana del Farmaco)	CTS within the AIFA	CTS within the AIFA	CTS within the AIFA. The pricing decision is made by the CPR (committee for pricing and reimbursement)	The Technical Scientific Committee
15. Latvia	The Centre of Health Economics of Latvia (CHE)	CHE	CHE	CHE	NA
16. Luxembourg	Ministère de la Sécurité Sociale, Contrôle médical: Department of medical control	NA	Ministère de la Sécurité Sociale, Contrôle médical: Department of medical control <a href="http://www.mss.etat.lu">www.mss.etat.lu</a>	Caisse nationale de santé (CNS)	NA
17. Malta	Ministry for Health, the Elderly and Community Care (The pharmacists at the Directorate of Pharmaceutical Policy and Monitoring)	NA	Ministry for Health, the Elderly and Community Care: The Government Formulary List Advisory Committee (GFLAC)	Ministry for Health, the Elderly and Community Care (the Superintendent of Public Health)	The Government Formulary List Advisory Committee (GFLAC)
18. Netherlands	Health Care Insurance Board (CVZ)	NA	CVZ	Ministry of Health, Welfare and Sport (VWS)	Medicinal Products Reimbursement Committee, Appraisal Committee <sup>216</sup>
19. New Zealand	Pharmaceutical Management Agency (PHARMAC)	PHARMAC	PHARMAC	PHARMAC for outpatient pharmaceuticals, Ministry of Health for vaccines	Pharmacology and Therapeutics Advisory Committee (PTAC) & various Subcommittees for specific therapy areas

<sup>216</sup> This committee is only involved in case of re-evaluation after 4 years of expensive hospital pharmaceuticals

	<b>Agency/organisation that performs the (single) rapid assessment*</b>	<b>Agency/organisation that performs the Full assessment</b>	<b>Agency/organisation that provides advice for making a reimbursement decision</b>	<b>Agency/organisation that makes the reimbursement decision</b>	<b>(Independent) committee that is involved in the process</b>
20. Norway	Norwegian Medicines Agency	Norwegian Knowledge Center for the Health Services (NOKC)	Norwegian Medicines Agency	Ministry of Health and Care Services, Norwegian Medicines Agency <sup>217</sup>	National advisory committee for drug reimbursement
21. Poland	Agency for Health Technology Assessment in Poland (AHTAPol)	AHTAPol <sup>218</sup>	AHTAPol and National Health Fund	Ministry of Health	Consultative Council <sup>219</sup>
22. Portugal	INFARMED (National Authority of Medicines and Health Products)	NA	INFARMED	Ministry of Health	NA
23. Scotland	Scottish Medicines Consortium (SMC)	NA	SMC	Regional Health Authority	SMC is an expert committee <sup>220</sup>
24. Slovakia	Subcommittees of the Categorisation Committee for drugs of the Ministry of Health <sup>221</sup>	NA	Categorisation Committee for drugs of the Ministry of Health	Ministry of Health	Categorisation Committee for drugs of the Ministry of Health
25. Slovenia	The Health Insurance Institute (ZZZS)	ZZZS	Committee for Reimbursement of Pharmaceuticals (ZZZS)	ZZZS	Committee for Reimbursement of Pharmaceuticals
26. Spain	Directorate-General for Pharmacy and Healthcare Products at the Ministry of Health, Social Policy and Equality	NA <sup>222</sup>	Directorate-General for Pharmacy and Healthcare Products at the Ministry of Health, Social Policy and Equality	Directorate-General for Pharmacy and Healthcare Products at the Ministry of Health, Social Policy and Equality, Region	Interministerial Pricing Committee
27. Sweden	TLV (Dental and Pharmaceuticals Benefits Board)	SBU	TLV and National Board of Health and Welfare	TLV	there is no independent committee, it is the TLV's committee

<sup>217</sup> Can make decision in case of 1) generic product, new strength, formulation or package size and no more costly than already reimbursed product 2) in case of new chemical entity, new combination or new indication and if the annual incremental fiscal impact does not exceed NOK 5 mill 5 years after approval

<sup>218</sup> Often assessment is performed by subcontractors but under responsibility of AHTAPol

<sup>219</sup> The Consultative Council works within AHTAPol but gives the recommendations independently

<sup>220</sup> The SMC is a consortium of stakeholders from Area Drug and Therapeutic Committees (ADTCs) and representation is derived from ADTCs across NHS Scotland. It includes physicians, pharmacists, health service managers, patients, health economists and representatives of product sponsors

<sup>221</sup> There are 22 medical subcommittees which are organised according to medical specialty. These subcommittees perform the assessments. In addition, there is one pharmacoeconomic subcommittee

<sup>222</sup> At regional level, health technologies agencies and hospitals perform full assessments to support decision making on rational use

	Agency/organisation that performs the (single) rapid assessment*	Agency/organisation that performs the Full assessment	Agency/organisation that provides advice for making a reimbursement decision	Agency/organisation that makes the reimbursement decision	(Independent) committee that is involved in the process
28. Switzerland	Federal Medicines Commission	NA	Federal Medicines Commission	Federal Office of Public Health (Ministry of Health)	Federal Medicines Commission
29. Turkey	The Social Security Institution (SSI)	SSI	SSI and Ministry of Health (MoH) <sup>223</sup>	SSI <sup>224</sup> and MoH	The Medical and Economic Evaluation Commission (MEEC) and the Reimbursement Commission (RC) (both fall under the SSI)
30. USA	There are a number of centre's that provide systematic reviews <sup>225</sup>	There are a number of centre's that provide systematic reviews <sup>225</sup>	There are a number of centre's that provide systematic reviews. <sup>225</sup>	Health plans decide on reimbursement of pharmaceuticals	NA

\* Often based on dossier submitted by product sponsor

NA= not applicable >> No rapid or full assessment performed in this jurisdiction

<sup>223</sup> The Medical and Economic Evaluation Commission (MEEC) that falls under the SSI evaluates all applications and declare a decision. The MoH is represented in the MEEC.

<sup>224</sup> The Reimbursement Commission (RC) that falls under the SSI finalises the decision which was prepared by the MEEC

<sup>225</sup> The Blue Cross Blue Shield (BCBS), Centres for Medicare and Medicaid Services (CMS) commission systematic reviews in its National Coverage Decisions(NCD). Another US based group, the Drug Effectiveness Review (DER) and the Department of Veterans Affairs (VA) undertake pharmaceuticals reviews

## Result table 10. Stakeholder involvement

Result table 10. Stakeholder involvement (jurisdictions 1-15)														
<b>NA=no national reimbursement evaluation</b> <b>P=provide data</b> <b>G=general consultation</b> <b>E=expert involvement</b> <b>O=other,.....</b>														
	1. Australia	2. Austria	3. Belgium	4. Canada	5. Czech Republic	6. Denmark	7. England& Wales	8. Estonia	9. Finland	10. France	11. Germany	12. Hungary	13. Ireland	14. Italy
Which modes of involvement are applicable to the stakeholders mentioned below in the pricing/reimbursement process (multiple modes can be applicable to one type of stakeholder) <sup>226</sup>														
Industry	P	P	PGE <sup>227</sup>	PG	PG <sup>228</sup>	P	PGE	PGE	P	P	PG	P G E	PG	PE <sup>229</sup>
Patients	G		P <sup>230</sup>	G	G <sup>228</sup>		PGE	GE		O <sup>231</sup>	GE			G
Medical doctors	G	E <sup>232</sup>	E <sup>227</sup>	E	E	GE <sup>233</sup>	PGE	GE	E	PE <sup>234</sup>	GE	PG	E	E <sup>235</sup>
Pharmacists		E <sup>232</sup>	E <sup>227</sup>	E			PGE	G		PE <sup>234</sup>	G	G	E	E <sup>235</sup>
Payer			E <sup>227</sup>		PG <sup>228</sup>	E <sup>233</sup>	PGE	PGE	G	P <sup>236</sup>		PGE		E <sup>235</sup>
Other stakeholder, .....								PGE <sup>237</sup>						

<sup>226</sup> Other roles of stakeholder than discussed in results table 8 (who is the initiator of the assessment) and results table 9 (agencies/organisations involved in the assessment/appraisal phase)

<sup>227</sup> Represented in CTG

<sup>228</sup> All data (assessment, data used and decision) are open to public. Anyone can comment on the document. In general this is mostly done by the Marketing Authorisation Holder and health insurers

<sup>229</sup> During price negotiations

<sup>230</sup> On occasion they send letters to CTG which may be discussed in the committee

<sup>231</sup> Optional hearing of patients association at the Transparency Committee

<sup>232</sup> Included in HEK

<sup>233</sup> The Committee consists of 6 medical doctors and one representative from The Danish Regions (Payer)

<sup>234</sup> Hearing of experts and member of Transparency committee

<sup>235</sup> As member of the CTS and CPR

<sup>236</sup> Payers are present at the Transparency Committee, provide data but can not vote

<sup>237</sup> Any interested body can initiate the process for excluding a pharmaceutical from the positive list or for changing the conditions under which the pharmaceutical is reimbursed. In this case the initiator also has to apply all relevant data. In such a case this party is the initiator, data provider and also expert if needed. The expert opinion of the market authorisation holder is also requested

10. Please indicate with a cross if different modes of involvement are applicable to the stakeholders mentioned below in the pricing/reimbursement process (multiple modes can be applicable to one type of stakeholder) <sup>238</sup> . (jurisdictions 16-31)	15. Latvia	16. Luxembourg	17. Malta	18. Netherlands	19. New Zealand	20. Norway	21. Poland	22. Portugal	23. Scotland	24. Slovakia	25. Slovenia	26. Spain	27. Sweden	28. Switzerland	29. Turkey	30. USA
<b>NA=no national reimbursement evaluation</b> <b>P=provide data</b> <b>G=general consultation</b> <b>E=expert involvement</b> <b>O=other,.....</b>																
Industry	P	PG	P	PG	PG	PG	P	PG	PGE <sup>239</sup>	P	P	PG	PG	PE <sup>240</sup>	PE <sup>241</sup>	NA
Patients			GE <sup>242</sup>	G	PG	G <sup>243</sup>	G		E <sup>244</sup>			O <sup>245</sup>	E	E <sup>240</sup>		NA
Medical doctors	E		PGE	PGE	PGE	E	PGE		GE <sup>244</sup>	E	E <sup>246</sup>	E	E	E <sup>240</sup>	GE	NA
Pharmacists	E		PG	E	PGE				GE <sup>244</sup>		E <sup>246</sup>	PGE	E	E <sup>240</sup>	GE	NA
Payer	P		<sup>247</sup>	G	PG		PG		GE <sup>244</sup>	E	E	P	N	E <sup>240</sup>	PGE	NA
Other stakeholder, .....			PGE <sup>248,249</sup>										G <sup>250</sup> E <sup>251</sup>	E <sup>252</sup>		NA

<sup>238</sup> Stakeholder as discussed in results table 8 (who is the initiator of the assessment) and results table 9 (agencies/organisations involved in the assessment/appraisal phase)

<sup>239</sup> 2 representatives of product sponsors are included in the SMC

<sup>240</sup> These stakeholders are represented in the Federal Medicines Commission

<sup>241</sup> there is a committee from industry that provides expert involvement

<sup>242</sup> A patient representative is a member of the GFLAC

<sup>243</sup> Patient organisation

<sup>244</sup> SMC

<sup>245</sup> Claims from patient organisations

<sup>246</sup> Included in pharmaceutical committee

<sup>247</sup> There is no national payer

<sup>248</sup> Priorities of the Government are taken into consideration

<sup>249</sup> These stakeholders include: National Antibiotic Committee; Diabetes Association; Advisory Committee for Immunization Practices; etc

<sup>250</sup> The TLV gathers informal opinions on the draft of the final report from the county councils through the Pharmaceutical Benefits Group for County Councils, pharmaceutical companies concerned, TLV's user council, and concerned disabled and pensioners' organisations

<sup>251</sup> User groups through the concerned disabled and pensioners' organisations, county council's pharmaceutical benefits group, the Swedish Association of the Pharmaceutical Industry (LIF), Chairperson of the Medical Committees (LOK), The Medical Products Agency, SBU, The National Board of Health and Welfare, Swedish Society of Medicine, and the Swedish Medical Association

<sup>252</sup> The Federal Medicines Commission also has 1 members from the hospitals 1 members from the Swiss cantons and 1 member of the licensing authority Swissmedic

<b>Result table 10. Summary table: Stakeholder involvement</b>											
NA=no national reimbursement evaluation  P=provide data G=general consultation E=expert involvement O=other,.....											
		<b>P</b>	<b>G</b>	<b>E</b>	<b>O</b>	<b>NA</b>		<b>%P</b>	<b>%G</b>	<b>%E</b>	<b>%O</b>
<b>Which modes of involvement are applicable to the stakeholders mentioned below in the pricing/reimbursement process (multiple modes can be applicable to one type of stakeholder)<sup>253</sup>.</b>											
Industry		29	16	7	0	1		100%	55%	24%	0%
Patients		3	12	7	2	1		10%	41%	24%	7%
Medical doctors		7	12	26	0	1		24%	41%	90%	0%
Pharmacists		5	9	15	0	1		17%	31%	52%	0%
Payer		10	10	12	0	1		34%	34%	41%	0%
Other stakeholder, .....		2	3	4	0	1		7%	10%	14%	0%

<sup>253</sup> Stakeholder as discussed in results table 8 (who is the initiator of the assessment) and results table 9 (agencies/organisations involved in the assessment/appraisal phase)

**Result table 11. Characteristics of the reimbursement process**

<b>Result table 11. Characteristics of the reimbursement process. (jurisdictions 1-15)</b>  <b>NA=no national reimbursement evaluation</b> <b>A=always</b> <b>S=sometimes</b> <b>N=never</b>	1. Australia	2. Austria	3. Belgium	4. Canada	5. Czech Republic	6. Denmark	7. England& Wales	8. Estonia	9. Finland	10. France	11. Germany	12. Hungary	13. Ireland	14. Italy
Is the reimbursement evaluation separated into an assessment and an appraisal phase?	A	S	N	NA <sup>254</sup>	N	N	A	A	N	A	A	A	A	A
Is there a process by which the product sponsors can appeal a decision by the government entity?	A	A	A	NA <sup>255</sup>	A	A <sup>256</sup>	A	A	A	A	S <sup>257</sup>	A	A	A
Is there a fixed procedure for reviewing previous reimbursement evaluations?	A	S	A <sup>258</sup>	NA <sup>254</sup>	A	A	A	N	A	A <sup>259</sup>	N <sup>260</sup>	S	N	S

<sup>254</sup> In Canada, a Common Drug Review evaluates manufacturers' applications for drug coverage on behalf of more than a dozen different federal, provincial, and territorial drug benefit programs. Because the participating drug plans have made the Common Drug Review a requirement for coverage, Common Drug Review evaluates virtually every product on the market. However, recommendations of the Common Drug Review are not binding; each of the participating drug programs retains authority over final coverage decisions

<sup>255</sup> In Canada, a Common Drug Review evaluates manufacturers' applications for drug coverage on behalf of more than a dozen different federal, provincial, and territorial drug benefit programs. Because the participating drug plans have made the Common Drug Review a requirement for coverage, Common Drug Review evaluates virtually every product on the market. However, recommendations of the Common Drug Review are not binding; each of the participating drug programs retains authority over final coverage decisions. There is however a process by which product sponsors can submit a 'request for reconsideration' (similar to appealing a recommendation) for the Common Drug Review programme

<sup>256</sup> The decision cannot be appealed, but the procedure can

<sup>257</sup> G-BA is not a government entity

<sup>258</sup> The Royal Decree of 21 December 2001 imposes an individual review of pharmaceuticals of class 1 (innovative pharmaceuticals) within a period of 18 months to 3 years after admission

<sup>259</sup> A fixed review procedure is applicable to pharmaceuticals for outpatient use: every 5 years. This is not applicable to pharmaceuticals for inpatient use. In addition, all pharmaceuticals can be re-evaluated at any time if relevant new information is available

<sup>260</sup> Marketing authorisation holders can request a new assessment when relevant new scientific data are available however there is no fixed procedure to always re-evaluate previous recommendations after a given period

<b>Result table 11. Characteristics of the reimbursement process (jurisdictions 16-31)</b>  <b>NA=no national reimbursement evaluation</b> <b>A=always</b> <b>S=sometimes</b> <b>N=never</b>	15. Latvia	16. Luxembourg	17. Malta	18. Netherlands	19. New Zealand	20. Norway	21. Poland	22. Portugal	23. Scotland	24. Slovakia	25. Slovenia	26. Spain	27. Sweden	28. Switzerland	29. Turkey	30. USA
Is the reimbursement evaluation separated into an assessment and an appraisal phase?	N	N	A	S	A	S	A	A	A	N	N	N	N	N	A	NA
Is there a process by which the product sponsors can appeal a decision by the government entity?	A	A	A	A <sup>261</sup>	N	A	N	A <sup>262</sup>	A <sup>263</sup>	A	A	A	A	A	A	NA
Is there a fixed procedure for reviewing previous reimbursement evaluations (are there always re-evaluations after a given period)?	N	S	S	N	N	N	N	S	N	A	S	S <sup>264</sup>	N	A	N	NA

<sup>261</sup> They can go to court

<sup>262</sup> If the decision is negative, the company can appeal to the supreme administrative court

<sup>263</sup> The product sponsor can request a review by an independent review panel (only 4 times in the last 10 years) and in case of new data a reassessment can be requested

<sup>264</sup> For selected pharmaceuticals like orphans and innovations with high impact on the budget



<b>Result table 11. Characteristics of the reimbursement process</b>  NA=no national reimbursement evaluation A=always S=sometimes N=never	<b>Number jurisdictions</b>	<b>Number jurisdictions NA</b>	<b>A</b>	<b>S</b>	<b>N</b>	<b>Total</b>	<b>%A</b>	<b>%S</b>	<b>%N</b>	<b>Total</b>
Is the reimbursement evaluation separated into an assessment and an appraisal phase?	30	2	13	4	11	28	46%	14%	39%	100%
Is there a process by which the product sponsors can appeal a decision by the government entity?	30	2	25	0	3	28	89%	0%	11%	100%
Is there a fixed procedure for reviewing previous reimbursement evaluations?	30	2	9	8	11	28	32%	29%	39%	100%

## Result table 12. Purpose of the assessment

Result table 12a. Purpose of the assessment: (single) rapid assessment (1-16)															
A=always S=sometimes N=never															
	1. Australia	2. Austria	3. Belgium	4. Canada	5. Czech Republic	6. Denmark	7. England & Wales	8. Estonia	9. Finland	10. France	11. Germany	12. Hungary	13. Ireland	14. Italy	
What is the purpose of the (single) rapid assessment?															
support reimbursement decisions	A	A	A	A	A	A	A	A	A	A	S	A	A	A	
support pricing decisions	A	A	A	N	N	N	N	A	A	A	A	S	A	A	
support guidance	N	N	A	N	N	N	A	S	N	A <sup>265</sup>	S	N	N	S	
other, .....	N	N	N	N	N	N	N	N	N	N	N	N	N	N	

Result table 12a. Purpose of the assessment (single) rapid assessment (jurisdictions 16-31)																
NA= Not applicable (no (single) rapid assessment in jurisdiction) A=always S=sometimes N=never																
	15. Latvia	16. Luxembourg	17. Malta	18. Netherlands	19. New Zealand	20. Norway	21. Poland	22. Portugal	23. Scotland	24. Slovakia	25. Slovenia	26. Spain	27. Sweden	28. Switzerland	29. Turkey	30. USA
What is the purpose of the (single) rapid assessment?																
support reimbursement decisions	A	A	A	A	A	A	A	A	A	A	A	A	A	A <sup>266</sup>	A	NA
support pricing decisions	A	A	A	N	S	A	A	N <sup>267</sup>	N	S	N	A	N	A	N	NA
Support guidance	S	N	A	A <sup>268</sup>	S	N	N	N	S <sup>269</sup>	S	N	N	N	N	N	NA
other, .....	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	NA

<sup>265</sup> Target population, Recommendation on best use.

<sup>266</sup> Occasionally a limitation is set for a whole class of pharmaceuticals (within the authorised indication)

<sup>267</sup> However, a new lower price can be negotiated during the reimbursement process. That new price becomes the maximum authorized retail price

<sup>268</sup> The Pharmacotherapeutic Compass ("Farmacotherapeutisch Kompas") gives information about pharmaceuticals available in the Netherlands. Every pharmaceutical is provided with an advice on prescription based on the assessment (pharmacotherapeutic and economic grounds). This website is primarily meant for doctors and pharmacists

<sup>269</sup> The recommendation might be incorporated in guidance documents

<b>Result table 12a. Summary table: Purpose of the assessment (single) rapid assessment</b>  NA=not applicable A=always S=sometimes N=never	Number of jurisdictions	NA		A	S	N	Total	%A	%S	%N	Total
<b>What is the purpose of the (single) rapid assessment?</b>											
support reimbursement decisions	30	1		28	1	0	29	97%	3%	0%	100%
support pricing decisions	30	1		16	3	10	29	55%	10%	34%	100%
support clinical guidance	30	1		5	7	17	29	17%	24%	59%	100%
other, .....	30	1		0	0	29	29	0%	0%	100%	100%

<b>Result table 12b. Purpose of the assessment: full assessment (jurisdictions 1-15)</b>	1. Australia	2. Austria	3. Belgium	4. Canada	5. Czech Republic	6. Denmark	7. England& Wales	8. Estonia	9. Finland	10. France	11. Germany	12. Hungary	13. Ireland	14. Italy
<b>NA=not applicable (no full assessment in this jurisdiction)</b> <b>A=always</b> <b>S=sometimes</b> <b>N=never</b>														
<b>What is the purpose of the full assessment?</b>														
support reimbursement decisions	A	A	A	S	NA	A	A	NA	NA	A	S	NA	S	A
support pricing decisions	A	A	A	N	NA	N	N	NA	NA	S	S	NA	S	A
support clinical guidance	N	N	A	S	NA	N	A	NA	NA	N	S	NA	N	A <sup>270</sup>
other, .....	N	N	N	N	NA	N	N	NA	NA	N	N	NA	N	N

<b>Result table 12b. Purpose of the assessment: full assessment (jurisdictions 16-31)</b>	15. Latvia	16. Luxembourg	17. Malta	18. Netherlands	19. New Zealand	20. Norway	21. Poland	22. Portugal	23. Scotland	24. Slovakia	25. Slovenia	26. Spain	27. Sweden	28. Switzerland	29. Turkey	30. USA
<b>NA=not applicable (no full assessment in this jurisdiction)</b> <b>A=always</b> <b>S=sometimes</b> <b>N=never</b>																
<b>What is the purpose of the full assessment?</b>																
support reimbursement decisions	A	NA	NA	NA	A	S	A	NA	N	NA	A	NA	A	NA	A	NA
support pricing decisions	A	NA	NA	NA	S	N	S	NA	N	NA	N	NA	S	NA	N	NA
support clinical guidance	S	NA	NA	NA	S	S	N	NA	N	NA	N	NA	A	NA	N	NA
other, .....	N	NA	NA	NA	N	N	N	NA	N	NA	N	NA	N	NA	N	NA

<sup>270</sup> To inform about good prescribing

Result table 12b. Summary table: Purpose of the assessment: full assessment	Number of jurisdictions	NA										
NA=not applicable A=always S=sometimes N=never				A	S	N	Total	%A	%S	%N	Total	
What is the purpose of the full assessment?												
support reimbursement decisions	30	13			13	4	0	17	76%	24%	0%	100%
support pricing decisions	30	13			5	6	6	17	29%	35%	35%	100%
support clinical guidance	30	13			4	5	8	17	24%	29%	47%	100%
other, .....	30	13			0	0	17	17	0%	0%	100%	100%

**Result table 13. Status of advice based on the assessment**

<b>Result table 13a. Status of advice based on the assessment: (Single) rapid assessment (jurisdictions 1-15)</b>  <b>NA= Not applicable (no (single) rapid assessment in jurisdiction)</b> <b>A=always</b> <b>S=sometimes</b> <b>N=never</b>															
	1. Australia	2. Austria	3. Belgium	4. Canada	5. Czech Republic	6. Denmark	7. England & Wales	8. Estonia	9. Finland	10. France	11. Germany	12. Hungary	13. Ireland	14. Italy	
<b>What is the status of the advice that are based on the assessment?</b>															
Advice to decision making body	S <sup>271</sup>	A	A	A	N	N	S	A	N	A	A	A	A	N	
Legislative (e.g. binding by law)	S <sup>272</sup>	N	N	N	A	A	S <sup>273</sup>	N	A	N	N	N	N	A	
(Clinical) guidance	N	N	A	N	S <sup>274</sup>	N	N	S	N	N	N	N	N	S	
Other, ....	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
<b>Are the assessments &amp; advice made public (complete or in summary form)?</b>															
Are the assessments made public (complete or in summary form)?	A	N	A	A	A	N	A	A	N	A	A	N	A	A <sup>275</sup>	
Available in English?	A	N	N	A	N	N	A	N	N	S	A <sup>276</sup>	N	A	N	
Is the advice made public (complete or in summary form)?	A	N	A	A	A	A	A	A	N	A	A	N	A	A	
Available in English?	A	N	N	A	N	N	A	N	N	S	N <sup>276</sup>	N	A	N	

<sup>271</sup> Each PBAC decision to recommend a pharmaceutical is advice to government, which makes the final decision about whether to add the pharmaceutical to the PBS

<sup>272</sup> Each PBAC decision not to recommend is binding by law: government cannot add the pharmaceutical to the PBS

<sup>273</sup> Only the positive decisions are mandatory. Negative recommendations are not

<sup>274</sup> Limitation for specialisation of prescribing physician or indication's limitation

<sup>275</sup> In summary form

<sup>276</sup> The recommendations for interpretation of the evidence (the outcome of the assessment report are available in English) but the recommendation made after the appraisal by G-BA are not available in English

<b>Result table 13a. Status of advice based on the assessment: (Single) rapid assessment (jurisdictions 16-31)</b>	15. Latvia	16. Luxembourg	17. Malta	18. Netherlands	19. New Zealand	20. Norway	21. Poland	22. Portugal	23. Scotland	24. Slovakia	25. Slovenia	26. Spain	27. Sweden	28. Switzerland	29. Turkey	30. USA
<b>NA= Not applicable (no (single) rapid assessment in jurisdiction)</b> <b>A=always</b> <b>S=sometimes</b> <b>N=never</b>																
<b>What is the status of the advice that are based on the assessment?</b>																
Advice to decision making body	A	A	A	A	A	S <sup>277</sup>	A	A	A	A	N	A	N	A	A	NA
Legislative (e.g. binding by law)	A	A	A	S <sup>278</sup>	N	S	N	N	N	N	A	N	A	N	N	NA
(Clinical) guidance	S	N	A	A <sup>279</sup>	S	N	N	N	N	N	S <sup>280</sup>	N	N	N	N	NA
Other, ....	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	NA
<b>Are the assessments &amp; advice made public (complete or in summary form)?</b>																
Are the assessments made public (complete or in summary form)?	A	N	N	A	S	S	S	S <sup>281</sup>	A <sup>282</sup>	A	N	N	N	N <sup>283</sup>	N	NA
Available in English?	N	N	NA	S	A	N	S	S	A	N	N	N	NA	NA	NA	NA
Is the advice made public (complete or in summary form)?	A	N	S	A	S <sup>284</sup>	S	A	S <sup>281</sup>	A	A	A	N	A	N	N	NA
Available in English?	N	N	S	S	A	N	N	S	A	N	N	N	N	NA	NA	NA

<sup>277</sup> If the decision is passed on to the MoH

<sup>278</sup> In case CVZ is asked to interpret the law (duiding) for a health insurer when there is a dispute between a health insurer and an insured person

<sup>279</sup> The Pharmacotherapeutic Compass ("Farmacotherapeutisch Kompas") gives information about pharmaceuticals available in the Netherlands. Every pharmaceutical is provided with an advice on prescription based on pharmacotherapeutic and economic grounds. This website is primarily meant for doctors and pharmacists

<sup>280</sup> Sometimes there are prescribing limitations

<sup>281</sup> All assessments of pharmaceuticals for inpatient use after January 2007 are available. All new pharmaceuticals (active substances and associations) for outpatient use are available since 2010

<sup>282</sup> In summary form

<sup>283</sup> This is forbidden by law

<sup>284</sup> The minutes of the Pharmacology and Therapeutics Advisory Committee (PTAC) are always publicly available at URL: <http://www.pharmac.govt.nz/healthpros/PTAC/PTACminutes> as well as the minutes of the PTAC subcommittees which are publicly available at URL: <http://www.pharmac.govt.nz/healthpros/PTAC/PTACSCMinutes>

Result table 13a. Summary table: Status of advice based on the assessment: (Single) rapid assessment	Number of jurisdictions	NA										
NA=not applicable A=always S=sometimes N=never				A	S	N	Total	%A	%S	%N	Total	
What is the status of the advice that are based on the assessment?												
Advice to decision making body	30	1		20	3	6	30	69%	10%	21%	100%	
Legislative (e.g. binding by law)	30	1		9	4	16	30	31%	14%	55%	100%	
(Clinical) guidance	30	1		3	6	20	30	10%	21%	69%	100%	
Other, ....	30	1		0	0	29	30	0%	0%	100%	100%	
Are the assessments & advice made public (complete or in summary form)?												
Are the assessments made public (complete or in summary form)?	30	1		14	4	11	29	48%	14%	38%	100%	
Available in English?	30	12		7	4	7	18	39%	22%	39%	100%	
Is the advice made public (complete or in summary form)?	30	1	18	4	7	29	62%	14%	24%	100%		
Available in English?	30	8	6	4	12	22	27%	18%	55%	100%		



<b>Result table 13b. Status of advice based on the assessment: full assessment (jurisdictions 1-15)</b>	1. Australia	2. Austria	3. Belgium	4. Canada	5. Czech Republic	6. Denmark	7. England & Wales	8. Estonia	9. Finland	10. France	11. Germany	12. Hungary	13. Ireland	14. Italy
<b>NA=not applicable (no full assessment in this jurisdiction)</b> <b>A=always</b> <b>S=sometimes</b> <b>N=never</b>														
<b>What is the status of the advice that are based on the assessment?</b>														
Advice to decision making body	A	A	A	S	NA	N	S	NA	NA	A	A	NA	A	N
Legislative (e.g. binding by law)	N	N	N	N	NA	A	S <sup>285</sup>	NA	NA	N	N	NA	N	A
(Clinical) guidance	N	N	A	S	NA	N	N	NA	NA	N	N	NA	N	S
Other, ...	N	N	N	N	NA	N	N	NA	NA	N	N	NA	N	N
<b>Are the assessments &amp; advice made public (complete or in summary form)?</b>														
Are the assessments made public (complete or in summary form)?	S	N	A	A	NA	N	A	NA	NA	A	A	NA	A	A <sup>286</sup>
Available in English?	A	N	N	A	NA	NA	A	NA	NA	S	A <sup>276</sup>	NA	A	N
Is the advice made public (complete or in summary form)?	S	N	A	A	NA	A	A	NA	NA	A	A	NA	A	A <sup>286</sup>
Available in English?	A	N	N	A	NA	N	A	NA	NA	S	N <sup>276</sup>	NA	A	N

<b>Result table 13b. Status of advice based on the assessment: full assessment (jurisdictions 16-31)</b>	15. Latvia	16. Luxembourg	17. Malta	18. Netherlands	19. New Zealand	20. Norway	21. Poland	22. Portugal	23. Scotland	24. Slovakia	25. Slovenia	26. Spain	27. Sweden	28. Switzerland	29. Turkey	30. USA
<b>NA=not applicable (no full assessment in this jurisdiction)</b> <b>A=always</b> <b>S=sometimes</b> <b>N=never</b>																
<b>What is the status of the advice that are based on the assessment?</b>																
Advice to decision making body	A	NA	NA	NA	A	S	A	NA	NA	NA	N	NA	A	NA	A	NA
Legislative (e.g. binding by law)	A	NA	NA	NA	N	N	N	NA	NA	NA	A	NA	N	NA	N	NA
(Clinical) guidance	A	NA	NA	NA	S	S	N	NA	NA	NA	S <sup>287</sup>	NA	A	NA	N	NA

<sup>285</sup> Only the positive decisions are mandatory. Negative recommendations are not

<sup>286</sup> summary

<b>Result table 13b. Status of advice based on the assessment: full assessment (jurisdictions 16-31)</b>  <b>NA=not applicable (no full assessment in this jurisdiction)</b> <b>A=always</b> <b>S=sometimes</b> <b>N=never</b>	15. Latvia	16. Luxembourg	17. Malta	18. Netherlands	19. New Zealand	20. Norway	21. Poland	22. Portugal	23. Scotland	24. Slovakia	25. Slovenia	26. Spain	27. Sweden	28. Switzerland	29. Turkey	30. USA
Other, ....	N	NA	NA	NA	N	N	N	NA	NA	NA	N	NA	N	NA	N	NA
<b>Are the assessments &amp; advice made public (complete or in summary form)?</b>																
Are the assessments made public (complete or in summary form)?	A	NA	NA	NA	S	A	S	NA	NA	NA	N	NA	A	NA	N	NA
Available in English?	N	NA	NA	NA	A	A	S	NA	NA	NA	N	NA	S	NA	NA	NA
Is the advice made public (complete or in summary form)?	A	NA	NA	NA	S <sup>288</sup>	A	A	NA	NA	NA	A	NA	A	NA	N	NA
Available in English?	N	NA	NA	NA	A	S	N	NA	NA	NA	N	NA	A	NA	NA	NA

<sup>287</sup> Sometimes there are prescribing limitations

<sup>288</sup> The minutes of the Pharmacology and Therapeutics Advisory Committee (PTAC) are always publicly available at URL: <http://www.pharmac.govt.nz/healthpros/PTAC/PTACminutes> as well as the minutes of the PTAC subcommittees which are publicly available at URL: <http://www.pharmac.govt.nz/healthpros/PTAC/PTACSCMinutes>

Result table 13b. Summary table: status of advice based on the assessment: full assessment			Number of jurisdictions	NA									
NA=not applicable A=always S=sometimes N=never						A	S	N	Total	%A	%S	%N	Total
What is the status of the advice that are based on the assessment?													
Advice to decision making body		30	13	11		3	3	17	65%	18%	18%	100%	
Legislative (e.g. binding by law)		30	13	4		1	12	17	24%	6%	71%	100%	
(Clinical) guidance		30	13	2		6	9	17	12%	35%	53%	100%	
Other, ....		30	13	0		0	17	17	0%	0%	100%	100%	
Are the assessments & advice made public (complete or in summary form)?													
Are the assessments made public (complete or in summary form)?		30	13	10		3	4	17	59%	18%	24%	100%	
Available in English?		30	17	7		3	3	13	54%	23%	23%	100%	
Is the advice made public (complete or in summary form)?		30	13	13		2	2	17	76%	12%	12%	100%	
Available in English?		30	15	6		2	7	15	40%	13%	47%	100%	

## Result table 14. Comparative evaluations

<b>Result table 14a. Comparative evaluations: (single) rapid assessment</b>	<b>Are (single) rapid assessments performed that include comparison of the efficacy or effectiveness between the, to be evaluated pharmaceutical, compared with an alternative intervention?</b>	<b>Name of comparative evaluation</b>
1. Australia	Yes	Comparative effectiveness
2. Austria	Yes	Medical-therapeutical evaluation
3. Belgium	Yes	Evaluation of therapeutic value
4. Canada	Yes	Comparative clinical effectiveness
5. Czech Republic	Yes	Therapeutic evaluation; effectiveness and safety assessment
6. Denmark	Yes	clinical evaluation
7. England& Wales	Yes	Clinical effectiveness
8. Estonia	Yes	Comparative efficacy
9. Finland	Yes	No specific name
10. France	Yes	Clinical Added Value; Amélioration du Service Médical Rendu
11. Germany	Yes	Benefit assessment
12. Hungary	Yes	Relative effectiveness/efficacy assessment
13. Ireland	Yes	Pharmacoeconomic evaluation
14. Italy	Yes	Therapeutic role or place in therapy
15. Latvia	Yes	Therapeutic evaluation
16. Luxembourg	Yes	Relative effectiveness assessment
17. Malta	Yes	Relative effectiveness assessment
18. Netherlands	Yes	Assessment of therapeutic value
19. New Zealand	Yes	Clinical evaluation
20. Norway	Yes	No specific name
21. Poland	Yes	Clinical effectiveness analysis
22. Portugal	Yes	Relative effectiveness assessment (therapeutic evaluation and fulfilment of medical need in case of no comparator)"
23. Scotland	Yes	Clinical effectiveness
24. Slovakia	Yes	Medical opinion
25. Slovenia	Yes	Relative effectiveness assessment (therapeutic evaluation in case of no comparator)
26. Spain	Yes	Therapeutic usefulness assessment
27. Sweden	Yes	Pharmacoeconomic evaluation
28. Switzerland	Yes	Therapeutic comparison
29. Turkey	Yes	Comparative effectiveness
30. USA	NA	NA

<b>Result table 14b. Comparative evaluations: full assessment</b>	<b>Are full assessments performed that include comparison of the efficacy or effectiveness between the to be evaluated pharmaceuticals compared with an alternative intervention?</b>	<b>Name of comparative evaluation</b>
1. Australia	Yes	Comparative effectiveness
2. Austria	Yes	medical-therapeutical evaluation
3. Belgium	Yes	evaluation of therapeutic value
4. Canada	Yes	comparative clinical effectiveness
5. Czech Republic	NA	NA
6. Denmark	Yes	clinical evaluation
7. England& Wales	Yes	clinical effectiveness
8. Estonia	NA	NA
9. Finland	NA	NA
10. France	Yes	Clinical added Value
11. Germany	Yes	benefit assessment
12. Hungary	NA	NA
13. Ireland	Yes	Health technology assessment
14. Italy	NA	therapeutic role or place in therapy
15. Latvia	Yes	therapeutic evaluation
16. Luxembourg	NA	NA
17. Malta	NA	NA
18. Netherlands	NA	NA
19. New Zealand	Yes	Clinical evaluations
20. Norway	NA	NA
21. Poland	Yes	Clinical effectiveness analysis
22. Portugal	NA	NA
23. Scotland	NA	NA
24. Slovakia	NA	NA
25. Slovenia	NA	NA
26. Spain	NA	NA
27. Sweden	Yes	Relative effectiveness or comparative effectiveness
28. Switzerland	NA	NA
29. Turkey	Yes	Comparative effectiveness
30. USA	NA	NA

## Result table 15. Elements included in the comparative evaluation

<b>Result table 15a. Elements included in the comparative evaluation: (single) rapid assessment (jurisdictions 1-15)</b>	1. Australia	2. Austria	3. Belgium	4. Canada	5. Czech Republic	6. Denmark	7. England & Wales	8. Estonia	9. Finland	10. France	11. Germany	12. Hungary	13. Ireland	14. Italy
<b>NA= not applicable (no (single) rapid assessment in jurisdiction)</b> <b>A=always</b> <b>S=sometimes</b> <b>N=never</b>														
<b>Are the following options included in the comparative evaluation?</b>														
Clinical efficacy assessment of A vs B	S	A	A	A	S <sup>289</sup>	A	A	A	A	A	A	A	A	A
Clinical effectiveness assessment of A vs B	A	S	A	S	S <sup>289</sup>	S	A	S <sup>290</sup>	S	A	A	S	A	S
Benefit/risk assessment of A vs B	A <sup>291</sup>	A	N	A	S	A	N	A	A	A	N <sup>292</sup>	S	N	S
Cost-effectiveness of A vs B	A	A	S	A	A	A	A	A	S	N	S	A	A	S
<b>Are there guidelines for conducting comparative evaluations?</b>	Y <sup>293</sup>	Y	N	Y	Y <sup>294</sup>	Y <sup>295</sup>	Y	Y	N	N	Y	Y	Y	Y <sup>296</sup>
<b>Are they available in English?</b>	Y	N	NA	Y	N	N	Y	Y	NA	NA	Y	Y	Y	Y

<sup>289</sup> If no effectiveness data are available, efficacy is assessed

<sup>290</sup> Only if data on effectiveness are available

<sup>291</sup> We prefer the term "harm" to "risk" in this context (e.g., see Subsection B.7 of the PBAC Guidelines) because it more adequately conveys that harm is a composite of the risk (likelihood) of negative outcomes multiplied by their severity

<sup>292</sup> IQWiG prefers the term 'harm' to 'risk' in this context

<sup>293</sup> Section B of the PBAC Guidelines. The PBAC Guidelines focus on presenting rather than conducting these assessments.<http://www.health.gov.au/internet/main/publishing.nsf/Content/pbacguidelines-index>

<sup>294</sup> Yes, according to the guidelines of the pharmacoeconomic society: [http://www.farmakoekonomika.cz/doc/cfes\\_guidelines-2009.doc](http://www.farmakoekonomika.cz/doc/cfes_guidelines-2009.doc)

<sup>295</sup> "Guidelines of the medical secretary (unpublished)"

<sup>296</sup> This is not a detailed document on methodology but a description of the general criteria (Criteria for ranking therapeutic innovation of new pharmaceuticals and elements for supplementing the dossier for admission to the reimbursement system (2007))

<b>Result table 15a. Elements included in the comparative evaluation: (single) rapid assessment (jurisdictions 16-31)</b>	15. Latvia	16. Luxembourg	17. Malta	18. Netherlands	19. New Zealand	20. Norway	21. Poland	22. Portugal	23. Scotland	24. Slovakia	25. Slovenia	26. Spain	27. Sweden	28. Switzerland	29. Turkey	30. USA
<b>NA= not applicable (no (single) rapid assessment in jurisdiction)</b> <b>A=always</b> <b>S=sometimes</b> <b>N=never</b>																
<b>Are the following options included in the comparative evaluation?</b>																
Clinical efficacy assessment of A vs B	A	S	S	A <sup>297</sup>	A	A	A	S <sup>298</sup>	A	A <sup>299</sup>	A	A	A	A	S	NA
Clinical effectiveness assessment of A vs B	S	S	A	A	A	N	S	S	A	S <sup>300</sup>	S <sup>300</sup>	S	S	A	A	NA
Benefit/risk assessment of A vs B	S	S	S	A	A	N	S	S	A	S <sup>300</sup>	A	A	N	N <sup>301</sup>	A	NA
Cost-effectiveness of A vs B	A	S	A	S	A	S	A	S	A	A	S	S	A	S	A	NA
<b>Are there guidelines for conducting comparative evaluation?</b>	Y	N	Y	Y	Y	Y	Y <sup>302</sup>	Y <sup>303</sup>	Y	Y	Y	Y <sup>304</sup>	Y	N	N <sup>305</sup>	NA
<b>Are they available in English?</b>	Y	NA	N <sup>306</sup>	Y	Y	N	Y	Y	Y	N	N	N	Y	NA	NA	NA

<sup>297</sup> Due to the timing of the assessment (after market authorization) the efficacy has more emphasis than the effectiveness

<sup>298</sup> Depending on the availability of data

<sup>299</sup> A new legislation is expected in October 2011. If no data on real life are available conditional reimbursement is provided.

<sup>300</sup> Only if data available

<sup>301</sup> Benefit/risk assessment is the task of the approval authority Swissmedic, however the safety of the pharmaceutical is also considered for the discussions regarding reimbursement

<sup>302</sup> "Guidelines for conducting Health Technology Assessment (HTA)" [http://www.aotm.gov.pl/assets/files/wytyczne\\_hta/2009/09.06.29\\_wytyczne\\_HTA\\_eng\\_MS.pdf](http://www.aotm.gov.pl/assets/files/wytyczne_hta/2009/09.06.29_wytyczne_HTA_eng_MS.pdf)

<sup>303</sup> As part of the guidelines for economic evaluation (Guidelines for economic pharmaceutical evaluation studies ). Accessible at [http://www.infarmed.pt/portal/page/portal/INFARMED/ENGLISH/PCAEC04\\_vering.pdf](http://www.infarmed.pt/portal/page/portal/INFARMED/ENGLISH/PCAEC04_vering.pdf)

<sup>304</sup> Guía de aplicación de criterios para la financiación pública y determinación de precios de medicamentos

<sup>305</sup> There is only a guideline on the procedure in Turkish

<sup>306</sup> A Standard Operating Procedure (SOP) is available for internal use only. It mostly offer guidelines regarding section format and is not detailed on the content

Result table 15a. Summary table: Elements included in the comparative evaluation: (single) rapid assessment	Number of jurisdictions	NA		A	S	N	Total	%A	%S	%N	Total			
NA= not applicable (no (single) rapid assessment in jurisdiction) A=always S=sometimes N=never  Y=yes N=no														
Are the following options included in the comparative evaluation?														
Clinical efficacy assessment of A vs B				30	1	24	5	0	29	83%	17%	0%	100%	
Clinical effectiveness assessment of A vs B				30	1	12	16	1	29	41%	55%	3%	100%	
Benefit/risk assessment of A vs B				30	1	13	9	7	29	45%	31%	24%	100%	
Cost-effectiveness of A vs B				30	1	18	10	1	29	62%	34%	3%	100%	
						Y	N		Total	%Y	%N		Total	
Are there guidelines for conducting comparative evaluations?				30	1	24	5		29	83%	17%		100%	
Are they available in English?				30	6	15	9		24	63%	38%		100%	



<b>Result table 15b. Elements included in the comparative evaluation: Full assessment (jurisdictions 1-15)</b>	1. Australia	2. Austria	3. Belgium	4. Canada	5. Czech Republic	6. Denmark	7. England & Wales	8. Estonia	9. Finland	10. France	11. Germany	12. Hungary	13. Ireland	14. Italy
<b>A=always S=sometimes N=never</b>														
<b>Are the following options included in the comparative evaluation?</b>														
Clinical efficacy assessment of A vs B	S	A	A	A	NA	A	A	NA	NA	A	A	NA	A	A
Clinical effectiveness assessment of A vs B	A	S	A	A	NA	S	A	NA	NA	A	A	NA	A	S
Benefit/risk assessment of A vs B	A <sup>307</sup>	A	S	A	NA	A	N	NA	NA	A	N <sup>308</sup>	NA	N	S
Cost-effectiveness of A vs B	A	A	N	S	NA	A	A	NA	NA	S	S	NA	A	S
<b>Are there guidelines for conducting the comparative evaluation?</b>	Y <sup>309</sup>	Y	N	Y	NA	Y <sup>310</sup>	Y	NA	NA	N	Y	NA	Y	Y <sup>311</sup>
<b>Are they available in English?</b>	Y	N	N	Y	NA	N	Y	NA	NA	NA	Y	NA	Y	Y

<b>Result table 15b. Elements included in the comparative evaluation: Full assessment (jurisdictions 16-31)</b>	15. Latvia	16. Luxembourg	17. Malta	18. Netherlands	19. New Zealand	20. Norway	21. Poland	22. Portugal	23. Scotland	24. Slovakia	25. Slovenia	26. Spain	27. Sweden	28. Switzerland	29. Turkey	30. USA
<b>A=always S=sometimes N=never</b>																
<b>Are the following options included in the comparative</b>																

<sup>307</sup> We prefer the term "harm" to "risk" in this context (e.g., see Subsection B.7 of the PBAC Guidelines) because it more adequately conveys that harm is a composite of the risk (likelihood) of negative outcomes multiplied by their severity

<sup>308</sup> IQWiG prefers the term 'harm' to 'risk' in this context

<sup>309</sup> Section B of the PBAC Guidelines. The PBAC Guidelines focus on presenting rather than conducting these assessments.

<http://www.health.gov.au/internet/main/publishing.nsf/Content/pbacguidelines-index>

<sup>310</sup> Guidelines of the medical secretary. This is an internal document that is not publicly available

<sup>311</sup> This is not a detailed document on methodology but a description of the general criteria (Criteria for ranking therapeutic innovation of new pharmaceuticals and elements for supplementing the dossier for admission to the reimbursement system (2007))

<b>Result table 15b. Elements included in the comparative evaluation: Full assessment (jurisdictions 16-31)</b>	15. Latvia	16. Luxembourg	17. Malta	18. Netherlands	19. New Zealand	20. Norway	21. Poland	22. Portugal	23. Scotland	24. Slovakia	25. Slovenia	26. Spain	27. Sweden	28. Switzerland	29. Turkey	30. USA
<b>A=always S=sometimes N=never</b>																
<b>evaluation?</b>																
Clinical efficacy assessment of A vs B	A	NA	NA	NA	A	A	A	NA	NA	NA	A	NA	A	NA	S	NA
Clinical effectiveness assessment of A vs B	S	NA	NA	NA	A	S	S	NA	NA	NA	S <sup>300</sup>	NA	A	NA	A	NA
Benefit/risk assessment of A vs B	S	NA	NA	NA	A	S	N	NA	NA	NA	A	NA	A	NA	A	NA
Cost-effectiveness of A vs B	A	NA	NA	NA	A	A	A	NA	NA	NA	S	NA	A	NA	A	NA
<b>Are there guidelines for conducting comparative evaluations?</b>	Y	NA	NA	NA	Y	N	Y <sup>312</sup>	NA	NA	NA	Y	NA	Y	NA	N <sup>313</sup>	NA
<b>Are they available in English?</b>	Y	NA	NA	NA	Y	NA	Y	NA	NA	NA	N	NA	N	NA	NA	NA

<sup>312</sup> "Guidelines for conducting Health Technology Assessment (HTA)" [http://www.aotm.gov.pl/assets/files/wytyczne\\_hta/2009/09.06.29\\_wytyczne\\_HTA\\_eng\\_MS.pdf](http://www.aotm.gov.pl/assets/files/wytyczne_hta/2009/09.06.29_wytyczne_HTA_eng_MS.pdf)

<sup>313</sup> There is only a guideline on the procedure in Turkish

Result table 15b. Summary table: Elements included in the comparative evaluation: Full assessment	Number of jurisdictions										
NA= not applicable (no (single) rapid assessment in jurisdiction) A=always S=sometimes N=never  Y=yes N=no	NA			A	S	N	Total	%A	%S	%N	Total
Are the following options included in the comparative evaluation?											
Clinical efficacy assessment of A vs B	30	13		15	2	0	17	88%	12%	0%	100%
Clinical effectiveness assessment of A vs B	30	13		10	7	0	17	59%	41%	0%	100%
Benefit/risk assessment of A vs B	30	13		9	4	4	17	53%	24%	24%	100%
Cost-effectiveness of A vs B	30	13		11	5	1	17	65%	29%	6%	100%
				Y	N		Total	%Y	%N		Total
Are there guidelines for conducting comparative evaluations?	17	13		13	4		17	76%	24%		100%
Are they available in English?	21	16		9	5		14	64%	36%		100%

**Results table 15c. Overview of guidelines that specify methods on relative effectiveness assessment (Pharmacoeconomic guidelines are only mentioned in case there are not separate guidelines that specify methods on relative effectiveness assessment)**

<b>Jurisdiction</b>	<b>Agency</b>	<b>Guideline</b>	<b>Comment</b>
1. Australia	PBAC	Guidelines for Preparing Submissions to the Pharmaceutical Benefits Advisory Committee. Version 4.3. Canberra: Pharmaceutical Benefits Advisory Committee (PBAC); 2008.	English, publicly available
2. Austria	HVB	Arbeitsbehelf Erstattungskodex. Hauptverband der österreichischen Sozialversicherungsträger (HBV); 2010.	German, publicly available
3. Belgium	INAMI/RIZI V	No guideline for relative effectiveness assessment. However a guideline for economic evaluations is in use: Cleemput I, Van Wilder P, Vrijens F, Huybrechts M, Ramaekers D. Richtlijnen voor farmaco-economische evaluaties in België. Health Technology Assessment (HTA). Brussel: Federaal Kenniscentrum voor de Gezondheidszorg (KCE); 2008. KCE Reports 78A (D/2008/10.273/23)	English, publicly available

<b>Jurisdiction</b>	<b>Agency</b>	<b>Guideline</b>	<b>Comment</b>
4. Bulgaria			
5. Canada	CADTH	Guidelines for the Economic Evaluation of Health Technologies: Canada. 3rd ed. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH); 2006.	English, publicly available
6. Czech Republic	SUKL	Guidelines of the pharmacoeconomic society: <a href="http://www.farmakoekonomika.cz/doc/cfes_guidelines-2009.doc">http://www.farmakoekonomika.cz/doc/cfes_guidelines-2009.doc</a>	Czech, publicly available
7. Denmark	DMA	Health Technology Assessment Handbook: Copenhagen: Kristensen FB & Sigmund H, Danish Centre for Health Technology Assessment (DACEHTA ); 2007 Danish Medicines Agency: Guidelines of the medical secretary	English, publicly available Danish, not publicly available
8. England& Wales (UK)	NICE	Guide to the Methods of Technology Appraisal. London: National Institute for Health and Clinical Excellence (NICE); 2008.	English, publicly available
9. Estonia	EHIF	Guideline for Pharmacoeconomic Analysis. Estonian Health Insurance Fund (EHIF); 2002. <a href="http://www.haigekassa.ee/eng/health-insurance-in-estonia/medicinal-products/pharmacoeconomic-analysis">http://www.haigekassa.ee/eng/health-insurance-in-estonia/medicinal-products/pharmacoeconomic-analysis</a>	English, publicly available
10. Finland	HILA	No guideline for relative effectiveness assessment	
11. France	HAS	No guideline for relative effectiveness assessment	
12. Germany	IQWiG	General Methods Version 3.0314. Cologne: Institute for Quality and Efficiency in Health Care (IQWiG); 2008.	English, publicly available
13. Hungary	ESKI	There is no guideline for relative effectiveness assessment. However a guideline for economic evaluations is in use: Methodological guidelines for conducting economic evaluation of healthcare interventions. a Hungarian proposal for methodology standards: Szende, Mogorósy, Muszbek, Nagy, Pallos, Dózsa; 2002.	English, publicly available
14. Ireland	NPCE, HIQA	There is no guideline specifically for relative effectiveness assessment. However a guideline for economic evaluations is in use: Guidelines for the Economics of Health Technologies in Ireland. Dublin: Health Information and Quality Authority (HIQA); 2010.	English, publicly available
15. Italy	AIFA	There is not a detailed document on methodology but a description of the general criteria (Criteria for ranking therapeutic innovation of new drugs and elements for supplementing the dossier for admission to the reimbursement system; Italian Medicines Agency (AIFA); 2007)	English, publicly available
16. Latvia	CHE	The Baltic Guideline for Economic Evaluations of Pharmaceuticals. <a href="http://www.haigekassa.ee/eng/health-insurance-in-estonia/medicinal-products/pharmacoeconomic-analysis">http://www.haigekassa.ee/eng/health-insurance-in-estonia/medicinal-products/pharmacoeconomic-analysis</a>	English, publicly available
17. Luxembourg	CNS	No guideline	
18. Malta	MoH	A Standard Operating Procedure (SOP) is available for internal use only. It mostly offers guidelines regarding format and is not detailed on methodology.	
19. Netherlands	CVZ	Dutch Assessment Procedures for the Reimbursement of Outpatient Medicines. Diemen: College voor Zorgverzekeringen (CVZ) and Ministry of Health, Welfare and Sport; 2010 <a href="http://www.cvz.nl/binaries/live/cvzinternet/hst_content/nl/documenten/rubriek+zorgpakket/cfh/assessment-outpatient-">http://www.cvz.nl/binaries/live/cvzinternet/hst_content/nl/documenten/rubriek+zorgpakket/cfh/assessment-outpatient-</a>	English, publicly available

314 There is also a specific guideline for economic evaluations: General Methods for evaluating the relation between cost and benefit - version 1.0. Cologne: Institute for Quality and Efficiency in Health Care (IQWiG); 2009

Jurisdiction	Agency	Guideline	Comment
		medicines.pdf Procedure guideline for expensive hospital pharmaceuticals: Procedure herbeoordeling intramurale geneesmiddelen. Diemen. College voor zorgverzekeringen, 2010 <a href="http://www.cvz.nl/binaries/live/cvzinternet/hst_content/nl/documenten/rapporten/2010/rpt1011+herbeoordeling+intramurale+geneesmiddelen.pdf">http://www.cvz.nl/binaries/live/cvzinternet/hst_content/nl/documenten/rapporten/2010/rpt1011+herbeoordeling+intramurale+geneesmiddelen.pdf</a>	Dutch, publicly available
20. New Zealand	PHARMAC	Pharmaceutical Management Agency (PHARMAC). Guidelines for funding applications to PHARMAC 2010. Available at URL: <a href="http://www.pharmac.govt.nz/2010/02/11/Guidelines%20for%20Suppliers%20Submissions.pdf">http://www.pharmac.govt.nz/2010/02/11/Guidelines%20for%20Suppliers%20Submissions.pdf</a> ; Pharmaceutical Management Agency (PHARMAC). Prescription for Pharmacoeconomic Analysis: Methods for Cost-utility Analysis (May 2007). Available at URL: <a href="http://www.pharmac.govt.nz/healthpros/EconomicAnalysis/pharmacoeconomics">http://www.pharmac.govt.nz/healthpros/EconomicAnalysis/pharmacoeconomics</a>	English, publicly available
21. Norway	NOKC	Norwegian guidelines for pharmacoeconomic analysis in connection with applications for reimbursement; Oslo: Norwegian Medicines Agency (NMA); 2005.	English, publicly available
22. Poland	AHTAPol	Guidelines for conducting Health Technology Assessment (HTA). Version 2.1. Warsaw: AHTAPol; 2009	English, publicly available
23. Portugal	INFARMED	Guidelines for economic drug evaluation studies. INFARMED, 1998	As part of the guidelines for economic evaluation. English, publicly available
24. Scotland (UK)	SMC	Guidance to Manufacturers for Completion of New Product Assessment Form (NPAF) (Revised June 2010). Glasgow: Scottish Medicines Consortium. Accessible at <a href="http://www.scottishmedicines.org.uk/files/New-Product-Assessment-Form-NPAF-Guidance-Notes-June-2010.doc">http://www.scottishmedicines.org.uk/files/New-Product-Assessment-Form-NPAF-Guidance-Notes-June-2010.doc</a>	English, publicly available
25. Slovakia	SLOVAHTA	There is a legislation of 15-20 pages including instructions for submission of data by marketing authorisation holder and how data are evaluated (URL: <a href="http://www.mzsr.sk/?kategorizacia-liekov-1&amp;sprava=odborne-usmernenie-ministerstva-zdravotnictva-slovenskej-republiky-ktorym-sa-meni-a-doplna-odborne-usmernenie-ministerstva-zdravotnictva-slovenskej-republiky-c-16652-2009-okclp-zo-dna-22-jula-2009-o-postupe-pri-podavani-ziadosti-o-zaradenie-lieku-ale">http://www.mzsr.sk/?kategorizacia-liekov-1&amp;sprava=odborne-usmernenie-ministerstva-zdravotnictva-slovenskej-republiky-ktorym-sa-meni-a-doplna-odborne-usmernenie-ministerstva-zdravotnictva-slovenskej-republiky-c-16652-2009-okclp-zo-dna-22-jula-2009-o-postupe-pri-podavani-ziadosti-o-zaradenie-lieku-ale</a> ) In addition there is a instructions document regarding the pharmacoeconomic assessment (Farmako-ekonomický rozbor lieku, URL: <a href="http://www.mzsr.sk/?farmako-ekonomicky-rozbor-lieku">http://www.mzsr.sk/?farmako-ekonomicky-rozbor-lieku</a> ).	Slovakian, publicly available
26. Slovenia	ZZZS	A regulation including some guidance is publicly available in Slovenian: <a href="http://www.zzs.si/zzzs/info/egradiva.nsf/o/54B4834F0D9B092DC1256CB40045469F?OpenDocument">http://www.zzs.si/zzzs/info/egradiva.nsf/o/54B4834F0D9B092DC1256CB40045469F?OpenDocument</a>	Slovenian, publicly available
27. Spain	MoH	Guía de aplicación de criterios para la financiación pública y determinación de precios de medicamentos	Spanish
28. Sweden	TLV and SBU	Working guidelines for the pharmaceutical reimbursement review. The Swedish Pharmaceutical Benefits Board; 2008	English, publicly available
29. Switzerland	Federal Medicines Commission	There is a guideline on the procedure in German which is not detailed on methodology: Handbuch betreffend die Spezialitätenliste (SL) Gültig ab 1. Februar 2008. <a href="http://www.bag.admin.ch/themen/krankenversicherung/06492/07568/index.html?lang=de">http://www.bag.admin.ch/themen/krankenversicherung/06492/07568/index.html?lang=de</a>	German, publicly available
30. Turkey	MoH	There is a guideline on the procedure in Turkish which is not detailed on methodology	Turkish, publicly available
31. USA	NA	NA	NA

**Result table 16. Information sources used for the assessment**

Result table 16a. Information sources used for the assessment: (single) rapid assessment: (jurisdictions 1-15)  A=always S=sometimes N=never	1. Australia	2. Austria	3. Belgium	4. Canada	5. Czech Republic	6. Denmark	7. England& Wales	8. Estonia	9. Finland	10. France	11. Germany	12. Hungary	13. Ireland	14. Italy
<b>Which information sources are used for the assessment?</b>														
Manufacturer report	A	A	A	A	A	A	A	A	A	A	A	A	A	A
Expert knowledge	A	A	S	A	A	S	A	A	S	A	N	S	S	A
Clinical guidelines	S	S	A	S	S	S	S	A	A	A	N	A	S	N
Publications by other HTA-organizations	A	S	S	S	S	S	S	A	S	A	S	S	N	N
Literature (e.g. published clinical studies)	A	S	A	A	A	S	A	A	A	A	A	A	A	N
European public assessment report (EPAR) / national public assessment report (NPAR) (including summary of product characteristics [SPC])	S <sup>315</sup>	A	A	S	A	A	S	S	A	A	A	A	N	A
Unpublished (raw) clinical data	S	S <sup>316</sup>	S	N	S	S	S	S	S	A	A	N	S	N
Confidential data	S	N	S	S	N	S	S	S	S	A	N	N	S	N
Other,.....											A <sup>317</sup>			

<sup>315</sup> AUSPAR for Australia

<sup>316</sup> Only if allowed to quote the data!

<sup>317</sup> Web based study registries

<b>Result table 16a. Information sources used for the assessment: (single) rapid assessment: (jurisdictions 16-31)</b>  <b>A=always</b> <b>S=sometimes</b> <b>N=never</b>																
	15. Latvia	16. Luxembourg	17. Malta	18. Netherlands	19. New Zealand	20. Norway	21. Poland	22. Portugal	23. Scotland	24. Slovakia	25. Slovenia	26. Spain	27. Sweden	28. Switzerland	29. Turkey	30. USA
<b>Which information sources are used for the assessment?</b>																
Manufacturer report	A	A	S	A	S	A	S	A	A	A	A	S	A	A	A	NA
Expert knowledge	S	A	A	S	A	S	A	A	A	S	S	A	S	S <sup>318</sup>	A	NA
Clinical guidelines	A	A	A	A	S	N	A	S	S	S	A	A	S	S	A	NA
Publications by other HTA-organizations	A	A	S	S	N	A	A	S	S	S	A	S	S	S	A	NA
Literature (e.g. published clinical studies)	A	A	A	A	A	S	A	A	S	A	A	A	A	A	A	NA
European public assessment report (EPAR) / national public assessment report (NPAR) (including summary of product characteristics [SPC])	A	A	A	A	N	A	A	A	S	S	A	A	A	S	S	NA
Unpublished (raw) clinical data	S	S	S	S	S	N	S	S <sup>319</sup>	S	S <sup>320</sup>	S	N	S	S	N	NA
Confidential data	S	S	N	N	S	N	S	S <sup>319</sup>	S <sup>321</sup>	N	S	N	S	S	N	NA
Other,.....		A <sup>322</sup>		A							N	S <sup>323</sup>				NA

<sup>318</sup> In general at the level of the Federal Medicines Commission, sometimes additional experts are consulted

<sup>319</sup> These data are only used for confirmation if there are doubts about results summarized, they do not influence the outcome of the assessment

<sup>320</sup> Very rarely

<sup>321</sup> The SMC will keep confidential data undisclosed for a of maximum of 12 months after which the SMC has the right to publish the data after all

<sup>322</sup> National pharmaceutical consumption statistics

<sup>323</sup> External expert report

Result table 16a. Summary table: Information sources used for the assessment: (single) rapid assessment													
NA= not applicable (no (single) rapid assessment in jurisdiction) A=always S=sometimes N=never	Number of jurisdictions	NA											
Which information sources are used for the assessment?													
Manufacturer report			30										1
Expert knowledge			30										1
Clinical guidelines			30										1
Publications by other HTA-organizations			30										1
Literature (e.g. published clinical studies)			30										1
European public assessment report (EPAR) / national public assessment report (NPAR) (including summary of product characteristics [SPC])			30										1
Unpublished (raw) clinical data			30										1
Confidential data	30	1											
Other.....	28	1											
A	S	N	Total	%A	%S	%N	Total						
25	4	0	29	86%	14%	0%	100%						
16	12	1	29	55%	41%	3%	100%						
13	13	3	29	45%	45%	10%	100%						
8	18	3	29	28%	62%	10%	100%						
24	4	1	29	83%	14%	3%	100%						
19	8	2	29	66%	28%	7%	100%						
2	21	6	29	7%	72%	21%	100%						
1	17	11	29	3%	59%	38%	100%						
2	2	23	27	7%	7%	85%	100%						



<b>Result table 16b. Information sources used for the assessment: Full assessment (jurisdictions 1-15)</b>	1. Australia	2. Austria	3. Belgium	4. Canada	5. Czech Republic	6. Denmark	7. England& Wales	8. Estonia	9. Finland	10. France	11. Germany	12. Hungary	13. Ireland	14. Italy
<b>A=always S=sometimes N=never</b>														
<b>Which information sources are used for the assessment?</b>														
Manufacturer report	A	A	A	N	NA	N	A	NA	NA	A	S <sup>324</sup>	NA	S <sup>325</sup>	N
Expert knowledge	A	A	S	A	NA	S	A	NA	NA	A	N	NA	A	A
Clinical guidelines	S	S	A	S	NA	A	S	NA	NA	A	N	NA	S	A
Publications by other HTA-organizations	A	S	S	A	NA	S	S	NA	NA	A	A	NA	S	A
Literature (e.g. published clinical studies)	A	S	A	A	NA	S	A	NA	NA	A	A	NA	A	A
European public assessment report (EPAR) / national public assessment report (NPAR) (including summary of product characteristics [SPC])	A	A	A	S	NA	N	S	NA	NA	A	A	NA	S	A
Unpublished (raw) clinical data	S	S <sup>326</sup>	S	N	NA	S	S	NA	NA	A	S <sup>324</sup>	NA	S	N
Confidential data	S	N	S	N	NA	S	S	NA	NA	A	N	NA	S	N
Other,.....		A	A	N	NA		A	NA	NA		A <sup>327</sup>	NA		

<b>Result table 16b. Information sources used for the assessment: Full assessment (jurisdictions 16-31)</b>	15. Latvia	16. Luxembourg	17. Malta	18. Netherlands	19. New Zealand	20. Norway	21. Poland	22. Portugal	23. Scotland	24. Slovakia	25. Slovenia	26. Spain	27. Sweden <sup>328</sup>	28. Switzerland	29. Turkey	30. USA
<b>A=always S=sometimes N=never</b>																
<b>Sources</b>																
Manufacturer report	A	NA	NA	NA	S	N	A	NA	NA	NA	A	NA	S	NA	A	NA
Expert knowledge	S	NA	NA	NA	A	S	A	NA	NA	NA	S	NA	N	NA	A	NA
Clinical guidelines	A	NA	NA	NA	S	S	A	NA	NA	NA	A	NA	N	NA	A	NA

<sup>324</sup> Always requested, however, since there is no legal obligation to provide the data, reports are not always submitted

<sup>325</sup> The marketing authorisation holder may be requested to submit a dossier that includes data on efficacy, cost and other relevant data in support of their product

<sup>326</sup> Only if allowed to quote the data!

<sup>327</sup> Web based study registries

<b>Result table 16b. Information sources used for the assessment: Full assessment (jurisdictions 16-31)</b>  <b>A=always</b> <b>S=sometimes</b> <b>N=never</b>	15. Latvia	16. Luxembourg	17. Malta	18. Netherlands	19. New Zealand	20. Norway	21. Poland	22. Portugal	23. Scotland	24. Slovakia	25. Slovenia	26. Spain	27. Sweden <sup>328</sup>	28. Switzerland	29. Turkey	30. USA
Publications by other HTA-organizations	A	NA	NA	NA	S	S	A	NA	NA	NA	A	NA	S	NA	A	NA
Literature (e.g. published clinical studies)	A	NA	NA	NA	A	A	A	NA	NA	NA	A	NA	A	NA	A	NA
European public assessment report (EPAR) / national public assessment report (NPAR) (including summary of product characteristics [SPC])	A	NA	NA	NA	N	A	A	NA	NA	NA	A	NA	S	NA	S	NA
Unpublished (raw) clinical data	S	NA	NA	NA	S	N	S	NA	NA	NA	S	NA	S	NA	N	NA
Confidential data	S	NA	NA	NA	S	N	S	NA	NA	NA	S	NA	N	NA	N	NA
Other,.....	N	NA	NA	NA	N	N	N	NA	NA	NA	N	NA	N	NA	N	NA

<sup>328</sup> The answer included is applicable to a full assessments that is performed by SBU. In case THL performs the full assessment the answers are A, S, S, S, A, A, S, S

Result table 16b. Summary table: Information sources used for the assessment: Full assessment															
NA= not applicable (no (single) rapid assessment in jurisdiction) A=always S=sometimes N=never			Number of jurisdictions												NA
Which information sources are used for the assessment?															
Manufacturer report	30	13													
Expert knowledge	30	13													
Clinical guidelines	30	13													
Publications by other HTA-organizations	30	13													
Literature (e.g. published clinical studies)	30	13													
European public assessment report (EPAR) / national public assessment report (NPAR) (including summary of product characteristics [SPC])	30	13													
Unpublished (raw) clinical data	30	13													
Confidential data	30	13													
Other .....	29	13													

A	S	N	Total	%A	%S	%N	Total
9	4	4	17	53%	24%	24%	100%
10	5	2	17	59%	29%	12%	100%
8	7	2	17	47%	41%	12%	100%
9	8	0	17	53%	47%	0%	100%
15	2	0	17	88%	12%	0%	100%
10	5	2	17	59%	29%	12%	100%
1	12	4	17	6%	71%	24%	100%
1	9	7	17	6%	53%	41%	100%
4	0	12	16	25%	0%	75%	100%

## Result table 17. Comparator/comparison

Result table 17a. Comparator/comparison: (single) rapid assessment (jurisdictions 1-15)														
<b>NA=not applicable (no (single) rapid assessment in this jurisdiction)</b> <b>X=applicable</b>  <b>Y=yes</b> <b>N=no</b>  <b>A=always</b> <b>S=sometimes</b> <b>N=never?</b>														
	1. Australia	2. Austria	3. Belgium	4. Canada	5. Czech Republic	6. Denmark	7. England& Wales	8. Estonia	9. Finland	10. France	11. Germany	12. Hungary	13. Ireland	14. Italy
<b>With what is the pharmaceutical compared with?</b>														
Whatever is used in registration trials			X											
Best possible care														
Best standard care							x329	X <sup>330</sup>	x331	x332	X	x333	x334	x335
Other, .....	X <sup>336</sup>	X <sup>337</sup>	X <sup>338</sup>	X <sup>339</sup>	X <sup>340</sup>	X <sup>341</sup>								
<b>Is comparison limited to pharmaceuticals?</b>														
	N	N	Y <sup>342</sup>	Y	N	Y	N	N	N	N	N	N <sup>343</sup>	N	Y

<sup>329</sup> Relevant comparator technologies are chosen as comparator – usually the treatment(s) used in current clinical practice in the NHS to manage the disease or condition (this may include non-licensed technologies if they are used in current clinical practice); sometimes the comparator is best supportive care, palliative therapy or no intervention

<sup>330</sup> Most widely used alternative or current therapy

<sup>331</sup> Most frequently used therapy (relevant therapy with the same indication)

<sup>332</sup> Standard care is defined as the validated care in the field

<sup>333</sup> The main comparator(s) should be the currently accepted standard therapy (therapies) that the new intervention is intended to replace. Selection of any other comparator(s) should be justified. Best standard care is what the clinical guidelines mention as the best available, the best current, a proven, and an established effective treatment

<sup>334</sup> The preferred comparator for the reference case is 'routine care,' that is, the technology or technologies most widely used in clinical practice in Ireland

<sup>335</sup> The pharmaceuticals that are used for this indication in practice

<sup>336</sup> "The therapy that prescribers would most replace with the proposed pharmaceutical in practice if the PBS subsidizes the proposed pharmaceutical as requested."

<sup>337</sup> The most similar comparator according to ATC level as long this is reasonable. This is mostly all pharmaceuticals within a therapeutic class however it can also be diverted from this

<sup>338</sup> Most frequently used pharmaceutical in practice

<sup>339</sup> 'Currently accepted therapy' which is defined as the single most prevalent clinical practice (if there is one that is dominant)

<sup>340</sup> Standard care - product that is the reference product within the relevant reference group

<sup>341</sup> All relevant comparators

<sup>342</sup> For the therapeutic value assessment the comparison is limited to pharmaceuticals, for place in practice the pharmaceutical is also compared to other technologies

Result table 17a. Comparator/comparison: (single) rapid assessment (jurisdictions 1-15)														
<b>NA=not applicable (no (single) rapid assessment in this jurisdiction)</b> <b>X=applicable</b>  <b>Y=yes</b> <b>N=no</b>  <b>A=always</b> <b>S=sometimes</b> <b>N=never?</b>														
	1. Australia	2. Austria	3. Belgium	4. Canada	5. Czech Republic	6. Denmark	7. England& Wales	8. Estonia	9. Finland	10. France	11. Germany	12. Hungary	13. Ireland	14. Italy
Which sources are used to identify the comparator?														
Indicated by the product sponsor	S <sup>344</sup>	A	S	S	N	S <sup>345</sup>	A <sup>346</sup>	A	S	S	N	A	S	S
Experts	S	A <sup>347</sup>	A <sup>348</sup>	S	S	S <sup>345</sup>	A <sup>346</sup>	A	S	S	A <sup>349</sup>	A	S	S
Clinical guidelines	S	N	A	N	S	S <sup>345</sup>	A <sup>346</sup>	A	S	S	N	A	N	S
(International) methodological guidelines	S	N	S	N	S	S <sup>345</sup>	A <sup>346</sup>	S	S	S	N	A	S	N
Other.....	N	N	N	N	A <sup>350</sup>	N	N	A <sup>351</sup>	N	N	N	N	N	N
If there are no direct comparisons, are indirect comparisons used in the comparative evaluation?														
	Y <sup>352</sup>	Y	Y	Y	Y	Y	Y	Y	Y	Y <sup>353</sup>	Y <sup>354</sup>	Y	Y	Y <sup>355</sup>

<sup>343</sup> Mostly pharmaceuticals are compared with pharmaceuticals however in exceptional cases when the comparator is another technology (surgical intervention vs pharmaceutical without any other comparator) than the non-pharmaceutical is accepted as the comparator

<sup>344</sup> PBAC invariably determines whether it accepts the nominated main comparator(s), or substitutes its own determination (with reasons).

<sup>345</sup> Determined by reimbursement committee

<sup>346</sup> All stakeholders are asked to contribute to the identification of the correct comparator

<sup>347</sup> The assessment body checks if the comparator indicated by the product sponsor is reasonable and may include another comparator

<sup>348</sup> Internal experts in consultation with committee

<sup>349</sup> Identified by internal experts of IQWiG

<sup>350</sup> List with reference groups: product that is the reference product within the relevant reference group

<sup>351</sup> Epidemiological data about treatments

<sup>352</sup> Preferably compared with frequentist method after exchangeability assessment and determination of most appropriate metric of comparative treatment effect of the pharmaceuticals of interest against the common reference

<sup>353</sup> The methods for indirect comparisons should be according to an internal HAS guideline

<sup>354</sup> Indirect comparisons can be used if studies are adequate for indirect comparison

<sup>355</sup> In general not, however if there are relevant data on morbidity or mortality they can be included

Result table 17a. Comparator/comparison: (single) rapid assessment (jurisdictions 16-31)																	
<b>NA=not applicable (no (single) rapid assessment in this jurisdiction)</b> <b>X=applicable</b>  <b>Y=yes</b> <b>N=no</b>  <b>A=always</b> <b>S=sometimes</b> <b>N=never?</b>																	
	15. Latvia	16. Luxembourg	17. Malta	18. Netherlands	19. New Zealand	20. Norway	21. Poland	22. Portugal	23. Scotland	24. Slovakia	25. Slovenia	26. Spain	27. Sweden	28. Switzerland	29. Turkey	30. USA	
<b>With what is the pharmaceutical compared with (X=applicable)?</b>																	
Whatever is used in registration trials										X	X	X <sup>356</sup>		X			NA
Best possible care			X				X <sup>357</sup>	X <sup>358</sup>		X	X	X <sup>356</sup>		X			NA
Best standard care	X		X <sup>359</sup>	X <sup>360</sup>	X <sup>361</sup>		X <sup>357</sup>	X <sup>358</sup>		X	X <sup>362</sup>	X <sup>356</sup>	X <sup>363</sup>	X	X <sup>364</sup>		NA
Other, .....	X <sup>365</sup>	X <sup>366</sup>	X <sup>367</sup>			X <sup>368</sup>	X <sup>357</sup>		X <sup>369</sup>			X <sup>356</sup>	X <sup>363</sup>				NA
<b>Is comparison limited to pharmaceuticals (Y=yes, N=no)?</b>																	
	N	N	N	N	N	Y	N	N <sup>370</sup>	N	N	N	N	N	N	N	N	NA

<sup>356</sup> The ideal is to compare with the best standard treatment. If this is not possible/applicable it may be best possible care, what is used in the registration trial or other (pharmaceuticals that belong to the same therapeutic subgroup)

<sup>357</sup> According to Polish HTA guidelines the primary comparator for the assessed intervention must be the so-called existing practice. It is also recommended to perform a comparison with other comparators, i.e. the following technologies: the most frequently used, the cheapest, the most efficient and compliant with the standards and guidelines for clinical management

<sup>358</sup> Usual care and/or best usual care

<sup>359</sup> Standard care – the medicine assessed is compared with other pharmaceuticals on the Government Formulary List given for the same clinical indication

<sup>360</sup> Defined as first line treatment according to clinical guidelines and for which the effectiveness is proven. If there is no standard care, the mostly used care is used for comparison

<sup>361</sup> The comparator(s) used in the analyses should be the treatment that most prescribers would replace in NZ clinical practice, and the treatment prescribed to the largest number of patients (if this differs from the treatment most prescribers would replace)

<sup>362</sup> Standard care as for example indicated in guidelines

<sup>363</sup> The most cost-effective care, or best standard care

<sup>364</sup> All comparators

<sup>365</sup> Most commonly used alternative for certain indication

<sup>366</sup> Actually reimbursed treatments with the same therapeutic indication

<sup>367</sup> Other medical substances

<sup>368</sup> The most significant medical treatment possibilities which can be the most prevalent treatment, the most inexpensive treatment or other alternatives

<sup>369</sup> The most appropriate comparator is the one that will most likely be replaced if the pharmaceutical under consideration is accepted by the SMC for use in Scotland

<sup>370</sup> In out patient care usually pharmaceuticals are the comparator however but non pharmacological measures can be included in the comparison. For inpatient pharmaceuticals it is more common to include non pharmacological interventions

Result table 17a. Comparator/comparison: (single) rapid assessment (jurisdictions 16-31)																	
<b>NA=not applicable (no (single) rapid assessment in this jurisdiction)</b> <b>X=applicable</b>  <b>Y=yes</b> <b>N=no</b>  <b>A=always</b> <b>S=sometimes</b> <b>N=never?</b>																	
	15. Latvia	16. Luxembourg	17. Malta	18. Netherlands	19. New Zealand	20. Norway	21. Poland	22. Portugal	23. Scotland	24. Slovakia	25. Slovenia	26. Spain	27. Sweden	28. Switzerland	29. Turkey	30. USA	
Which sources are used by the assessment body to identify the comparator (A=always, S=sometimes, N=never)?																	
Indicated by the product sponsor	S	N	S <sup>371</sup>	S	S	A	A	S	A <sup>372</sup>	S	A	A	A	S	A	NA	
Experts	S	A	A <sup>371</sup>	S	S	N	A	A	A	S	A	S	S	S	S	NA	
Clinical guidelines	A	S	A <sup>371</sup>	A	S	N	A	S	S	S	A	A	S	S	A	NA	
(International) methodological guidelines	A	S	A <sup>371</sup>	S	?	N	A	A	N	S	A	A	S	S	A	NA	
Other.....	N	N	N	N	N	N	N		N	S	A <sup>373</sup>	A <sup>374</sup>	N	N	N	NA	
If there are no direct comparisons, are indirect comparisons used in the comparative evaluation (Y=yes, N=no)?																	
	Y <sup>375</sup>	Y	Y	Y	Y <sup>376</sup>	Y	Y <sup>377</sup>	Y	Y <sup>378</sup>	Y	Y	Y	Y	Y	N	NA	

<sup>371</sup> Identified by pharmacists doing HTAs based on multiple sources

<sup>372</sup> But always validated by SMC

<sup>373</sup> what other countries have choose in their assessments

<sup>374</sup> Technical team's expert knowledge, relevant scientific literature

<sup>375</sup> Only information from systematic reviews, meta-analyses and economic modeling are considered

<sup>376</sup> Bayesian methods are not used, frequentist methods are preferred

<sup>377</sup> The recommended method for performing indirect comparisons of studies with a common comparator depend on the outcome measures used – in the case of odd ratios, it is recommended to use logical regression or metaregression, and in the case of measures such as relative risks, risk difference, difference of mean values or hazard ratios, the recommended methods include adjusted indirect comparison Bucher or metaregression. In justified cases, network meta-analysis can be used

<sup>378</sup> Bayesian analysis are preferred, naive indirect comparisons are not preferred. The SMC is developing a section on indirect comparison to be implemented in the manufacturers guideline in the summer of 2011

<b>Result table 17a. : Summary table: Comparator/comparison (single) rapid assessment</b>											
NA=not applicable (no (single) rapid assessment in this jurisdiction) X=applicable  Y=yes N=no  A=always S=sometimes N=never M=missing value											
	<b>X</b>	<b>%X</b>									<b>Jurisdictions NA</b>
<b>With what is the pharmaceutical compared with (X=applicable)?</b>											
Whatever is used in registration trials	5	17%									1
Best possible care	7	24%									1
Best standard care	20	69%									1
Other, .....	14	48%									1
	<b>Y</b>	<b>N</b>			<b>Total</b>	<b>%Y</b>	<b>%N</b>			<b>Total</b>	
<b>Is comparison limited to pharmaceuticals?</b>	5	24			29	17%	83%			100%	1
<b>Which sources are used by the assessment body to identify the comparator (A=always, S=sometimes, N=never)?</b>	<b>A</b>	<b>S</b>	<b>N</b>	<b>M</b>	<b>Total</b>	<b>%A</b>	<b>%S</b>	<b>%N</b>	<b>%M</b>	<b>Total</b>	
Indicated by the product sponsor	11	15	3	0	29	38%	52%	10%	0%	100%	1
Experts	11	16	2	0	29	38%	55%	7%	0%	100%	1
Clinical guidelines	12	13	4	0	29	41%	45%	14%	0%	100%	1
(International) methodological guidelines	9	13	6	1	29	31%	45%	21%	3%	100%	1
Other.....	4	1	24	0	29	14%	3%	83%	0%	100%	1
	<b>Y</b>	<b>N</b>			<b>Total</b>	<b>%Y</b>	<b>%N</b>			<b>Total</b>	
<b>If there are no direct comparisons, are indirect comparisons used in the comparative evaluation ?</b>	26	1			27	96%	4%			100%	1



<b>Result table 17b. Comparator/comparison: Full assessment (jurisdictions 1-15)</b>														
<b>NA=not applicable (no full assessment in this jurisdiction)</b> <b>X=applicable</b>  <b>Y=yes</b> <b>N=no</b>  <b>A=always</b> <b>S=sometimes</b> <b>N=never?</b>														
	1. Australia	2. Austria	3. Belgium	4. Canada	5. Czech Republic	6. Denmark	7. England& Wales	8. Estonia	9. Finland	10. France	11. Germany	12. Hungary	13. Ireland	14. Italy
<b>How are the multiple technologies selected (A=always, S=sometimes, N=never)?</b>														
All technologies for a specific indication	S	N	S	S	NA	S	N	NA	NA	S	S	NA	N	N
All pharmaceuticals within a therapeutic class	S	S	S	S	NA	S	N	NA	NA	S	S	NA	N	A
Other, .....	A <sup>379</sup>	S <sup>380</sup>			NA	N	A <sup>381</sup>	NA	NA		S <sup>382</sup>	NA	A <sup>383</sup>	N
<b>With what is the pharmaceutical compared with (X=applicable)?</b>														
Whatever is used in registration trials			X		NA			NA	NA			NA		
Best possible care					NA			NA	NA			NA		
Best standard care					NA		X <sup>384</sup>	NA	NA	X <sup>385</sup>		NA	X	
Other, .....	X <sup>379</sup>	X <sup>386</sup>	X <sup>387</sup>	X <sup>388</sup>	NA	X <sup>389</sup>		NA	NA		X <sup>390</sup>	NA		X <sup>391</sup>
<b>Is comparison limited to pharmaceuticals (Y=yes, N=no)?</b>														
	N	N	Y <sup>392</sup>	N	NA	Y	N	NA	NA	N	N	NA	N	Y

<sup>379</sup> As determined by the scope of the cost-effectiveness review

<sup>380</sup> Selected on a case by case basis

<sup>381</sup> All stakeholders are asked to contribute to the identification of the correct process (STA or MTA) and technologies

<sup>382</sup> Selected pharmaceuticals

<sup>383</sup> The preferred comparator for the reference case is 'routine care', that is the technology or technologies most routinely used in clinical practice in Ireland. The scope of the evaluation (number of comparators) may be refined in consultation with key stakeholders

<sup>384</sup> Relevant comparator technologies are chosen as comparator – usually the treatment(s) used in current clinical practice in the NHS to manage the disease or condition (this may include non-licensed technologies if they are used in current clinical practice); sometimes the comparator is best supportive care, palliative therapy or no intervention

<sup>385</sup> Standard care is defined as the validated care in the field

<sup>386</sup> The most similar comparator according to ATC level as long this is reasonable. This is mostly all pharmaceuticals within a therapeutic class however it can also be diverted from this

<sup>387</sup> Most frequently used pharmaceutical in practice

<sup>388</sup> 'Currently accepted therapy' which is defined as the single most prevalent clinical practice (if there is one that is dominant)

<sup>389</sup> All relevant comparators

<sup>390</sup> All technologies for a specific indication or within a therapeutic class or selected comparators

<sup>391</sup> All pharmaceuticals within a therapeutic class

<b>Result table 17b. Comparator/comparison: Full assessment (jurisdictions 1-15)</b>  <b>NA=not applicable (no full assessment in this jurisdiction)</b> <b>X=applicable</b>  <b>Y=yes</b> <b>N=no</b>  <b>A=always</b> <b>S=sometimes</b> <b>N=never?</b>														
	1. Australia	2. Austria	3. Belgium	4. Canada	5. Czech Republic	6. Denmark	7. England& Wales	8. Estonia	9. Finland	10. France	11. Germany	12. Hungary	13. Ireland	14. Italy
<b>Which sources are used by the assessment body to identify the comparator (A=always, S=sometimes, N=never)?</b>														
Indicated by the product sponsor	S <sup>393</sup>	A	S	S	NA	S <sup>394</sup>	A <sup>395</sup>	NA	NA	S	N	NA	A <sup>396</sup>	N
Experts	S <sup>393</sup>	A <sup>397</sup>	A <sup>398</sup>	S	NA	S <sup>394</sup>	A <sup>395</sup>	NA	NA	S	N	NA	A <sup>396</sup>	S
Clinical guidelines	S <sup>393</sup>		A	S	NA	S <sup>394</sup>	A <sup>395</sup>	NA	NA	S	S <sup>399</sup>	NA	A <sup>396</sup>	S
(International) methodological guidelines	S <sup>393</sup>		S	S	NA	S <sup>394</sup>	A <sup>395</sup>	NA	NA	S	N	NA	A <sup>396</sup>	S
Other.....	N	N	N	N	NA	N	N	NA	NA	N	N <sup>400</sup>	NA	N	N
<b>If there are no direct comparisons, are indirect comparisons used in the comparative evaluation (Y=yes, N=no)?</b>	Y <sup>401</sup>	Y		Y		Y		NA	NA	Y <sup>402</sup>	N <sup>403</sup>	NA	Y	Y <sup>404</sup>

<sup>392</sup> For the therapeutic value assessment the comparison is limited to pharmaceuticals, for place in practice the pharmaceutical is also compared to other technologies

<sup>393</sup> PBAC invariably determines whether it accepts the nominated main comparator(s), or substitutes its own determination (with comparative reasons)

<sup>394</sup> Determined by reimbursement committee

<sup>395</sup> all stakeholders are asked to contribute to the identification of the correct comparator

<sup>396</sup> Key stakeholders are consulted in identifying and refining the correct comparators

<sup>397</sup> The assessment body checks if the comparator indicated by the product sponsor is comparative reasonable and may include another comparator

<sup>398</sup> Internal experts in consultation with committee

<sup>399</sup> Identified by internal experts of IQWiG

<sup>400</sup> Sometimes it is decided by G-BA

<sup>401</sup> Preferably determined by frequentist method after exchangeability assessment and determination of most appropriate metric of comparative treatment effect of the pharmaceuticals of interest against the common reference

<sup>402</sup> The methods for indirect comparisons should be according to an internal HAS guideline

<sup>403</sup> In general no quantitative indirect comparisons are performed, sometimes a qualitative description is provided in the conclusion

<sup>404</sup> In general not, however if there are relevant data on morbidity or mortality they can be included

Result table 17b. Comparator/comparison: Full assessment (jurisdictions 16-31)																
<b>NA=not applicable (no full assessment assessment in this jurisdiction)</b> <b>X=applicable</b>  <b>Y=yes</b> <b>N=no</b>  <b>A=always</b> <b>S=sometimes</b> <b>N=never?</b>																
	15. Latvia	16. Luxembourg	17. Malta	18. Netherlands	19. New Zealand	20. Norway	21. Poland	22. Portugal	23. Scotland	24. Slovakia	25. Slovenia	26. Spain	27. Sweden	28. Switzerland	29. Turkey	30. USA
<b>How are the multiple technologies selected (X=applicable)?</b>																
All technologies for a specific indication	S	NA	NA	NA	S	A	S	NA	NA	NA	S	NA	A	NA	A	NA
All pharmaceuticals within a therapeutic class	A	NA	NA	NA	S	N	N	NA	NA	NA	S	NA	A	NA	N	NA
Other, .....		NA	NA	NA	N	N	S <sup>405</sup>	NA	NA	NA	N	NA	N	NA	N	NA
<b>With what is the pharmaceutical compared with (X=applicable)?</b>																
Whatever is used in registration trials		NA	NA	NA				NA	NA	NA	X	NA	A	NA		NA
Best possible care		NA	NA	NA			X	NA	NA	NA	X	NA		NA		NA
Best Standard care	X	NA	NA	NA	X <sup>406</sup>		X	NA	NA	NA	X <sup>407</sup>	NA		NA	X <sup>408</sup>	NA
Other, .....	X <sup>409</sup>	NA	NA	NA		X <sup>410</sup>	X	NA	NA	NA		NA		NA		NA
<b>Is comparison limited to pharmaceuticals (Y=yes, N=no)?</b>																
	N	N	Y		N	NA	Y	N	NA	NA	N	NA	NA	N	Y	N
<b>Which sources are used by the assessment body to identify the comparator (A=always, S=sometimes, N=never)?</b>																
Indicated by the product sponsor	S	NA	NA	NA	S	N	A	NA	NA	NA	A	NA	A	NA	A	NA

<sup>405</sup> According to Polish HTA guidelines the primary comparator for the assessed intervention must be the so-called existing practice. It is also recommended to perform a comparison with other comparators, i.e. the following technologies: ' - the most frequently used, - the cheapest, - the most efficient, - compliant with the standards and guidelines for clinical management

<sup>406</sup> The comparator(s) used in the analyses should be the treatment that most prescribers would replace in NZ clinical practice, and the treatment prescribed to the largest number of patients (if this differs from the treatment most prescribers would replace)

<sup>407</sup> Standard care as for example indicated in guidelines

<sup>408</sup> All comparators

<sup>409</sup> Most commonly used alternative for certain indication

<sup>410</sup> All technologies for a specific indication

<b>Result table 17b. Comparator/comparison: Full assessment (jurisdictions 16-31)</b>		15. Latvia	16. Luxembourg	17. Malta	18. Netherlands	19. New Zealand	20. Norway	21. Poland	22. Portugal	23. Scotland	24. Slovakia	25. Slovenia	26. Spain	27. Sweden	28. Switzerland	29. Turkey	30. USA
<b>NA=not applicable (no full assessment assessment in this jurisdiction)</b> <b>X=applicable</b>																	
<b>Y=yes</b> <b>N=no</b>																	
<b>A=always</b> <b>S=sometimes</b> <b>N=never?</b>																	
Experts	S	NA	NA	NA	NA	S	A	A	NA	NA	NA	A	NA	A	NA	S	NA
Clinical guidelines	A	NA	NA	NA	NA	S	A	A	NA	NA	NA	A	NA	A	NA	A	NA
(International) methodological guidelines	A	NA	NA	NA	NA	?	S	S	NA	NA	NA	A	NA	A	NA	A	NA
Other.....		NA	NA	NA	NA				NA	NA	NA	A <sup>411</sup>	NA		NA	N	NA
<b>If there are no direct comparisons, are indirect comparisons used in the comparative evaluations (Y=yes, N=no)?</b>	Y <sup>412</sup>	NA	NA	NA	NA	Y <sup>413</sup>	Y	Y <sup>414</sup>	NA	NA	NA	Y	NA	N	NA	N	NA

<sup>411</sup> what other countries have choose in their assessments

<sup>412</sup> Only information from systematic reviews, meta-analyses and economic modeling are considered

<sup>413</sup> Bayesian methods are not used, frequentist methods are preferred

<sup>414</sup> The recommended method for performing indirect comparisons of studies with a common comparator depend on the outcome measures used – in the case of odd ratios, it is recommended to use logical regression or metaregression, and in the case of measures such as relative risks, risk difference, difference of mean values or hazard ratios, the recommended methods include adjusted indirect comparison Bucher or metaregression. In justified cases, network meta-analysis can be used

Result table 17b. Summary table: Comparator/comparison: Full assessment												
NA=not applicable (no full assessment assessment in this jurisdiction) X=applicable  Y=yes N=no  A=always S=sometimes N=never?	X	%X									Jurisdictions NA	
How are the multiple technologies selected (X=applicable)?												
All technologies for a specific indication	12	71%									13	
All pharmaceuticals within a therapeutic class	11	65%									13	
Other, .....	6	35%									13	
With what is the pharmaceutical compared with (X=applicable)?	X	%X										
Whatever is used in registration trials	3	18%									13	
Best possible care	2	12%									13	
Best standard care	8	47%									13	
Other, .....	10	59%									13	
	Y	N					Total	%Y	%N		Total	
Is comparison limited to pharmaceuticals?	3	14					17	18%	82%		100%	13
How is the comparator identified by the assessment body?	A	S	N	M	Total	%A	%S	%N	%M	Total		
Indicated by the product sponsor	7	7	3	0	17	41%	41%	18%	0%	100%	13	
Experts	8	8	1	0	17	47%	47%	6%	0%	100%	13	
Clinical guidelines	10	6	1	0	17	59%	35%	6%	0%	100%	13	
(International) methodological guidelines	6	8	2	1	17	35%	47%	12%	6%	100%	13	
Other.....	1	0	16	0	17	6%	0%	94%	0%	100%	13	
	Y	N					Total	%Y	%N		Total	
If there are no direct comparisons, are indirect comparisons used in the comparative evaluations?	14	3					17	82%	18%		100%	13

## Result table 18. Outcomes

<b>Result table 18a. (single) rapid assessment</b>	<b>How are endpoints selected that are included in the assessment?</b>	<b>Which clinical endpoints are accepted for the assessment (overall survival, disease specific survival, event-free survival etc)?</b>
1. Australia	According to their rigor (i.e., more confident conclusions can be drawn from the primary analyses of direct randomised trials than from say secondary or subgroup analyses or from nonrandomised comparisons) and relevance to patients	Any/all. There is no pre-determined minimum standard of outcome (endpoint) according to type of outcome.
2. Austria	Submitted by marketing authorisation holder and validated by assessment body	No general rules, on a case by case basis. Hard clinical endpoints are preferred.
3. Belgium	Identified by internal experts in consultation with committee	Difference in mortality, morbidity and quality of life is preferred
4. Canada	Selected by the marketing authorisation holder according to the submission guidelines	Final clinical outcomes which is defined as relevant and noticeable to patients, including Survival (overall) and/or non-subjective clinical outcome measures, or disease or condition-related events that enable health benefits to be expressed in life-years, QALYs, or events (e.g., myocardial infarction, stroke, or fracture), and surrogate outcomes
5. Czech Republic	Identified by the assessment body according to the indication.	All are accepted however overall survival is preferred
6. Denmark	Selected by medical secretariat	All (clinical relevant endpoints are preferred)
7. England& Wales (UK)	Identified in scoping exercise	Outcome measures can be either intermediate or final endpoints. The clinical outcome measures would usually be expected to have an impact on survival or health-related quality of life (HRQL) and be able to be translated into quality-adjusted life years (QALYs) for the evaluation of cost effectiveness
8. Estonia	Selected by the assessment agency	Clinically important outcomes. Depending on the overall treatment goal. If treatment is life prolonging/saving, then overall survival is paramount. If not available, other alternatives. Overall survival, QALY and other clinically relevant events are preferred.
9. Finland	Submitted by marketing authorisation holder	All. Hard clinical endpoints are and QALYs are preferred
10. France	Critically reviewed by HAS (validated outcomes are preferably selected)	All endpoints, however outcomes related to mortality and/or morbidity are preferred
11. Germany	Selected by assessors (based on legal definitions), however, organisations of patient representatives are consulted for endpoint definition	Mortality, morbidity (complaints and complications), health-related quality of life. In addition, invested time and effort related to the disease and the intervention can be considered as well as patient satisfaction. However, these aspects are normally regarded only as secondary outcomes.
12. Hungary	Endpoints from clinical trials are used	Depends on the disease, however hard endpoints are preferred
13. Ireland	Submitted by marketing authorisation holder and validated by assessment body	For the reference case, outcomes should be expressed as QALYs. In exceptional circumstances a CEA may be conducted using intermediate or final endpoints, provided clear empiric evidence is provided to justify the outcome selected
14. Italy	By the assessment body based on the therapeutic effect	All endpoints that are considered relevant, preferably mortality & morbidity
15. Latvia	Selected by the agency's investigators, based on the 'Baltic	Prevention of death, reduced incidence of complications, reduced incidence of side-

<b>Result table 18a. (single) rapid assessment</b>	<b>How are endpoints selected that are included in the assessment?</b>	<b>Which clinical endpoints are accepted for the assessment (overall survival, disease specific survival, event-free survival etc)?</b>
	guideline for economic evaluations of pharmaceuticals' according to their clinical relevance	effects, incidence of well controlled therapy symptoms, etc
16. Luxembourg	Endpoints are selected by agency according to their clinical relevance	All clinical endpoints are accepted
17. Malta	According to scientific literature after discussing issues with experts	Onset of symptoms, decrease of pain (for pain medication), hospitalisation, overall survival/ survival rate, disease progression, event-free survival (Survival rate and disease progression are preferred)
18. Netherlands	Selected by the assessment agency based on the EMEA guidelines and comparative evaluation guidelines	All endpoints are accepted, however clinical relevant endpoints such as morbidity, mortality and quality of life are preferred
19. New Zealand	Identified by assessment body from the clinical trial and other evidence and sometimes expert opinion	Can be either overall survival, disease specific survival, event-free survival, depending on evidence. Overall survival > disease specific survival > event-free survival
20. Norway	Presented by marketing authorisation holder	All endpoints are accepted
21. Poland	Identified by assessment body: the clinical analysis should evaluate the health effects which represent clinically significant endpoints, playing an important role in a given disease	Patient-oriented clinically significant endpoints (deaths, cases or recoveries, quality of life, adverse effects (divided into serious and non-serious) and/or medical events) or surrogate endpoints. Patient-oriented clinically significant endpoints are preferred
22. Portugal	Preferably from RCT	Depends on the disease. For oncology overall survival is preferred over progression free survival
23. Scotland (UK)	Selected by SMC	Hard clinical endpoints are accepted such as overall survival and quality of life. QALY's are the preferred outcome.
24. Slovakia	Submitted by marketing authorisation holder and verified by assessors	All clinical endpoints are accepted, final clinical endpoints are preferred.
25. Slovenia	Presented by marketing authorisation holder but critically evaluated	All, preference for long-term endpoints
26. Spain	Selected by the agency, usually the endpoints from clinical trials are selected	All of them, depending on the clinical relevance in the pathology and those selected in the clinical studies. Final clinical endpoints are preferred
27. Sweden	Submitted by marketing authorisation holder and critically reviewed by TLV	Morbidity, mortality, QALY, WTP. Hard endpoints are preferred
28. Switzerland	Selected by the agency's investigators based on the submitted data of the marketing authorisation holder	Clinically relevant endpoint (e.g. cardiovascular events, overall survival, increasingly frequently used is progression-free survival)
29. Turkey	Provided by the manufacturer	All clinical relevant endpoints
30. USA	NA	NA

<b>Result table 18b. Outcomes: (single) rapid assessment (jurisdictions 1-15)</b>  <b>NA=not applicable (no (single) rapid assessment in this jurisdiction)</b> <b>Y=yes</b> <b>N=no</b> <b>M=Missing value</b>														
	1. Australia	2. Austria	3. Belgium	4. Canada	5. Czech Republic	6. Denmark	7. England& Wales	8. Estonia	9. Finland	10. France	11. Germany	12. Hungary	13. Ireland	14. Italy
<b>Are the following endpoints included in the assessment?</b>														
<b>Are surrogate endpoints included?</b>	Y <sup>415</sup>	Y	Y <sup>416</sup>	Y <sup>417</sup>	Y <sup>418</sup>	Y <sup>419</sup>	Y <sup>420</sup>	Y <sup>421</sup>	Y <sup>422</sup>	Y <sup>416</sup>	Y <sup>423</sup>	Y	Y <sup>424</sup>	Y <sup>425</sup>
<b>Are composite endpoints included?</b>	Y <sup>415</sup>	Y	Y <sup>426</sup>	Y	Y <sup>418</sup>	Y <sup>427</sup>	Y	Y <sup>428</sup>	Y <sup>422</sup>	Y	Y <sup>429</sup>	Y	Y	Y <sup>425</sup>
<b>Are generic quality of life end-points included?</b>	Y <sup>430</sup>	Y	Y	Y	Y <sup>431</sup>	N	Y <sup>432</sup>	Y <sup>433</sup>	Y	Y <sup>434</sup>	Y	Y	Y	N

<sup>415</sup> If they form the primary outcome in the primary analysis of the relevant direct randomised trial

<sup>416</sup> If no other endpoints are available and if they are considered clinically relevant

<sup>417</sup> Surrogate endpoints may be used as primary endpoints when appropriate (when the surrogate is reasonably likely or well known to predict clinical outcome). If data are not available to support the relationship between surrogate and Final Clinical Outcomes, a cost-consequence should be provided

<sup>418</sup> In general they are accepted however the use should be justified by the marketing authorisation holder

<sup>419</sup> If available, however considered less relevant for the outcome of the decision

<sup>420</sup> Outcomes that are related to the outcome of interest but may be more easily assessed within the context of a clinical study

<sup>421</sup> If no directly clinically relevant measures have been used in trials

<sup>422</sup> If no other endpoints are available

<sup>423</sup> Surrogate outcomes are considered only as proof of a(n) (additional) benefit of an intervention if appropriate statistical methods applied beforehand showed that the effect of an intervention (with a comparable mechanism of action) on the patient-relevant outcome to be substituted was explained to a sufficient degree by the effect on the surrogate outcome. In the case of extremely serious diseases in terms of morbidity and mortality without treatment alternatives, surrogate outcomes of unclear validity may have to be accepted as outcomes that potentially indicate a benefit of an intervention.

<sup>424</sup> Where it has a validated, well established link, with an important patient outcome

<sup>425</sup> If considered relevant

<sup>426</sup> Only if they are regarded as clinical relevant

<sup>427</sup> If available, e.g. cardiologic areas

<sup>428</sup> When these are standard and have been widely used in trials

<sup>429</sup> If all components are patient relevant endpoints. Quality criteria are applicable: for example separate reporting of all components

<sup>430</sup> When they are reported in the relevant direct randomised trials, because they assess patient-relevant outcomes

<sup>431</sup> If submitted by the manufacturer, however this does not happen that often

<sup>432</sup> The measurement of changes in health related quality of life should be reported directly from patients and the value of changes in patients' HRQL (that is, utilities) should be based on public preferences using a choice-based method

<sup>433</sup> If the applicant has decided to submit cost-utility analysis in addition to cost-effectiveness analysis

<sup>434</sup> As complementary data



<b>Result table 18b. Outcomes: (single) rapid assessment (jurisdictions 1-15)</b>														
<b>NA=not applicable (no (single) rapid assessment in this jurisdiction) Y=yes N=no M=Missing value</b>	1. Australia	2. Austria	3. Belgium	4. Canada	5. Czech Republic	6. Denmark	7. England& Wales	8. Estonia	9. Finland	10. France	11. Germany	12. Hungary	13. Ireland	14. Italy
<b>Are utilities used?</b>	Y <sup>435</sup>	N	N	Y	Y	N	Y <sup>436</sup>	Y	Y	N	N	Y	Y <sup>437</sup>	N
<b>Are disease specific quality of life end-points included?</b>	Y <sup>438</sup>	Y	Y	Y	Y <sup>431</sup>	Y	Y <sup>439</sup>	Y <sup>440</sup>	Y	Y <sup>441</sup>	Y	Y	Y	Y <sup>442</sup>
<b>Are safety data taken into account?</b>	Y <sup>443</sup>	Y	Y	Y	Y <sup>444</sup>	Y <sup>445</sup>	Y <sup>446</sup>	Y	Y	Y	Y <sup>447</sup>	Y	Y <sup>448</sup>	Y <sup>449</sup>
<b>Are contra-indications considered?</b>	Y	Y	Y	Y	N	Y	Y <sup>450</sup>	Y	Y	Y <sup>451</sup>	Y <sup>452</sup>	N	Y	Y

<sup>435</sup> If based on HUI2, HUI3, EQ-5D, SF-6D or AQOL

<sup>436</sup> The EQ-5D is the preferred measure of HRQL in adults. The methods to elicit EQ-5D utility values should be fully described. When EQ-5D data are not available or are inappropriate for the condition or effects of treatment, the valuation methods should be fully described and comparable to those used for the EQ-5D. Data collected using condition-specific, preference-based measures may be presented in separate analyses. The use of utility estimates from published literature must be supported by evidence that demonstrates that they have been identified and selected systematically

<sup>437</sup> EQ-5D, SF-6D are accepted to calculate utilities

<sup>438</sup> When they are reported in the relevant direct randomised trials, because they assess patient-relevant outcomes.

<sup>439</sup> When an alternative measure is preferred, those submitting analysis should provide reasons, supported by empirical data on the properties of the instrument used. They should also indicate any evidence that will help the Committee understand to what extent their choice of instrument has impacted on the valuation of the QALYs gained. If direct valuations of descriptions of health states based on HRQL measures other than the EQ-5D are used, the valuation methods must be comparable to those used for the EQ-5D

<sup>440</sup> Only in addition to CEA data

<sup>441</sup> When Quality of life scales are validated and appropriate to the specific disease

<sup>442</sup> If considered relevant, this is however the exemption

<sup>443</sup> As a minimum, the number of trial participants reporting (a) any adverse event, (b) any adverse event resulting in discontinuation of the randomised treatment, (c) any adverse event resulting in hospitalisation, (d) any adverse event resulting in death, and (e) each and every other type of adverse event where the frequency or severity differs substantially across randomised groups, preferably on an intention-to-treatment basis

<sup>444</sup> Deaths due to side-effects and major vs minor side-effects are preferred

<sup>445</sup> all, with special emphasis on potential serious side effects

<sup>446</sup> There is a preference for adverse effects that are important to patients and/or their careers

<sup>447</sup> In particular, adverse effects can be defined as relevant that may: • Completely or almost completely counterbalance the benefit of an intervention; • Substantially differ from adverse effects occurring with (an) otherwise equivalent treatment option(s); • Occur predominantly with treatment options that may be particularly effective; • Have a dose-effect relationship; • Be regarded by patients as especially important; • Be accompanied by serious morbidity or even increased mortality, or be associated with substantial impairment in Quality of life

<sup>448</sup> All adverse effects that are of clinical or economic importance should be included

<sup>449</sup> Preferred are the severity of unintended effects and frequency

<sup>450</sup> Indirectly as contraindications would possibly affect the comparator

<b>Result table 18b. Outcomes: (single) rapid assessment (jurisdictions 1-15)</b>  <b>NA=not applicable (no (single) rapid assessment in this jurisdiction)</b> <b>Y=yes</b> <b>N=no</b> <b>M=Missing value</b>	1. Australia	2. Austria	3. Belgium	4. Canada	5. Czech Republic	6. Denmark	7. England& Wales	8. Estonia	9. Finland	10. France	11. Germany	12. Hungary	13. Ireland	14. Italy
<b>Is a benefit-risk analysis part of the analysis?</b>	Y <sup>453</sup>	Y <sup>453</sup>	N	Y <sup>453</sup>	Y <sup>454</sup>	Y <sup>453</sup>	N	Y	Y <sup>453</sup>	N	N <sup>455</sup>	Y <sup>453</sup>	N	Y <sup>453</sup>
<b>Is the ease of use considered?</b>	N	N	Y	Y	Y	Y	Y <sup>456</sup>	Y	Y	N <sup>457</sup>	N	Y	Y <sup>458</sup>	Y <sup>459</sup>
<b>Is experience with the pharmaceutical considered?</b>	Y	Y	Y	Y	Y	Y	Y <sup>460</sup>	N	Y <sup>422</sup>	Y	N	Y	N	Y

<b>Result table 18b. Outcomes: (single) rapid assessment (jurisdictions 16-31)</b>  <b>NA=not applicable (no (single) rapid assessment in this jurisdiction)</b> <b>Y=yes</b> <b>N=no</b>	15. Latvia	16. Luxembourg	17. Malta	18. Netherlands	19. New Zealand	20. Norway	21. Poland	22. Portugal	23. Scotland	24. Slovakia	25. Slovenia	26. Spain	27. Sweden	28. Switzerland	29. Turkey	30. USA
<b>Are the following endpoints included in the assessment?</b>																
<b>Are surrogate endpoints included?</b>	Y <sup>461</sup>	Y <sup>462</sup>	Y	Y <sup>463</sup>	Y <sup>462</sup>	Y	Y <sup>464</sup>	Y <sup>465</sup>	Y <sup>466</sup>	Y <sup>467</sup>	Y	Y	Y <sup>468</sup>	Y	Y	NA

<sup>451</sup> It is not a major criteria and it is taken into account on a case by case basis

<sup>452</sup> For the inclusion criteria for study selection

<sup>453</sup> Qualitative

<sup>454</sup> In case of orphan pharmaceutical and very innovative pharmaceuticals. It is a qualitative assessment

<sup>455</sup> A benefit / risk assessment is possible according to the methods paper, but has not been done so far

<sup>456</sup> Included in the HRQL

<sup>457</sup> Unless it is demonstrated that the ease of use has clinical impact

<sup>458</sup> This is considered part of HRQL

<sup>459</sup> But not so relevant for the decision making

<sup>460</sup> If experience (as in surgical procedures) affects the efficacy/effectiveness

<sup>461</sup> This depends on illness. They are only included if clinical trials reporting significant outcomes are not available (e.g., rheumatoid arthritis, multiple sclerosis etc.)

<sup>462</sup> If no clinically relevant endpoints are available

<sup>463</sup> If clinical relevant endpoints are not available yet and there is an established connection between the surrogate marker and the clinical relevant endpoint

<b>Result table 18b. Outcomes: (single) rapid assessment (jurisdictions 16-31)</b>		15. Latvia	16. Luxembourg	17. Malta	18. Netherlands	19. New Zealand	20. Norway	21. Poland	22. Portugal	23. Scotland	24. Slovakia	25. Slovenia	26. Spain	27. Sweden	28. Switzerland	29. Turkey	30. USA
<b>NA=not applicable (no (single) rapid assessment in this jurisdiction)</b> <b>Y=yes</b> <b>N=no</b>																	
<b>Are composite endpoints included?</b>	Y <sup>469</sup>	Y	Y <sup>470</sup>	Y	Y <sup>471</sup>	Y	Y	Y	Y <sup>465</sup>	Y <sup>467</sup>	Y	Y	Y	Y <sup>472</sup>	Y	Y	NA
<b>Are generic quality of life end-points included?</b>	N	N	Y <sup>470</sup>	Y <sup>473</sup>	Y	Y	Y	Y	Y <sup>474</sup>	Y	Y <sup>467</sup>	Y	Y	Y <sup>475</sup>	Y	N	NA
<b>Are utilities used?</b>	N	N	N	N	Y	Y	Y	Y	N <sup>476</sup>	N <sup>477</sup>	Y	Y	N	Y	N	N	NA
<b>Are disease specific quality of life end-points included?</b>	N	N	Y <sup>478</sup>	Y	Y	Y	Y	Y	Y <sup>474</sup>	Y	Y <sup>467</sup>	Y	Y	Y	Y	N	NA
<b>Are safety data taken into account?</b>	Y	Y	Y <sup>479</sup>	Y <sup>480</sup>	Y <sup>481</sup>	N <sup>482</sup>	Y	Y <sup>483</sup>	Y <sup>484</sup>	Y	Y	Y	Y	Y	Y	Y <sup>485</sup>	NA
<b>Are contra-indications considered?</b>	Y	Y	Y	Y	Y	N	N	Y	N <sup>486</sup>	Y	Y	Y	Y	Y	?	Y <sup>487</sup>	NA

<sup>464</sup> If no clinical trials with patient-oriented clinically significant endpoints have been found, surrogates can be assessed as the outcomes. In this case it is recommended to present the relationship between the surrogates used and the clinically significant endpoints in the analysis

<sup>465</sup> If no better evidence is available

<sup>466</sup> Only accepted as leads to hard endpoints

<sup>467</sup> However decided on a case by case basis

<sup>468</sup> Only validated surrogate endpoints are accepted - e.g. surrogate endpoints recommended by EMA, FDA, ICH etc.

<sup>469</sup> if clinical trials reporting single outcomes are not available

<sup>470</sup> No policy is determined yet regarding this as it has not been the case yet

<sup>471</sup> If other endpoints are not available

<sup>472</sup> Only in rare and selected cases

<sup>473</sup> EQ-5D is preferred

<sup>474</sup> If considered relevant for the disease

<sup>475</sup> On a case-by-case decision

<sup>476</sup> They are only included in cost effectiveness assessment

<sup>477</sup> Only in cost-effectiveness analysis

<sup>478</sup> For example in oncology/ palliative care

<sup>479</sup> Deaths due to side-effects, major vs minor side-effects, contra-indications

<sup>480</sup> Drop-out from study due to side effects is considered a very relevant outcome however all endpoints available may be used. Also considered very relevant are severe side-effects and frequent side-effects

<sup>481</sup> drop-out from study due to side effects, deaths due to side-effects, major side-effects, irreversible side-effects

<sup>482</sup> Only if they are provided by the marketing authorisation holder. The manufacturer has to demonstrate seriousness of disease/condition, that long-term treatment is necessary (more than 3 mo), efficacy and cost-effectiveness to be granted reimbursement.

<sup>483</sup> If there are major differences on safety versus comparator

<sup>484</sup> If relative safety is an issue. Difference in side-effects or mortality are preferred

<sup>485</sup> Serious side-effects and side-effects that have impact on the budget

<b>Result table 18b. Outcomes: (single) rapid assessment (jurisdictions 16-31)</b>  <b>NA=not applicable (no (single) rapid assessment in this jurisdiction)</b> <b>Y=yes</b> <b>N=no</b>	15. Latvia	16. Luxembourg	17. Malta	18. Netherlands	19. New Zealand	20. Norway	21. Poland	22. Portugal	23. Scotland	24. Slovakia	25. Slovenia	26. Spain	27. Sweden	28. Switzerland	29. Turkey	30. USA
<b>Is a benefit-risk analysis part of the analysis?</b>	Y <sup>453</sup>	Y <sup>453</sup>	Y <sup>453</sup>	Y <sup>453</sup>	Y <sup>453</sup>	N	Y <sup>453</sup>	Y <sup>488</sup>	Y <sup>453</sup>	Y <sup>489</sup>	Y <sup>453</sup>	Y <sup>453</sup>	N	N <sup>490</sup>	Y <sup>453</sup>	NA
<b>Is the ease of use considered?</b>	N	Y	Y	Y	Y <sup>491</sup>	Y	Y <sup>492</sup>	N	Y	Y	Y	Y	Y	Y	Y	NA
<b>Is experience with the pharmaceutical considered?</b>	N	Y	Y	Y	N	N	Y	Y	Y <sup>493</sup>	Y	Y	Y	N	Y	Y	NA

<sup>486</sup> Contra-indication should be considered by the clinicians. It is assumed that the assessment is only performed for the patient groups that is indicated for the pharmaceutical (this contra-indication is outside of the scope)

<sup>487</sup> Sometimes

<sup>488</sup> Numbers needed to treat (NNT) or numbers needed to harm (NNH)

<sup>489</sup> It can be, however it is not obligatory

<sup>490</sup> Benefit/risk assessment is the task of the approval authority Swissmedic, however the safety of the pharmaceutical is also considered for the discussions regarding reimbursement

<sup>491</sup> But only to a limited extent. It should contribute to the outcome of treatment

<sup>492</sup> Only if it is important

<sup>493</sup> On occasion

Result table 18b. Outcomes: (single) rapid assessment											
NA=not applicable Y=yes N=No M=Missing value											
	Number of jurisdictions	NA		Y	N	M	Total	%Y	%N	%M	Total
Are the following endpoints included in the assessment?											
Are surrogate endpoints included?	30	1		29	0	0	29	100%	0%	0%	100%
Are composite endpoints included?	30	1		28	0	1	29	97%	0%	3%	100%
Are generic quality of life end-points included?	30	1		23	5	1	29	79%	17%	3%	100%
Are utilities used?	30	1		14	15	0	29	48%	52%	0%	100%
Are disease specific quality of life end-points included?	30	1		26	3	0	29	90%	10%	0%	100%
Are safety data taken into account?	30	1		28	1	0	29	97%	3%	0%	100%
Are contra-indications considered?	30	1		23	5	1	29	79%	17%	3%	100%
Is a benefit-risk analysis part of the analysis?	30	1		21	8	0	29	72%	28%	0%	100%
Is the ease of use considered?	30	1		23	6	0	29	79%	21%	0%	100%
Is experience with the pharmaceutical considered?	30	1		22	7	0	29	76%	24%	0%	100%

<b>Result table 18c. Outcomes: Full assessment</b>	<b>How are endpoints selected that are included in the assessment?</b>	<b>Which clinical endpoints are accepted for the assessment (overall survival, disease specific survival, event-free survival etc)?</b>
1. Australia	According to their rigor (i.e., more confident conclusions can be drawn from the primary analyses of direct randomised trials than from say secondary or subgroup analyses or from nonrandomised comparisons) and relevance to patients	Any/all. There is no pre-determined minimum standard of outcome (endpoint) according to type of outcome.
2. Austria	Submitted by marketing authorisation holder and validated by assessment body.	No general rules, on a case by case basis. Hard clinical endpoints are preferred.
3. Belgium	Identified by internal experts in consultation with committee	Difference in mortality, morbidity and quality of life is preferred
4. Canada	consultations with experts (clinicians), consideration of Patient-reported outcomes, discussion with advisory committee members, international work (vis-à-vis methods, esp pertaining to surrogate outcomes)	Final clinical outcomes which are defined as relevant and noticeable to patients, including survival (overall) and/or non-subjective clinical outcome measures, or disease or condition-related events that enable benefits to be expressed in life-years, QAYS, or events (e.g, MI, stroke, fracture) or surrogate outcomes (preferably validated)
5. Czech Republic	NA	NA
6. Denmark	selected by medical secretariat	All (clinical relevant are preferred)
7. England& Wales (UK)	Identified in scoping exercise	Outcome measures can be either intermediate or final endpoints. The clinical outcome measures would usually be expected to have an impact on survival or health-related quality of life (HRQL) and be able to be translated into quality-adjusted life years (QALYs) for the evaluation of cost effectiveness.
8. Estonia	NA	NA
9. Finland	NA	NA
10. France	Critically reviewed by HAS (validated outcomes are preferably selected)	All endpoints, however outcomes related to mortality and/or morbidity are preferred
11. Germany	Selected by assessors (based on legal definitions), however, organisations of patient representatives are consulted for endpoint definition	Mortality, morbidity (complaints and complications), health-related quality of life. In addition, invested time and effort related to the disease and the intervention can be considered as well as patient satisfaction. However, these aspects are normally regarded only as secondary outcomes.
12. Hungary	NA	NA
13. Ireland	Identified as part of scoping exercise	For the reference case, outcomes should be expressed as QALYs. In exceptional circumstances a CEA may be conducted using intermediate or final endpoints, provided clear empiric evidence is provided to justify the outcome selected
14. Italy	By the assessment body based on the therapeutic effect	All endpoints that are considered relevant, preferably mortality & morbidity

<b>Result table 18c. Outcomes: Full assessment</b>	<b>How are endpoints selected that are included in the assessment?</b>	<b>Which clinical endpoints are accepted for the assessment (overall survival, disease specific survival, event-free survival etc)?</b>
15. Latvia	Selected by the agency's investigators, based on the 'Baltic guideline for economic evaluations of pharmaceuticals' according to their clinical relevance	Prevention of death, reduced incidence of complications, reduced incidence of side-effects, incidence of well controlled therapy symptoms, etc.
16. Luxembourg	NA	NA
17. Malta	NA	NA
18. Netherlands	NA	NA
19. New Zealand	Identified by assessment body from the clinical trial and other evidence and sometimes expert opinion	Can be either overall survival, disease specific survival, event-free survival, depending on evidence. Overall survival > disease specific survival > event-free survival
20. Norway	Identified by NOKC with clinicians	Patient-centred endpoints are preferred
21. Poland	The clinical analysis should evaluate the health effects which represent clinically significant endpoints, playing an important role in a given disease	Patient-oriented clinically significant endpoints (deaths, cases or recoveries, quality of life, adverse effects (divided into serious and non-serious) and/or medical events) or surrogate endpoints. Patient-oriented clinically significant endpoints are preferred.
22. Portugal	NA	NA
23. Scotland (UK)	NA	NA
24. Slovakia	NA	NA
25. Slovenia	Presented by marketing authorisation holder but critically evaluated	All, preference for long-term endpoints
26. Spain	NA	NA
27. Sweden	Selected by the agency	Morbidity, mortality, QALY
28. Switzerland	NA	NA
29. Turkey	Provided by the manufacturer	All clinical relevant endpoints
30. USA	NA	NA

<b>Result table 18d. Outcomes: Full assessment ( 1-15)</b>														
<b>NA=not applicable (no full assessment in this jurisdiction)</b> <b>Y=yes</b> <b>N=no</b>														
	1. Australia	2. Austria	3. Belgium	4. Canada	5. Czech Republic	6. Denmark	7. England& Wales	8. Estonia	9. Finland	10. France	11. Germany	12. Hungary	13. Ireland	14. Italy
<b>Are the following endpoints included in the assessment?</b>														
<b>Are surrogate endpoints included?</b>	Y <sup>494</sup>	Y	Y <sup>495</sup>	Y	NA	Y <sup>496</sup>	Y <sup>497</sup>	NA	NA	Y <sup>495</sup>	Y <sup>498</sup>	NA	Y	Y <sup>499</sup>
<b>Are composite endpoints included?</b>	Y <sup>415</sup>	Y	Y <sup>500</sup>	Y	NA	Y <sup>501</sup>	Y	NA	NA	Y	Y <sup>502</sup>	NA	Y	Y <sup>425</sup>
<b>Are generic quality of life end-points included?</b>	Y <sup>503</sup>	Y	Y	Y	NA	N	Y <sup>504</sup>	NA	NA	Y <sup>505</sup>	Y	NA	Y	N
<b>Are utilities used?</b>	Y <sup>506</sup>	N	N	Y	NA	N	Y <sup>507</sup>	NA	NA	N	N	NA	Y	N
<b>Are disease specific quality of life end-points included?</b>	Y <sup>508</sup>	Y	Y	Y	NA	Y	Y <sup>509</sup>	NA	NA	Y <sup>510</sup>	Y	NA	Y	Y <sup>511</sup>

<sup>494</sup> If they form the primary outcome in the primary analysis of the relevant direct randomised trial

<sup>495</sup> If no other endpoints are available and if they are considered clinically relevant

<sup>496</sup> If available, however considered less relevant for the outcome of the decision

<sup>497</sup> Outcomes that are related to the outcome of interest but may be more easily assessed within the context of a clinical study

<sup>498</sup> Surrogate outcomes are considered only as proof of a(n) (additional) benefit of an intervention if appropriate statistical methods applied beforehand showed that the effect of an intervention (with a comparable mechanism of action) on the patient-relevant outcome to be substituted was explained to a sufficient degree by the effect on the surrogate outcome. In the case of extremely serious diseases in terms of morbidity and mortality without treatment alternatives, surrogate outcomes of unclear validity may have to be accepted as outcomes that potentially indicate a benefit of an intervention

<sup>499</sup> If considered relevant

<sup>500</sup> Only if they are regarded as clinical relevant

<sup>501</sup> If available, e.g. cardiologic areas

<sup>502</sup> If all components are patient relevant endpoints. Quality criteria are applicable: for example separate reporting of all components

<sup>503</sup> When they are reported in the relevant direct randomised trials, because they assess patient-relevant outcomes

<sup>504</sup> The measurement of changes in health related quality of life should be reported directly from patients and the value of changes in patients' HRQL (that is, utilities) should be based on public preferences using a choice-based method

<sup>505</sup> As complementary data

<sup>506</sup> If based on HUI2, HUI3, EQ-5D, SF-6D or AQOL

<sup>507</sup> The EQ-5D is the preferred measure of HRQL in adults. The methods to elicit EQ-5D utility values should be fully described. When EQ-5D data are not available or are inappropriate for the condition or effects of treatment, the valuation methods should be fully described and comparable to those used for the EQ-5D. Data collected using condition-specific, preference-based measures may be presented in separate analyses. The use of utility estimates from published literature must be supported by evidence that demonstrates that they have been identified and selected systematically

<sup>508</sup> When they are reported in the relevant direct randomised trials, because they assess patient-relevant outcomes



<b>Result table 18d. Outcomes: Full assessment ( 1-15)</b>  <b>NA=not applicable (no full assessment in this jurisdiction)</b> <b>Y=yes</b> <b>N=no</b>	1. Australia	2. Austria	3. Belgium	4. Canada	5. Czech Republic	6. Denmark	7. England& Wales	8. Estonia	9. Finland	10. France	11. Germany	12. Hungary	13. Ireland	14. Italy
<b>Are safety data taken into account?</b>	Y <sup>512</sup>	Y	Y	Y	NA	Y <sup>513</sup>	Y <sup>514</sup>	NA	NA	Y	Y <sup>515</sup>	NA	Y	Y <sup>516</sup>
<b>Are contra-indications considered?</b>	Y	Y	Y	Y	NA	Y	Y <sup>517</sup>	NA	NA	Y <sup>518</sup>	Y <sup>519</sup>	NA	Y	Y
<b>Is a benefit-risk analysis part of the analysis?</b>	Y <sup>520</sup>	Y <sup>520</sup>	N	Y <sup>520</sup>	NA	Y <sup>520</sup>	N	NA	NA	N	N <sup>521</sup>	NA	N	Y <sup>520</sup>
<b>Is the ease of use considered?</b>	N	N	Y	Y	NA	Y	Y <sup>522</sup>	NA	NA	N <sup>523</sup>	N	NA	Y	Y <sup>524</sup>
<b>Is experience with the pharmaceutical considered?</b>	Y	Y	Y	Y	NA	Y	Y <sup>525</sup>	NA	NA	Y	N	NA	N	Y

<sup>509</sup> When an alternative measure is preferred, those submitting analysis should provide reasons, supported by empirical data on the properties of the instrument used. They should also indicate any evidence that will help the Committee understand to what extent their choice of instrument has impacted on the valuation of the QALYs gained. If direct valuations of descriptions of health states based on HRQL measures other than the EQ-5D are used, the valuation methods must be comparable to those used for the EQ-5D

<sup>510</sup> When Quality of life scales are validated and appropriate to the specific disease

<sup>511</sup> If considered relevant, this is however the exemption

<sup>512</sup> As a minimum, the number of trial participants reporting (a) any adverse event, (b) any adverse event resulting in discontinuation of the randomised treatment, (c) any adverse event resulting in hospitalisation, (d) any adverse event resulting in death, and (e) each and every other type of adverse event where the frequency or severity differs substantially across randomised groups, preferably on an intention-to-treatment basis

<sup>513</sup> All, with special emphasis on potential serious side effects

<sup>514</sup> There is a preference for adverse effects that are important to patients and/or their careers

<sup>515</sup> In particular, adverse effects can be defined as relevant that may: • Completely or almost completely counterbalance the benefit of an intervention; • Substantially differ from adverse effects occurring with (an) otherwise equivalent treatment option(s); • Occur predominantly with treatment options that may be particularly effective; • Have a dose-effect relationship; • Be regarded by patients as especially important; • Be accompanied by serious morbidity or even increased mortality, or be associated with substantial impairment in Quality of life

<sup>516</sup> Preferred are the severity of unintended effects and frequency

<sup>517</sup> Indirectly as contraindications would possibly affect the comparator

<sup>518</sup> It is not a major criteria and it is taken into account on a case by case basis

<sup>519</sup> For the inclusion criteria for study selection

<sup>520</sup> Qualitative

<sup>521</sup> A benefit / risk assessment is possible according to the methods paper, but has not been done so far

<sup>522</sup> Included in the HRQL

<sup>523</sup> Unless it is demonstrated that the ease of use has clinical impact

<sup>524</sup> But not so relevant for the decision making

<sup>525</sup> If experience (as in surgical procedures) affects the efficacy/effectiveness

<b>Result table 18d. Outcomes: Full assessment ( 16-31)</b>	15. Latvia	16. Luxembourg	17. Malta	18. Netherlands	19. New Zealand	20. Norway	21. Poland	22. Portugal	23. Scotland	24. Slovakia	25. Slovenia	26. Spain	27. Sweden	28. Switzerland	29. Turkey	30. USA
<b>NA=not applicable (no full assessment in this jurisdiction)</b> <b>Y=yes</b> <b>N=no</b>																
<b>Are the following endpoints included in the assessment?</b>																
<b>Are surrogate endpoints included?</b>	Y <sup>526</sup>	NA	NA	NA	Y <sup>462</sup>	Y <sup>527</sup>	Y <sup>528</sup>	NA	NA	NA	Y	NA	Y	NA	Y	NA
<b>Are composite endpoints included?</b>	Y <sup>529</sup>	NA	NA	NA	Y <sup>530</sup>	N	Y	NA	NA	NA	Y	NA	Y	NA	Y	NA
<b>Are generic quality of life end-points included?</b>	N	NA	NA	NA	Y	Y	Y	NA	NA	NA	Y	NA	Y	NA	N	NA
<b>Are utilities used?</b>	N	NA	NA	NA	Y	Y	Y	NA	NA	NA	Y	NA	Y	NA	N	NA
<b>Are disease specific quality of life end-points included?</b>	N	NA	NA	NA	Y	Y <sup>531</sup>	Y	NA	NA	NA	Y	NA	Y	NA	N	NA
<b>Are safety data taken into account?</b>	Y	NA	NA	NA	Y <sup>532</sup>	Y <sup>533</sup>	Y	NA	NA	NA	Y	NA	Y	NA	Y <sup>534</sup>	NA
<b>Are contra-indications considered?</b>	Y	NA	NA	NA	Y	N	N	NA	NA	NA	Y	NA	Y	NA	Y <sup>535</sup>	NA
<b>Is a benefit-risk analysis part of the analysis?</b>	Y <sup>520</sup>	NA	NA	NA	Y <sup>520</sup>	Y <sup>536</sup>	Y <sup>520</sup>	NA	NA	NA	Y <sup>453</sup>	NA	Y	NA	Y <sup>520</sup>	NA
<b>Is the ease of use considered?</b>	N	NA	NA	NA	Y	Y	Y <sup>537</sup>	NA	NA	NA	Y	NA	Y	NA	Y	NA
<b>Is experience with the pharmaceutical considered?</b>	N	NA	NA	NA	N	N	Y	NA	NA	NA	Y	NA	N	NA	Y	NA

<sup>526</sup> This depends on illness. They are only included if clinical trials reporting significant outcomes are not available (e.g., rheumatoid arthritis, multiple sclerosis etc.)

<sup>527</sup> Only if there is an established link

<sup>528</sup> If no clinical trials with patient-oriented clinically significant endpoints have been found, surrogates can be assessed as the outcomes. In this case it is recommended to present the relationship between the surrogates used and the clinically significant endpoints in the analysis

<sup>529</sup> If clinical trials reporting single outcomes are not available

<sup>530</sup> If other endpoints are not available

<sup>531</sup> EQ-5d preferred

<sup>532</sup> drop-out from study due to side effects, deaths due to side-effects, major side-effects, irreversible side-effects

<sup>533</sup> Death, drop out, major vs minor

<sup>534</sup> Serious side-effects and side-effects that have impact on the budget

<sup>535</sup> Sometimes

<sup>536</sup> Quantitative through modeling

<sup>537</sup> Only if it is important

Result table 18d Summary table:. Outcomes: Full assessment											
NA=not applicable Y=yes N=No M=Missing value											
	Number of jurisdictions	NA		Y	N	M	Total	%Y	%N	%M	Total
Are the following endpoints included in the assessment?											
Are surrogate endpoints included?	30	13		17	0	0	17	100%	0%	0%	100%
Are composite endpoints included?	30	13		16	1	0	17	94%	6%	0%	100%
Are generic quality of life end-points included?	30	13		13	4	0	17	76%	24%	0%	100%
Are utilities used?	30	13		9	8	0	17	53%	47%	0%	100%
Are disease specific quality of life end-points included?	30	13		15	2	0	17	88%	12%	0%	100%
Are safety data taken into account?	30	13		17	0	0	17	100%	0%	0%	100%
Are contra-indications considered?	30	13		15	2	0	17	88%	12%	0%	100%
Is a benefit-risk analysis part of the analysis?	30	13		12	5	0	17	71%	29%	0%	100%
Is the ease of use considered?	30	13		12	5	0	17	71%	29%	0%	100%
Is experience with the pharmaceutical considered?	30	13		11	6	0	17	65%	35%	0%	100%

## Result table 19. Level of evidence and extrapolation

<b>Result table 19a. Level of evidence and extrapolation: (single) rapid assessment (jurisdictions 1-15)</b>  <b>NA=not applicable (no (single) rapid assessment in this jurisdiction)</b> <b>A=always</b> <b>S=sometimes</b> <b>N=never</b>														
	1. Australia	2. Austria	3. Belgium	4. Canada	5. Czech Republic	6. Denmark	7. England& Wales	8. Estonia	9. Finland	10. France	11. Germany	12. Hungary	13. Ireland	14. Italy
<b>Is a classification system used to indicate the quality of the studies included (internal validity)?</b>	A <sup>538</sup>	A <sup>539</sup>	S <sup>540</sup>	S <sup>541</sup>	A <sup>542</sup>	A <sup>543</sup>	A	N	N	N <sup>544</sup>	A	N	N	S <sup>545</sup>
<b>Is the generalisability of the study data (e.g. RCTs) to the proposed population considered (external validity)?</b>	A <sup>546</sup>	A	A	A	S <sup>547</sup>	A	A	A	A	A	A	S	A	S
<b>Is the effectiveness of the comparative evaluation assessed as part of the analysis?</b>	A	S	A	A	A	S	A	S <sup>548</sup>	S	A	A	S	A	S
<b>How is the effectiveness assessed if not available through clinical trial data?</b>														
Qualitative description based on efficacy data	S <sup>549</sup>	S <sup>550</sup>	A	A	S	S	A	S	S	A	N	N	S	N <sup>551</sup>
Quantitative extrapolation (e.g. modeling) of efficacy data	S <sup>552</sup>	N	N	A	S	N	A	N	N	N	N	N	S	N

<sup>538</sup> The approach pre-dates, but is generally consistent with GRADE

<sup>539</sup> Hierarchy is used that was developed by the assessment body

<sup>540</sup> The selection of the classification system (internal validity) is dependent on body of literature

<sup>541</sup> Grade

<sup>542</sup> Own developed classification system based on EBM

<sup>543</sup> 'Quality of evidence', with a ranking in levels A - D for evidence, defined by the UK NHS.

<sup>544</sup> The internal validity is always considered but no classification system is used

<sup>545</sup> No specific instrument

<sup>546</sup> The term used is "applicability".

<sup>547</sup> Mainly for evaluations of new pharmaceuticals

<sup>548</sup> If data are available

<sup>549</sup> Less often

<sup>550</sup> The qualitative description is limited to whether data are generalisable

<sup>551</sup> AIFA ask for a registry if they feel the clear need for effectiveness data that are not available yet

Result table 19a. Level of evidence and extrapolation: (single) rapid assessment (jurisdictions 1-15)															
NA=not applicable (no (single) rapid assessment in this jurisdiction) A=always S=sometimes N=never															
	1. Australia	2. Austria	3. Belgium	4. Canada	5. Czech Republic	6. Denmark	7. England& Wales	8. Estonia	9. Finland	10. France	11. Germany	12. Hungary	13. Ireland	14. Italy	
If data on long-term effects are absent, are short term clinical data extrapolated?															
No extrapolation	S <sup>553</sup>	A	N	S	S <sup>554</sup>	S	N	S	S	A	A	S	S	A	
Qualitative description based on short-term data	S <sup>555</sup>	N	A	S	N	S	A	S	S	N	N	S	S	N	
Quantitative extrapolation (e.g. modeling) of short-term data	S <sup>552</sup>	N	N	S	S	N	A	S	S	N	N	S	S	N	

Result table 19a. Level of evidence and extrapolation: (single) rapid assessment (jurisdictions 16-31)															
NA=not applicable (no (single) rapid assessment in this jurisdiction) A=always S=sometimes N=never															
	15. Latvia	16. Luxembourg	17. Malta	18. Netherlands	19. New Zealand	20. Norway	21. Poland	22. Portugal	23. Scotland	24. Slovakia	25. Slovenia	26. Spain	27. Sweden	28. Switzerland	29. Turkey
Is a classification system used to indicate the quality of the	N <sup>556</sup>	S <sup>557</sup>	N	A <sup>558</sup>	S <sup>559</sup>	N	A <sup>560</sup>	N	N	S	S <sup>541</sup>	S <sup>561</sup>	S	N	A <sup>562</sup>

<sup>552</sup> More often

<sup>553</sup> Rarely: but, for example, cure of infection by an antibiotic rarely needs long-term data

<sup>554</sup> Specially in orphan and innovative pharmaceuticals

<sup>555</sup> The PBAC has defined two distinct concepts ("extrapolation" and "transformation" e.g., surrogate to "target clinical outcome") that seem to be combined here

<sup>556</sup> Criteria stated in the 'Baltic Guideline for Economic Evaluations of Pharmaceuticals'

<sup>557</sup> Grade

<sup>558</sup> EBRO classification (Evidence Based Richtlijn Ontwikkeling)

<sup>559</sup> Scottish Intercollegiate Guidelines Network (SIGN) see <http://www.pharmac.govt.nz/EconomicAnalysis/pharmacoeconomics>

<sup>560</sup> Jadad scale or QUADAS scale or NOS questionnaire (it depends on the type of study); a separate assessment using modified scales may also be considered; however, their selection should be justified; GRADE

<sup>561</sup> Scientific Evidence Level and Grade of Recommendation

<sup>562</sup> Own developed hierarchy

<b>Result table 19a. Level of evidence and extrapolation: (single) rapid assessment (jurisdictions 16-31)</b>	15. Latvia	16. Luxembourg	17. Malta	18. Netherlands	19. New Zealand	20. Norway	21. Poland	22. Portugal	23. Scotland	24. Slovakia	25. Slovenia	26. Spain	27. Sweden	28. Switzerland	29. Turkey	30. USA
<b>NA=not applicable (no (single) rapid assessment in this jurisdiction)</b> <b>A=always</b> <b>S=sometimes</b> <b>N=never</b>																
<b>studies included (internal validity)?</b>																
<b>Is the generalisability of the study data (e.g. RCTs) to the proposed population considered (external validity)?</b>	A	S	S	A	A	S	A	A	A	A	S	S	A	S	S	NA
<b>Is the effectiveness of the comparative evaluation assessed as part of the analysis?</b>	S	S	A	A	A	S <sup>563</sup>	S	S	A	S <sup>564</sup>	S	S <sup>565</sup>	S	S	A	NA
<b>How is the effectiveness assessed if not available through clinical trial data?</b>																
Qualitative description based on efficacy data	S	A	S	S	S	N	S	A	A	N	S	?	N	N	S	NA
Quantitative extrapolation (e.g. modeling) of efficacy data	S	N	N	N	S	S <sup>566</sup>	S	S	S	N	S	?	A	N	A	NA
<b>If data on long-term effects are absent, are short term clinical data extrapolated?</b>																
No extrapolation	S	N	A	S	S	N	S	S	N	S	S	A	N	S	N	NA
Qualitative description based on short-term data	S	A	N	S	S	N	S	S	S <sup>567</sup>	S	S	N	N	S	S	NA
Quantitative extrapolation (e.g. modeling) of short-term data	S	N	N	N	S	S <sup>566</sup>	S	S <sup>567</sup>	S	S	S	N	A	N	A	NA

<sup>563</sup> Only if data are available and part of CE analysis

<sup>564</sup> Only if data are available

<sup>565</sup> For the comparator, not for the new pharmaceutical

<sup>566</sup> In case of CE analysis

<sup>567</sup> Rarely

Result table 19a. Summary table:. Level of evidence and extrapolation: (single) rapid assessment	Number of jurisdictions	NA											
NA=not applicable (no (single) rapid assessment in this jurisdiction)													
A=always													
S=sometimes													
N=never													
M=missing													
Is a classification system used to indicate the quality of the studies included (internal validity)?	30	1		9	9	11	0	29	31%	31%	38%	100%	
Is the generalisability of the study data (e.g. RCTs) to the proposed population considered (external validity)?	30	1		19	10	0	0	29	66%	34%	0%	100%	
Is the effectiveness of the comparative evaluation assessed as part of the analysis?	30	1		14	15	0	0	29	48%	52%	0%	100%	
How is the effectiveness assessed if not available through clinical trial data?													
Qualitative description based on efficacy data	30	1		7	14	7	1	29	25%	50%	25%	100%	
Quantitative extrapolation (e.g. modeling) of efficacy data	30	1		4	10	14	1	29	14%	36%	50%	100%	
If data on long-term effects are absent, are short term clinical data extrapolated?													
No extrapolation	30	1		6	16	7	0	29	21%	55%	24%	100%	
Qualitative description based on short-term data	30	1		3	17	9	0	29	10%	59%	31%	100%	
Quantitative extrapolation (e.g. modeling) of short-term data	30	1	3	15	11	0	29	10%	52%	38%	100%		

<b>Result table 19b. Level of evidence and extrapolation: Full assessment (jurisdictions 1-15)</b>														
<b>NA=not applicable (no full assessment in this jurisdiction) A=always S=sometimes N=never</b>	1. Australia	2. Austria	3. Belgium	4. Canada	5. Czech Republic	6. Denmark	7. England & Wales	8. Estonia	9. Finland	10. France	11. Germany	12. Hungary	13. Ireland	14. Italy
<b>Is a classification system used to indicate the quality of the studies included (internal validity)?</b>	A <sup>568</sup>	A <sup>569</sup>	S <sup>570</sup>	Y <sup>571</sup>	NA	A <sup>572</sup>	A	NA	NA	N <sup>573</sup>	A	NA	S	S <sup>574</sup>
<b>Is the generalisability of the study data (e.g. RCTs) to the proposed population considered (external validity)?</b>	A <sup>575</sup>	A	A	A	NA	A	A	NA	NA	A	A	NA	A	S
<b>Is the effectiveness of the comparative evaluation assessed as part of the analysis?</b>	A	S	A	A	NA	S	A	NA	NA	A	A	NA	A	S
<b>How is the effectiveness assessed if not available through clinical trial data?</b>														
Qualitative description based on efficacy data	S <sup>576</sup>	S <sup>577</sup>	A	A	NA	S	A	NA	NA	A	N	NA	S	N <sup>578</sup>
Quantitative extrapolation (e.g. modeling) of efficacy data	S <sup>579</sup>	N	N	A	NA	N	A	NA	NA	N	N	NA	S	N
<b>If data on long-term effects are absent, are short term clinical data extrapolated?</b>														
No extrapolation	S <sup>580</sup>	A	N	S	NA	S	N	NA	NA	A	A	NA	N	A

<sup>568</sup> The approach pre-dates, but is generally consistent with GRADE

<sup>569</sup> Hierarchy is used that was developed by the assessment body

<sup>570</sup> Jadad score

<sup>571</sup> GRADE is sometimes used; otherwise, critical appraisal & quality assessment used to inform analysis (e.g., subgroup) and subsequent interpretation

<sup>572</sup> 'Quality of evidence', with a ranking in levels A - D for evidence, defined by the UK NHS

<sup>573</sup> The internal validity is always considered but no classification system is used

<sup>574</sup> No specific instrument

<sup>575</sup> The term used is "applicability"

<sup>576</sup> Less often

<sup>577</sup> The qualitative description is limited to whether data are generalisable

<sup>578</sup> AIFA ask for a registry if they feel the clear need for effectiveness data that are not available yet

<sup>579</sup> More often

<sup>580</sup> Rarely: but, for example, cure of infection by an antibiotic rarely needs long-term data



Qualitative description based on short-term data	S <sup>581</sup>	N	A	S	NA	S	A	NA	NA	N	N	NA	A	N
Quantitative extrapolation (e.g. modeling) of short-term data	S <sup>552</sup>	N	N	S	NA	N	A	NA	NA	N	N	NA	A	N

<b>Result table 19b. Level of evidence and extrapolation: Full assessment (jurisdictions 16-31)</b>  <b>NA=not applicable (no full assessment in this jurisdiction)</b> <b>A=always</b> <b>S=sometimes</b> <b>N=never</b>	15. Latvia	16. Luxembourg	17. Malta	18. Netherlands	19. New Zealand	20. Norway	21. Poland	22. Portugal	23. Scotland	24. Slovakia	25. Slovenia	26. Spain	27. Sweden	28. Switzerland	29. Turkey	30. USA
<b>Is a classification system used to indicate the quality of the studies included (internal validity)?</b>	N <sup>582</sup>	NA	NA	NA	S <sup>583</sup>	A <sup>584</sup>	Y <sup>585</sup>	NA	NA	NA	S <sup>541</sup>	NA	A <sup>586</sup>	NA	A <sup>587</sup>	NA
<b>Is the generalisability of the study data (e.g. RCTs) to the proposed population considered (external validity)?</b>	A	NA	NA	NA	A	A	A	NA	NA	NA	S	NA	A	NA	S	NA
<b>Is the effectiveness of the comparative evaluation assessed as part of the analysis?</b>	S	NA	NA	NA	A	A	S	NA	NA	NA	S	NA	S	NA	A	NA
<b>How is the effectiveness assessed if not available through clinical trial data?</b>																
Qualitative description based on efficacy data	S	NA	NA	NA	S	S	S	NA	NA	NA	S	NA	N	NA	S	NA
Quantitative extrapolation (e.g. modeling) of efficacy data	S	NA	NA	NA	S	S	S	NA	NA	NA	S	NA	S	NA	A	NA
<b>If data on long-term effects are absent, are short term clinical data extrapolated?</b>																
No extrapolation	S	NA	NA	NA	S	S	S	NA	NA	NA	S	NA	N	NA	N	NA
Qualitative description based on short-term data	S	NA	NA	NA	S	S	S	NA	NA	NA	S	NA	S	NA	S	NA
Quantitative extrapolation (e.g. modeling) of short-term data	S	NA	NA	NA	S	S	S	NA	NA	NA	S	NA	S	NA	A	NA

<sup>581</sup> The PBAC has defined two distinct concepts ("extrapolation" and "transformation" e.g., surrogate to "target clinical outcome") that seem to be combined here.

<sup>582</sup> Criteria stated in the 'Baltic Guideline for Economic Evaluations of Pharmaceuticals'

<sup>583</sup> Scottish Intercollegiate Guidelines Network (SIGN) see <http://www.pharmac.govt.nz/EconomicAnalysis/pharmacoeconomics>

<sup>584</sup> Risk of bias tool and GRADE

<sup>585</sup> Jadad scale or QUADAS scale or NOS questionnaire (it depends on the type of study); a separate assessment using modified scales may also be considered; however, their selection should be justified; GRADE

<sup>586</sup> Strength of evidence 1 - 4

<sup>587</sup> Own developed hierarchy

Result table 19b. Summary table: Level of evidence and extrapolation: Full assessment												
NA=not applicable (no (single) rapid assessment in this jurisdiction)	Number of jurisdictions	NA		A	S	N	M	Total	%A	%S	%N	Total
A=always												
S=sometimes												
N=never												
M=missing												
Is a classification system used to indicate the quality of the studies included (internal validity)?	29	12		9	6	2	0	17	53%	35%	12%	100%
Is the generalisability of the study data (e.g. RCTs) to the proposed population considered (external validity)?	29	12		14	3	0	0	17	82%	18%	0%	100%
Is the effectiveness of the comparative evaluation assessed as part of the analysis?	29	12		10	7	0	0	17	59%	41%	0%	100%
How is the effectiveness assessed if not available through clinical trial data?												
Qualitative description based on efficacy data	29	12		4	10	3	0	17	24%	59%	18%	100%
Quantitative extrapolation (e.g. modeling) of efficacy data	29	12		3	8	6	0	17	18%	47%	35%	100%
If data on long-term effects are absent, are short term clinical data extrapolated?												
No extrapolation	29	12		4	8	5	0	17	24%	47%	29%	100%
Qualitative description based on short-term data	29	12		3	10	4	0	17	18%	59%	24%	100%
Quantitative extrapolation (e.g. modeling) of short-term data	29	12		3	8	6	0	17	18%	47%	35%	100%

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