



Managed entry agreements for pharmaceuticals: The European experience¹

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LIST OF ABBREVIATIONS

ADHD	Attention Deficit & Hyperactivity Disorder
AHTAPol	Agency for Health Technology Assessment in Poland (Agencja Oceny Technologii Medycznych (AOTM))
AIFA	Italian Medicines Agency (Agenzia Italiana del Farmaco)
ASMR	Amélioration du Service Médical Rendu (Improvement of Medical Benefit assessment)
ATC	Anatomical Therapeutic Chemical
CED	Coverage with Evidence Development
CEPS	Comité Economique des Produits de Santé (France)
CVZ	Health Insurance Board (College voor zorgverzekeringen)
CC	County Council (Sweden)
EMA	European Medicines Agency
EMINet	European Medicines Information Network
EU	European Union
EUnetHTA	European network for Health Technology Assessment
DH	Department of Health (UK)
HTA	Health Technology Assessment
INFARMED	National Authority of Medicines and Health Product (Autoridade Nacional do Medicamento e Produtos de Saúde), (Portugal)
INN	International Non-proprietary Name
MEAs	Managed Entry Agreements
MS	Member States
NICE	National Institute for Health and Clinical Excellence (England)
NIHDI	National Institute of Health and Disability Insurance (Belgium)
NHF	National Health Fund (Poland)
NHS	National Health Service
OIR	Only in Research
PAS	Patient Access Scheme
PASLU	Patient Access Scheme Liaison Unit (UK)
PBA	Performance-Based Agreement
PVAs	Price-Volume Agreements
PPRS	Pharmaceutical pricing regulation scheme
RSA	Risk-Sharing Agreement
SUKL	State Institute for Drug Control (Státní ústav pro kontrolu léčiv), (Czech Republic)
TLV	Swedish Dental and Pharmaceutical Benefits Agency (Tandvårds- och

	läkemedelsförmånsverket)
VBP	Value-based pricing
UK	United Kingdom

EXECUTIVE SUMMARY

Background

Stretched health care budgets, increasing availability of potentially life-saving high-cost drugs and increasing patient expectations, mean that manufacturers seeking inclusion in reimbursement lists need to demonstrate that their drugs can provide additional benefit in relation to current therapies and value-for-money in order to obtain coverage. Data and the overall evidence base available at registration are often insufficient to accurately estimate the clinical and cost-effectiveness of a drug in clinical practice or its budget impact in real life. Uncertainty, due to lack of information on effectiveness, may delay reimbursement decisions and patient access. Delays together with the threat of non-inclusion in positive lists may dis-incentivise industry from investing in high-risk areas with low market potential such as orphan drugs.

Against this background, formal arrangements between payers and manufacturers with the aim of sharing the financial risk due to uncertainty surrounding the introduction of new technologies have been developed and introduced in order to enable access to new medicines. These agreements can take different forms, including price-volume agreements (PVAs), outcome guarantee, coverage with evidence development (CED), and disease management programmes. A variety of names have been used to describe these schemes (e.g. risk-sharing agreements (RSAs), performance-based agreements (PBAs), patient access schemes (PAS), etc.), which have been recently summarised with the concept of “managed entry agreements (MEAs)”.

Objectives

The aim of this study is threefold. First, to collect quantitative information on MEAs such as the number of agreements by therapeutic area and the types of agreement implemented. Based on this information draw some conclusions on the kind of uncertainty (related to budget impact, clinical and cost-effectiveness or both) payers are trying to address. Second, to develop a taxonomy for MEAs which will be used to classify the identified agreements. Third, to assess MEAs’ ability to address uncertainty, maximise effective use of technology, limit budget impact.

Methods

Data on MEAs implemented in the EU were collected between October 2011 and January 2012 using an online survey developed by EMINet.

Further insights and materials were obtained during the meetings and interviews with drug reimbursement authorities, industry and patients representatives.

Results

Three-quarters (75%) of all the agreements in the study countries aimed to address budget impact, either alone (42%) or in combination with cost effectiveness (16%), use (15%) or both (2%). At country level, two main trends seem to emerge. In some countries, Italy, Portugal, Lithuania, the Czech Republic, and Belgium there was a strong focus on budget impact. While in others, Sweden, the Netherlands and the UK, cost effectiveness seems to be the driving force when deciding to engage in a MEA.

The most common features of MEA across countries were PVAs (40%), followed by requirement for data collection (29.4%), and limited access to eligible patients (12.6%). PVAs are widely used in Italy, Portugal, and Lithuania; data collection is a common requirement in Italy, the Netherlands, the Czech Republic and Sweden. Further, Italy, the Czech Republic and Belgium, limit access of certain medicines to eligible patients in an attempt to manage budget impact and use.

In terms of therapeutic groups, antineoplastic and immune-modulating agents represented 37.3% of all the MEAs implemented in the study countries, followed by alimentary tract and metabolism 16.5% and nervous system 9.8%. All member states apart from Sweden (only one MEA for ATC-L vs. 3 MEA for both ATC-B and ATC-N) the greatest proportion of agreement involved ATC-L drugs.

Discussion

Managing budget impact is one the main objectives of MEAs in Belgium, the Czech Republic, Italy, Lithuania, Portugal, and the UK. This is reflected in the design of MEAs in these countries which includes features of PVAs, budget caps, and a compensation mechanism in Belgium, limited access through specialised healthcare centres in the Czech Republic, PVAs, discounts and conditional treatment continuation in Italy, PVAs, payback, and expenditure cap in Lithuania, PVAs in Portugal PVAs, and discounts, dose capping, initial free doses in the

UK. Sweden takes a more indirect approach by requesting the manufacturer to submit utilisation data to TLV which will be used at the end of the conditional reimbursement period to update the reimbursement decision.

There are two main ways to address uncertainty relating to clinical and/or cost-effectiveness. The first is to grant reimbursement for a limited time period during which additional evidence on the drug effectiveness will be collected and to update the reimbursement decision afterwards based on the new cost-effectiveness results. This model is used in the Netherlands, Sweden and Portugal. The second way is to decrease the price or to limit utilisation so that the cost-effective ratio is improved because of lower costs. Discounts are very common in the UK as part of patient access schemes while Italy uses a combination of discounts, payment-by-result and conditional treatment continuation to improve cost-effectiveness. However, this option does not address the underlying issue of uncertainty in cost-effectiveness unless linked with data collection which is intended for updating coverage decision.

The main strategy used to optimise utilisation is to limit prescribing and reimbursement to specific therapeutic indication and to those patients sub-groups who are most likely to benefit. The instruments used include limiting prescribing to specialised healthcare centres, use of biomarkers, and physician certification that the patient meets the eligibility requirements together with monitoring. The Czech Republic for example limits access to specific patient subgroups and to specialised healthcare centres. In Italy, patients eligibility is monitored through the registries and physician are request to certify that a patient meets the prescribing requirements in order for him to obtain the drug at the pharmacy.

Conclusions

European countries are using a variety of instruments to tackle uncertainty arising from lack of information about budget impact, cost-effectiveness, use in real life, and access. Despite the non-negligible number of agreements implemented, little information is available on the impact of these schemes and whether they are meeting their objectives. Moreover, the little amount of information available in the public domain is hampering cross-country learning and the ability of patients to engage in the process.

Previously proposed taxonomies do not well suit the reality at country level, where complex agreements with financial and health outcomes features are implemented. While there is

scope for improvement, the taxonomy employed in this study aims to address this issue by using a more versatile classification system which on one level focuses on the objectives countries are trying to achieve through MEAs and on a second level highlights and summarises the features of the implemented agreements. Further there is the need to agree on a common definition of MEAs and to define the boundaries between a MEA and a non-MEA.

1 Background

Stretched health care budgets, increasing availability of potentially life-saving high-cost drugs and increasing patient expectations, mean that manufacturers seeking inclusion in reimbursement lists need to demonstrate that their drugs can provide additional benefit and value-for-money in order to obtain coverage. Achieving value for money in health care is high in the health reform literature and agenda; particularly in the area of introducing new technologies and therapies (Scottish Medicines Consortium 2011; OECD 2010; UK Department of Health and ABPI 2008; Network 2007). Countries increasingly try to achieve this by using health technology assessment (HTA) as a tool to evaluate the clinical and cost-effectiveness of new drugs. However, data and the overall evidence base available at registration are often insufficient to accurately estimate the clinical and cost-effectiveness of a drug in clinical practice or its budget impact in real life. Uncertainty, due to lack of information on effectiveness, may delay reimbursement decisions and patient access. Delays together with the threat of non-inclusion in positive lists may dis-incentivise industry from investing in high-risk areas with low market potential such as orphan drugs.

Against this background, formal arrangements between payers and manufacturers with the aim of sharing the financial risk due to uncertainty surrounding the introduction of new technologies have been developed and introduced in order to enable access to new medicines. These agreements can take different forms, including price-volume agreements (PVAs), outcome guarantee, coverage with evidence development (CED), and disease management programmes. A variety of names have been used to describe these schemes (e.g. risk-sharing agreements (RSAs), performance-based agreements (PBAs), patient access schemes (PAS), etc.), which have been recently summarised with the concept of “managed entry agreements (MEAs)” (Klemp, Frønsdal, Facey, and HTAi Policy Forum 2011).

The literature on MEAs is mainly discursive given the lack of publicly available data to evaluate them. One suggestion emerging from the literature is that MEAs have the potential to deliver benefits such as faster access to new medicines (Russo et al. 2010), coverage, and an instrument to deal with uncertainty. However, for this to occur, several challenges need to be overcome. Among them are the current general lack of transparency and evidence surrounding these schemes (Adamski et al. 2010), the potential threat of resistance on the provider side described as provider push-back (Carlson, Garrison, and Sullivan 2009; Carlson

et al. 2010), the need for good information systems (Carlson, Garrison, and Sullivan 2009; Carlson et al. 2010) together with the ability to monitor outcome and resource use (McCabe et al. 2009), the responsibility for funding additional data collection (Trueman, Grainger, and Downs 2010) and for conducting the analysis (taking into account potential conflicts of interest), and, very importantly, the development of clear and objective decision-making criteria to guide data collection, evaluation and the final reimbursement decision (de Pouvourville 2006; Stafinski, McCabe, and Menon 2010; Breckenridge and Walley 2008; Carlson et al. 2010; de Pouvourville 2006).

MEAs have also received increasing attention at EU level in recent years. In this context, one of the three independent platforms within the EU process on corporate responsibility in the field of pharmaceuticals looks at access to medicines in Europe. The aim of this platform is to foster collaboration between Member States and relevant stakeholders in order to find common, non-regulatory approaches to timely and equitable access to medicines after their marketing authorisation. This is achieved through the implementation of several projects chaired by the EC and implemented by Member States. One of these projects (“Capacity building on managed entry agreements for innovative medicines”) examines specifically MEAs and aims to investigate agreements currently implemented in EU Member States in order to draw lessons based on their experience.

2 Conceptual framework and objectives

Several authors have contributed to the development of frameworks for classification, design and evaluation of MEAs. A widely used taxonomy for MEAs divides them in two main types: non-health outcome and health-outcome-based agreements (Carlson et al. 2010). These two groups are then further divided into sub-groups based on their individual characteristics. Non-health outcome agreements, for example, are divided according to the level of application, population vs. patient level. These two groups are further divided according to the financial outcome of the agreement, market share or price-volume agreement for population level agreement and utilisation caps or manufacturer funded treatment initiation for patient level agreements. The main distinction among health-outcome agreements is based on the nature of reimbursement, notably conditional or performance-based. Conditional coverage can be implemented either as coverage with evidence development (e.g. in research only or with research only) or as conditional treatment continuation. The main aim of the first is to generate additional evidence to address uncertainty highlighted during the drug review process while the main aim of the second is to treat only patients who benefit of the drug. Performance-linked reimbursement can be implemented either as an outcome guarantee or pattern or process of care. Outcome guarantee protects payers from potentially wasting resources on poorly performing drugs by making manufacturers liable for their products' performance. Patterns or process of care agreement could be described as types of disease management programmes since they investigate elements such as patient adherence to treatment. An alternative taxonomy has been proposed recently (Klemp, Frønsdal, Facey, and HTAi Policy Forum 2011), providing a simpler classification than the previous one and allows more flexibility when applied to individual schemes. A further taxonomy distinguishes between commercial agreements (discount agreements), payment for performance and coverage with evidence development (Jaroslowski and Toumi 2011). Despite the apparent diversity in these taxonomies, they are all based on the same basic structure, notably the separation of non-health outcome (financial) from health-outcome agreements.

Other frameworks focus on features and critical elements of MEAs with the aim of contributing to a better understanding and evaluation of existing systems and improving the design of future ones. Features and critical elements have been analysed (Carbonneil,

Quentin, and Lee-Robin 2009; Towse and Garrison 2010) and evaluation frameworks have been proposed (McCabe, Stafinski, et al. 2010; Menon et al. 2010). A checklist to guide the design and evaluation of MEAs (health-outcome based MEAs) has been recently proposed (Menon et al. 2010). The checklist analyses three main areas, notably, system level characteristics, scheme organisational characteristics, and study design characteristics. An earlier framework looked at elements such as governance procedures, manufacturer's level of engagement, scope, level of operation, evaluation criteria, changes in reimbursement as a result of the agreement, evaluation criteria and scheme financing (McCabe, Stafinski, et al. 2010).

Theoretical approaches to the study of MEAs are also growing. In 2005, a study analysed budget impact from a supplier's perspective (Zaric and O'Brien 2005), while in 2009 delisting was compared after a trial period vs. rebates based on net monetary benefit (NMB) to investigate the conditions under which either arrangement is preferable from the perspective of the payer and the manufacturer (Zaric and Xie 2009). Using a theoretical approach, another study analysed situations in which payers will prefer a managed entry agreement over non-managed entry agreement and concluded that payers' decisions will depend on monitoring costs, marginal production costs, and the utility patients will derive from treatment. In this context, a payer will prefer a MEA when the cost of treating a patient who should not be treated is high and the monitoring costs relatively low; on the other hand, if the treatment costs are low, a payer will prefer a non-MEA (Antonanzas, Juarez-Castello, and Rodriguez-Ibeas 2011). A recent study looked at the economics of MEAs to determine if these arrangements are beneficial to payers from an economic welfare perspective with reference to the UK (Barros 2011). The study concluded that the overall welfare effects of these schemes are ambiguous because more patients than necessary may be treated and because manufacturers, anticipating such agreements, are likely to raise prices and therefore caution against their use was urged (Barros 2011).

Whether MEAs can meet payer, industry, and patient expectations is still unclear, mainly because of the scant evidence available on their outcomes and their performance often available on a case-by-case basis. Performance evaluation is further constrained by limited availability of information on the existing schemes and the details of such arrangements (timeframe, patient eligibility, indicators used to monitor outcomes).

In the light of that, the aim of this study is threefold. First, to collect quantitative information on MEAs such as the number of agreements by therapeutic area and the types of agreement implemented. Based on this information draw some conclusions on the kind of uncertainty (related to budget impact, clinical and cost-effectiveness or both) payers are trying to address. Second, to develop a taxonomy for MEAs which will be used to classify the identified agreements. Third, to assess MEAs' ability to address uncertainty, maximise effective use of technology, limit budget impact.

The analysis focuses on two levels, country level and supra-national level with the aim of highlighting emerging trends. Section 3 outlines the methodology for the EU survey and stakeholder's interviews, section 4 presents the quantitative results from the EU survey, while section 5 presents qualitative evidence from interviews with stakeholder. Section 6, discusses the findings of the study. Finally, section 7 provides an analysis of strengths, weaknesses, opportunities, and threats (SWOT) while section 8 draws the main conclusions.

This survey is the third in a series of studies conducted by European Medicines Information Network (EMINet) in collaboration with the European Union (EU) and Member States. The first study was a literature review on the subject and aimed to provide an overview of the status of MEAs implementation in Europe. The second study investigated availability of MEAs for oncological drugs. This study aims to add this previous work by providing the latest available information on MEAs in EU Member States and to develop a taxonomy which enables the classification of the different types of schemes found in Europe.

3 Methods

The report contains a variety of information arrived at through primary and secondary data collection. Secondary data relates to a systematic review of the literature, whereas primary data collection was conducted through an EU-wide survey of Member States (The EU Survey) and a wider stakeholder analysis through semi-structured interviews. The methods employed are discussed below in further detail.

3.1 Systematic literature review

A systematic literature review was conducted to collect information on MEAs in EU Member States. After having reviewed and tested an extensive list of relevant key words used in the literature to define MEAs (39 different combination of words plus variants), we retained the following key words: “access with evidence”, “conditional coverage” , “conditional reimbursement”, “cost sharing scheme” , “cost sharing schemes” , “coverage with evidence” , “evidence development” , “money back” , “outcomes based contracting” , “outcome/s guarantee” , “patient access scheme/s”, “payment by results” , “pharmaceutical risk sharing” , “price volume agreement/s”, “risk sharing agreement/s”, “risk sharing deals” , “risk sharing scheme/s”.

For the peer-reviewed literature, the following databases were searched: PubMed, Web of Science, and Scopus. Google and Google Scholar were used to retrieve information from the grey literature. For Google and Google Scholar, the first three and four pages respectively were screened beyond which the items retrieved became redundant and increasingly irrelevant. Official websites of national health authorities such as Ministries of Health and HTA agencies were also searched. Country reports of the pharmaceutical price information network were also searched. Only schemes relating to pharmaceuticals were included while medical devices and diagnostic tools were excluded. The search did not apply any language or time limit and all study, newspaper article, report, or document containing information about existing MEA in the study countries was included. The search was first conducted in April 2011 and was updated in October 2011.

3.2 The EU survey

Primary data on MEAs implemented in EU Member States and Norway were collected between October 2011 and January 2012 by using an online survey developed by EMINet and discussed with the European Commission and AIFA, who chairs the MEA working group. The survey comprised two parts; the first part was designed to collect information on the different types of MEAs available (e.g. definition, availability of a legal framework and legislation, and administrative requirements, among others) (see Appendix 1). The second part aimed to identify the characteristics of individual agreements (e.g. drug involved, duration and objective of the agreement, implementation requirements, etc.) (see Appendix 2), to the extent possible.

In October 2011, invitation emails were sent to all the MEAs focal points of the nineteen² countries participating in the activities of the EU platform on access to medicines (MEA working group)³ to invite them to participate to the online survey. Responses were received between October 2011 and January 2012.

The following countries submitted information on MEAs: Belgium, Czech Republic, Denmark (MEAs are not implemented), Finland (MEAs are not implemented), France (only survey 1), Italy, Lithuania, Malta (survey 2 incomplete), the Netherlands, Norway (two MEAs have been implemented but have now come to an end), Portugal, Slovakia, Sweden, the United Kingdom (Appendix 3).

Country responses were downloaded and entered into a common database. The analysis that ensued was performed using Excel and Stata.

3.3 Stakeholder input

In addition to the officially requested input from Member States plus Norway on their use of MEAs, further input was requested from stakeholders, as follows:

² Belgium, Cyprus, Czech Republic, Denmark, France, Finland, Hungary, Italy, Latvia, Lithuania, Malta, the Netherlands, Norway, Poland, Portugal, Slovakia, Spain, Sweden, the United Kingdom

³ The EU platform on access to medicines is one of the three working areas of the Process on Corporate Responsibility in the field of Pharmaceuticals.

Interviews with reimbursement authorities

To supplement the official data received from national respondents, further insights on the implementation of MEAs were obtained (a) during the meeting of the working group on MEAs in Rome on November 14th, 2011, (b) telephone interviews and email correspondence between December 2011 and April 2012, and (c) a meeting in Paris on the 14th of May, 2012. Semi-structured interviews focused on a series of questions as shown in Appendix 4.

Interviewees from whom further insights were obtained, included official representatives of Ministries of Health (France, the Netherlands, Poland, the UK), regulatory and HTA/Medicines agencies (Italy, Denmark, Germany, Portugal, Sweden), an expert from academia (Spain), and representatives from a large sickness fund in Germany. Based on this information, a number of case studies have been added as a separate section to this study building on discussions and interviews with officials and insights obtained from these.

Interviews with manufacturers

Input from EFPIA has been requested. This was discussed both with EFPIA and individually through a number of EFPIA member companies and the industry input was provided by EFPIA. The industry questionnaire is available in Appendix 5.

Interviews with patient representative groups

Semi-structured telephone interviews were conducted with patient representative organisations in Belgium, Italy, Sweden, and the UK in April and May 2012. The patient questionnaire is available in the Appendix 6.

3.4 Taxonomy

In terms of typology, countries have designed a variety of different MEAs in an attempt to achieve three main objectives namely (a) managing budget impact, (b) achieving cost-effective purchasing and (c) monitoring (rational) use. Because creating different groups based on the type of agreement (e.g. PVAs, cost capping, discount, etc.) would have led to the creation of too many group types and to classification issues for agreements whose design entails features of more than one type of agreement, it was decided to base the taxonomy on the objectives countries are trying to achieve through MEAs as proposed in the literature (Klemp, Frønsdal, Facey, and HTAi Policy Forum 2011).

To illustrate the range of different instruments countries are using to achieve these three objectives (budget impact, cost-effective use and monitoring use), the core features of the implemented agreements have been summarised in seven different groups, notably, (a) PVAs, (b) discount, (c) price capping, (d) paying-for-performance, (e) price-match, (f) data collection, and (g) conditional treatment continuation. In this way, it was possible to assign more than one feature to each agreement and therefore addressing the classification issue, which would have arisen if these groups were used for taxonomy rather than characterisation purposes.

A number of terms are used in the literature to identify MEAs and the same agreement can be associated with different names depending on the sources of reference. Therefore, it was felt that some harmonisation of the terminology employed was needed. The taxonomy employed to re-classify the schemes into systematic categories broadly follows the taxonomy proposed in 2010 (Carlson et al. 2010) by distinguishing between non-health and health outcome based schemes but uses a different sub-category classification system because it is more appropriately suited to classify the schemes identified.

Within the first group (non-health outcome-based schemes) there are schemes which aim to contain the cost without taking into consideration health outcomes, notably: discount, price-capping, dose-capping schemes and price-volume agreements (PVAs).

In the second group (health outcome-based schemes), health outcomes are part of the agreement and any discount or reimbursement depends on them. This group comprises outcome-guarantee schemes (e.g. rebates or reimbursement if the medicine fails to achieve the expected results), CED⁴ (may not be linked to any discount or reimbursement and its primary objective is to collect additional clinical data to address knowledge gaps affecting the cost-effectiveness of the product) and disease management programmes which are based on a more holistic approach to a particular disease and its management.

⁴ CED in the UK include “only in research” recommendations (OIR), though it should be noted that these arrangements do not meet the definition of a Patient Access Scheme).

4 MEAs in context

Although MEAs are implemented at country level and in some cases even at subnational level (e.g. at sickness fund level in Germany), it is essential to see them in their supra-national/EU dimension. The context in this dimension is provided by the EU Transparency Directive⁵ and its current revision, the European Medicines Agency (EMA) proposal to introduce adaptive licensing, EU initiatives to harmonise registries at EU level, and discussions in the literature around the need to introduce a model of managed introduction of new medicines which spans from horizon scan activities to post-marketing studies and surveillance.

4.1 EMA: Adaptive licencing

Adaptive licensing has recently been proposed by the EMA as an instrument to balance early access to new medicines to patients with the need of collecting information on the drug benefits and harms. To achieve that, a “staggered approval” is suggested⁶, based on an iterative process of evidence collection followed by regulatory evaluation and license adaptation (EMA 2010; Eichler et al. 2008). The idea would be to initially focus on a population of good responders, followed by adaptation of the licensing conditions as more evidence becomes available (Eichler et al. 2008; EMA 2010). Similar adaptive approaches to drug licensing have been suggested in other countries such as Canada, the US, Singapore (Eichler et al. 2012).

The rationale behind adaptive licensing is the same which led to the development of coverage with evidence development MEAs: enabling patients early to access new drugs while collecting real-life data in order to update the final decision. What is different is the type of decision, for MEAs it is the final reimbursement decision and the related restrictions or recommendations on how a medicine should be used within a health service (UK⁷), for licensing it is about whether the drug should be made accessible at all to patients or sub-

⁵ For which the Commission has published its proposals and these are currently under discussion.

⁶ This “staggered approach” is suggested for situations not covered by conditional marketing authorisations or marketing authorisations under exceptional circumstances.

⁷ In the UK, PAS are not part of pricing & reimbursement decisions. PAS are separate from P&R decisions, PAS are offered in the context of NICE appraisals, which produce guidance for the NHS but do not constitute reimbursement decisions.

groups of patients in the first place. Another difference is the scope, since licensing is partly centralised at EU level, adaptive licensing has the potential to impact all MS in the same way, while the outcome of MEAs, which concerns coverage decisions or recommendations on the use of a medicine, affects each MS in a different way, especially because not all countries are implementing MEA and the drugs concerned vary across MS.

4.2 EUnetHTA

New Technologies is one of the eight work packages (WP) of EUnetHTA Joint Action 2010-12. The aim of this WP is to promote collaboration on new technologies and contribute to reduce duplicative work by fostering exchange of information on and developing tools to facilitate evidence generation (Strand A) and to exchange information on current assessments of new technologies (Strand B). This WP is co-led by the La Haute Autorité de santé in France and the Ludwig Boltzmann Institut in Germany.

4.3 EU initiatives in the field of registries for rare diseases

There are four complementary EU initiatives to improve patient registries for rare diseases: the EPIRARE project, the PARENT joint action, the EUCERD joint action and the International Rare Disease Research Consortium (IRDiRC). The overall aim of these initiatives is to establish common data sets, quality criteria, and a political framework (EUCERD 2011).

4.3.1 The Joint Action on Patient Registries (PARENT)

Starting in September 2012, this initiative will include partners from health ministries and HTA agencies with the aim of rationalising and harmonising the development and governance of patient registries, and enabling the analysis of secondary data for public health and research purposes. This will be achieved by supporting MS in developing comparable and coherent patient registries in fields where this need has been identified (e.g. chronic diseases, rare diseases, medical technology), and supporting MS in the provision of objective, reliable, timely, transparent, comparable and transferable information on the relative efficacy and effectiveness of health technologies.

4.3.2 The European Union Committee of Experts on Rare Diseases

Since January 2012, EUCERD's work to promote exchange of experiences, practices, and policies in the area of rare diseases is supported by a Joint Action. Building on previous work

of the EC Rare disease task force, one of EUCERD's tasks will be to investigate issues around registries such as post-marketing data collection, multi-purpose registries, and sustainability of registries.

4.3.3 The International Rare Disease Research Consortium (IRDiRC)

The IRDiRC was launched in 2011 to promote international collaboration in the area of rare diseases research (IRDiRC). Specific challenges which will be dealt with by the consortium are lack of an exhaustive rare disease classification system including standard terms of reference and common ontologies, as well as harmonised regulatory requirements (IRDiRC). Tackling these issues will greatly enhance potential for international data sharing and research in the area of rare diseases which is currently hampered by limited access to harmonised data/samples, molecular and clinical characterisation, translational/preclinical research, clinical research and cross-cutting aspects (EUCERD 2011). Working together with researchers and organisations working in the field, the IRDiRC goal for 2020 is to deliver 200 new therapies and diagnostic tests for all rare diseases (IRDiRC).

4.3.4 European Platform for Rare Disease Registries (EPIRARE)

EPIRARE started as a three-year project in 2011. It aims to build on the adoption of the EU Council Recommendation on rare diseases (2009/872/CE), which recommends support of registries and databases for epidemiological purpose. The specific aims are first, to define the needs of the EU registries and databases on rare disease; second, to identify key issues from a legal perspective; third to agree on a common data set and data validation; and fourth, to agree on the platform scope, governance and long-term sustainability (EpiRare). The platform comprises 23 partners (academia, international organisations, national health agencies, health care providers, etc.) from 14 countries.

4.4 Managed entry of new pharmaceuticals

The concept of managed entry of new medicines goes from horizon scanning for new compounds which are likely to enter the market within the next 1 to 3 years, to forecasting use and expenditure of the new medicine, to HTA assessment, to pricing and reimbursement, to the development of MEAs and continues with post marketing studies and surveillance (Joppi et al. 2009). However, evidence from a recent literature review on

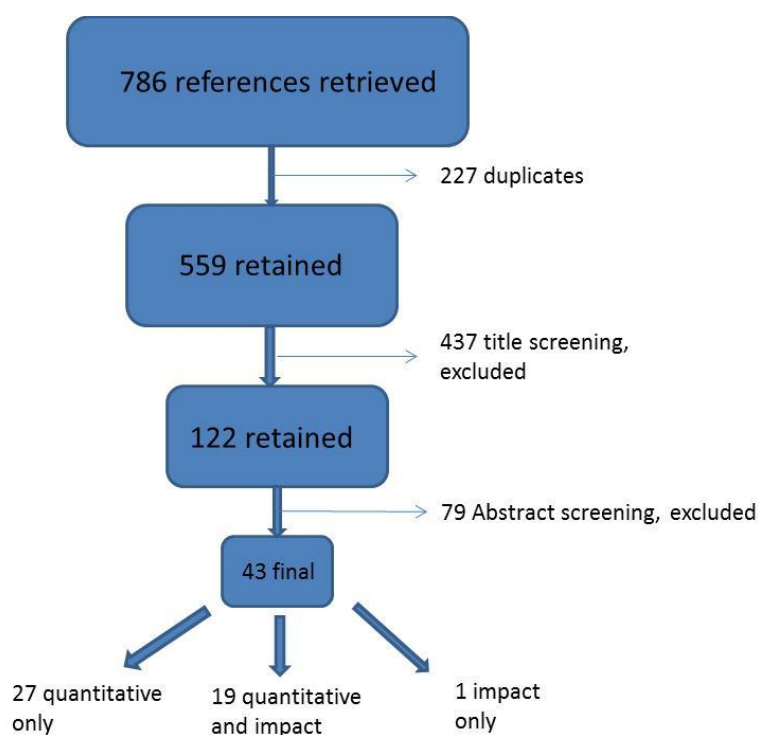
the subject showed that despite several European countries are implementing parts of this model, no European country is currently implementing the full-model (Wettermark et al. 2010).

Following a drug from its pre-market days through HTA assessment and up to post-marketing studies allows more time to collect evidence which will feed into HTA, it enables to assess early the likely budget impact of the new drug and to verify forecasts with post-marketing data. Finally, information from post-launch studies can be used to update national recommendation on the use of the drug. If linked with adaptive licensing this can become a powerful instrument to manage the introduction of new medicines so as to minimise the impact on the healthcare system.

5 Results of the systematic literature review

We retrieved 43 items, 34 from the peer-reviewed literature and 9 from the grey literature (including websites of country medicines and HTA agencies). As shown in Figure 5.1, of these 43 items, 27 contained quantitative (number and type of MEAs) information only, 19 provided quantitative and qualitative information and 1 study presented qualitative (impact) only.

Figure 5.1: Results of the systematic literature review



Source: The authors.

Table 5.1 highlights a few differences between findings from the survey and those from the systematic literature review. For some countries who reported implementing MEAs in the survey, there was no information in the literature (e.g. Czech Republic, Malta); other countries implemented MEAs according to the literature but did not participate in the survey (Germany, Estonia, Hungary, Spain). In these countries, the number of agreements reported to exist in the literature may be incomplete or include agreements, which have now come to an end.

For some of the member states who participated in the survey, no direct comparison between the numbers of MEAs reported by the literature and survey was possible because the former only mentioned the use of MEAs but not the number of agreements implemented (Belgium).

For countries where a comparison of the number of MEA reported by primary and secondary evidence was possible, some discrepancies were evident. Denmark did not consider the two payback schemes implemented in by Roche and Novartis for valsartan and vardenafil respectively as MEA. The reason is that these were campaigns targeted to patient and there was no agreement with the NHS (Engraff 2011). In fact vardenafil is not even covered by the NHS.

In the UK, the 2009 Pharmaceutical Price Regulation Scheme (PPRS) includes the option for pharmaceutical companies to propose Patient Access Schemes (PAS), which are national level arrangements to improve the cost-effectiveness of a medicine being considered as part of a NICE technology appraisal. A scheme is only classified as a PAS if it forms part of NICE appraisal guidance. Pharmaceutical companies may, in addition, offer schemes or discounts to the local NHS outside NICE appraisals as long as these do not contravene any aspect of the PPRS, but decisions on whether to participate in such schemes are a matter for the local NHS and such arrangements are not classified as PAS. The Department of Health does not hold information on these local arrangements and information on them was not included in the list of PAS submitted as part of the survey. Similarly, information was not provided on NICE guidance including “only-in-research” recommendations as these do not meet the definition of a Patient Access Scheme, though some commentators have suggested that they can be seen as CED agreements.

In Italy, information from the literature and the AIFA website included PVAs (although the exact number was not available) and the monitoring registries (full list available on the AIFA website) but did not mention therapeutic plans or the AIFA restricting notes for prescribing. The number of MEAs from the literature was therefore significantly lower than the number of MEAs reported in the survey.

Table 5.1: Comparison between findings of the survey and the literature

Country	No. MEAs identified in the literature	No. MEAs reported in the EMINet EU survey	Literature references
Belgium	<p>Total no. of MEAs: NA</p> <p>A payback system was in place between 2002-2006 which was replaced by a provision fund was developed in 2006</p>	8	(de Swaef and Antonissen 2007)
Cyprus	0	5	
Czech Republic	0	21	
Denmark	<p>Total no. of MEAs: 2</p> <p>Both outcome guarantee</p>	0	(Moldrup 2004)
England and Wales	<p>Total no. of MEAs: 43</p> <p>15 PAS featured in NICE guidance.</p> <p>13 sets of local arrangements including 4 based on PAS proposals which were not included in NICE guidance (so did not become operational PAS) but are implemented in some primary care trusts (PCTs).</p> <p>11 sets of NICE guidance including “only in research” recommendations.</p> <p>Another 2 were not part of any of these groups.</p>	<p>15 PAS, featured in 18 sets of NICE technology appraisal guidance (some PAS apply to a drug’s use in more than one indication).</p> <p>Information accurate at time of submission (Dec 2011).</p>	<p>(Anon 2007; Boggild et al. 2009; Breckenridge and Walley 2008; Briggs et al. 2010; Carroll and Wasiak 2009; Carlson et al. 2010; Chapman et al. 2003; Chapman and Reeve 2002; Chapman et al. 2004; Dobson 2008; Duerden et al. 2004; Fogarty et al. 2010; Garber and McClellan 2007; IMS 2007; Jarosławski and Toumi 2011; Lexchin 2011; Lilford 2010; McCabe, Chilcott, et al. 2010; Muston, Perard, and Nixon 2008; Włodarczyk et al. 2006; NHS Devon 2011; Raftery 2010; Richards 2010; Scolding 2010; Stafinski, McCabe, and Menon 2010; Sudlow and Counsell 2003; Bellelli, Lucchi, and Minicuci 2005; Towse 2010; Towse and</p>

Country	No. MEAs identified in the literature	No. MEAs reported in the EMINet EU survey	Literature references
			Garrison 2010; Trueman, Grainger, and Downs 2010; Pickin et al. 2009) Country official website: (National Institute for Health and Clinical Excellence (NICE) 2011; Anon 2007)
Estonia	Total no. of MEAs: NA PVAs are in place	NA	(Pudersell et al. 2007)
France	Total no. of MEAs: 7 PVA (1), Payback (2), CED (4)	Number of MEAs: NA (only submitted survey 1) PVA, daily treatment cost cap, CED are implemented	Literature: (Carbonneil, Quentin, and Lee-Robin 2009; Stafinski, McCabe, and Menon 2010; Whalen 2007)
Germany	Total no. of MEAs: 15 PVA (3), Utilisation cap (1), Cost capping (1), Discount (1), Outcome-guarantee (4), Disease management (5)	NA	Literature: (Adamski et al. 2010; Anonym 2008; Carlson et al. 2010; Hogan & Hartson 2008; IMS 2007; Pugatch, Healy, and Chu 2010; Rutten, Uyl-de Groot, and Vulto 2009; Senior 2009)
Hungary	Total no. of MEAs: NA A payback scheme is in place since 2003	NA	(Kovács et al. 2007)
Italy	Total no. of MEAs: 78 monitoring registries PVAs are in place	Number of MEAs: 227 <ul style="list-style-type: none"> ▪ AIFA restricting notes for prescription (32) ▪ Monitoring registries (for 78 therapeutic 	Literature: (Agenzia Italiana del Farmaco 2008; Carbonneil, Quentin, and Lee-Robin 2009; De Ambrosis 2008; Garattini and Casadei 2011; IMS 2007; Messori, Fadda, and

Country	No. MEAs identified in the literature	No. MEAs reported in the EMINet EU survey	Literature references
		<p>indications) (the monitoring registries can be limited to data collection or can also include cost-sharing and payment by result agreements)</p> <ul style="list-style-type: none"> ▪ Therapeutic plans (>350 medicinal products clustered according to the 2nd ATC level and resulting in 32 categories) ▪ PVAs (85) 	<p>Trippoli 2011; Russo et al. 2010; Martini, Folino Gallo, and Montilla 2007)</p> <p>Country official website: (Agenzia Italiana del Farmaco (AIFA) 2011)</p>
Lithuania	Total no. of MEAs: NA PVAs are in place	Number of MEAs: 35 PVAs (26), payment by result (9)	(Adamski et al. 2010)
Malta	NA	1 dose cap scheme	
Netherlands	45	39 CED	Literature: (Carbonneil et al. 2009; Niezen et al. 2006; Stichting Farmaceutische Kengetallen 2010)
Poland	NA	NA	
Portugal	Total no. of MEAs: NA PVAs are in place	Number of MEAs: 84 PVAs (74), CED (2), PVAs and CED (8)	Literature: (Teixeira and Vieira 2008)
Scotland	Total no. of MEAs: 14 Discount (8), free doses (4), outcome-guarantee (1), NA (1)	The survey was completed by the Department of Health (in England) which does not hold information on PAS in	Literature: (Adamski et al. 2010) Country official website: (Scottish Medicines

Country	No. MEAs identified in the literature	No. MEAs reported in the EMINet EU survey	Literature references
		Scotland. (In many cases, but not all, the same PAS will be in place across the UK).	Consortium 2011)
Spain	Total no. of MEAs: 2 Both outcome guarantee PVAs are in place	NA	Literature: (Gaceta Médica 2011; Kovács et al. 2007; PortalFarma 2011; Vogler, Espin, and Habl 2009)
Sweden	18 CED	15 CED	Literature: (Carlson et al. 2010; Persson, Willis, and Odegaard 2010; Anell and Persson 2005)

Source: The authors from the literature and the EMINet survey.

6 Results of the EU survey and stakeholder interviews

6.1 The EU Survey

This section presents the results of the EMINet survey on MEAs in EU member states. First, we will present the qualitative results from survey 1 on the main features of MEA models implemented in Europe. In the subsequent sections we will present quantitative and qualitative information from survey 2 including the objectives, common elements, disease focus, legal requirements, and so on.

6.1.1 Overview

Table 6.1 outlines the evidence provided by Member States as part of survey 1 on the types of schemes available in their territory. Evidence shows that a large variety of schemes are implemented across Europe to achieve four main objectives, notably limiting budget impact, improving cost-effectiveness, improving drug use, and increasing access. These schemes range from simple financial schemes (e.g. discount, pay-back, budget cap, PVAs) to more complex schemes involving data collection (e.g. coverage with evidence development) and performance-based schemes.

Table 6.1: Models of managed entry agreement in EU Member States (based on survey 1 and 2)

Name and description	Objectives	Features
Belgium		
<u>Budget capping</u>	1,2	<ul style="list-style-type: none"> - Budget cap - May be linked to data collection as part of an observational study or risk-sharing
<u>Compensation mechanism</u>	1,2	<ul style="list-style-type: none"> - Compensation mechanism - Data collection
<u>Price-volume agreement</u>	1	
Cyprus		
<u>Price-volume agreement upfront agreement: price reduction as the number of cases increases (within the same indication)</u>	1,2	<ul style="list-style-type: none"> - Registry
<u>Price-volume agreement upfront agreement: payments according to Dose capping due to dosage scheme uncertainty or wastage uncertainty</u>	1	<ul style="list-style-type: none"> - Patients registry
<u>Price-volume agreement upfront agreement: Discounts or free goods requested in case of uncertain and/ or unfavourable efficacy or cost effectiveness data</u>	1,2	<ul style="list-style-type: none"> - Patients registry - Usually in line with NICE decisions - Patient access scheme if available
<u>Discounts for usage extension</u>	1,2	<ul style="list-style-type: none"> - Registry
Czech Republic		
<u>Very innovative products (VILP) + AIFA notes: Conditional reimbursement for 12 months for specific indications where the data on efficiency are to be collected.</u>	1,2	<ul style="list-style-type: none"> - Limited reimbursement (specific patient subgroups, after failure of alternative treatment, limited number of doses) - Data collection
France		

<u>Price/volume agreement</u> : For each drug, different levels of sales are and associated repayments are defined. Repayments are later converted into a price cut.	1,2	
<u>Agreement on daily cost of treatment</u> : A target of daily cost of treatment is set. If it is exceeded, the company repays the excess.	1	
<u>Study requirement</u> : The company is required to carry on a specific study concerning the real-life use of the drug. The price can be revised on the basis of its results.	3	
<u>Risk-sharing agreement</u> : A price is set on higher basis than the existing evaluation of the product. If after additional studies, the product gets a better evaluation, the price is maintained. If not, it is decreased and the company pays back the difference.	Uncertainty around effectiveness in real-life	
Italy		
<u>Risk sharing</u> : Discount on price of initial therapy cycle(s) for non-responder patients, identified following clinical evaluation in a pre-set time frame.	2	<ul style="list-style-type: none"> - Discount for non-responders - Conditional treatment continuation (only for patients who positively respond to the drug) - Monitoring Registry
<u>Payment by results</u> : Initial cycle(s) fully reimbursed by manufacturer for non-responder patients (fully reimbursed by the National Health Service for responders), identified following clinical evaluation in a pre-set time frame.	2	<ul style="list-style-type: none"> - Full reimbursement for non-responders - Conditional treatment continuation (only for patients who positively respond to the drug) - Monitoring Registry
<u>Cost sharing</u> : Discount on price of initial therapy cycle(s) for all eligible patients.	1	<ul style="list-style-type: none"> - Initial discount for all eligible patients - Conditional treatment continuation (only for patients who positively respond to the drug) - Monitoring Registry
<u>Monitoring Registries</u> : Registries track the eligibility of patients and the complete flow of treatments. This	2	<ul style="list-style-type: none"> - Collection of patient level data including information on eligibility

guarantees appropriateness of use of medicines according to their approved indications.		for treatment, length of treatment, administered doses, epidemiological data, adverse drug reactions.
<u>Volume based agreements</u> : The Italian Medicines Agency negotiates a volume of sales, related to a target population, with the manufacturer. The volume of sales, exceeding the pre-set threshold, will have to be paid back by the manufacturer to the National Health Service.	1	- Monitoring databases providing sales and expenditures of pharmaceuticals
<u>AIFA-Notes</u> : reimbursement is limited to specific patient sub-groups. The AIFA Note is reported by the general practitioner on the prescription form and this will allow the patient to get the medicinal product free of charge.	3	
<u>Therapeutic Plans</u> : diagnosis and treatment must be reported exclusively by specialised health care centres identified at regional level. This tool guarantees the reimbursement of certain medicines for the authorised therapeutic indications only under close monitoring of the specialists.	3	
Lithuania		
<u>Price volume agreements</u>	1	- The manufacturer has to return a part of the excess expenditure to the NHIF. - Collection of information about medicines consumption and expenditure
<u>Pay back agreements</u>	1	- Pay back mechanism is applied to pharmaceuticals, when reimbursed price is too high compared with similar pharmaceuticals. - Collection of information about medicines consumption and expenditure
<u>Expenditure cap agreement</u>	1	- The manufacturer has to return the excess expenditure to the NHIF entirely. - For drugs which are already on the market and whose expenditure

		<p>is more than 1 million and 1 percent of all expenditure for drug reimbursement.</p> <ul style="list-style-type: none"> - Collection of information about medicines consumption and expenditure
Malta		
<u>Dose capping</u>	NA	<ul style="list-style-type: none"> - Dose capping
The Netherlands		
<u>Coverage with evidence development</u> : Coverage is granted under the condition that cost-effectiveness is determined within a four-year period.	2	<ul style="list-style-type: none"> - Submission of a cost-utility analysis to support continued reimbursement after the initial 4-year study period.
Portugal		
<u>Price-volume agreement</u> : The manufacturer is required to reimburse the NHS if expenditure has exceeded the agreed budget	1	<ul style="list-style-type: none"> - Definition of the universe of patients eligible patients - Establishment of an annual budget limit for NHS. - Re-evaluation of therapeutic added-value and cost-effectiveness at the end of the first two year period. - If the re-evaluation is positive, the agreement is extended for another two-year (for hospital medicines) and new budget limits are established, based on previous sales data, new maximum prices (if they changed) and forecasted evolution of the medicine and the market. - Alternatively, the medicine is included in a global list of reimbursed medicines (without agreement). The manufacturer must submit quarterly data on sales (volume, expenditure and prices) to Infarmed - Promotional activities are limited to the therapeutic indications approved for the medicine - Some agreements have an additional pay-back scheme, in order to guarantee acceptable prices for NHS, while maintaining list prices. For these agreements, the manufacturer must reimburse the NHS of the difference between approved list price and discounted price

		for NHS.
<u>Coverage with evidence development</u> : reimbursement extension after the initial two-year period is conditional to the provision of additional data on cost-effectiveness	2	<ul style="list-style-type: none"> - Re-evaluation of therapeutic added-value and cost-effectiveness at the end of the first two year period. - If the re-evaluation is positive, the agreement is extended for another two-year (for hospital medicines) and new budget limits are established, based on previous sales data, new maximum prices (if they changed) and forecasted evolution of the medicine and the market. - Alternatively, the medicine is included in a global list of reimbursed medicines (without agreement). The manufacturer must submit quarterly data on sales (volume, expenditure and prices) to Infarmed - Promotional activities are limited to the therapeutic indications approved for the medicine - Some agreements have an additional pay-back scheme, in order to guarantee acceptable prices for NHS, while maintaining list prices. For these agreements, the manufacturer must reimburse the NHS of the difference between approved list price and discounted price for NHS.
Sweden		
<u>Coverage with evidence development</u> :	1,2	<ul style="list-style-type: none"> - Depending on the type of uncertainty the manufacturer is required to submit data on use and/or cost-effectiveness
UK - England and Wales		
<u>Patient access schemes</u> : are schemes proposed by a pharmaceutical company and agreed between the company and the Department of Health, with input from NICE, in order to facilitate patient access to cost-effective innovative medicines.	1,4	<ul style="list-style-type: none"> - Discount - Initial free doses - Dose capping

Legend: Objectives 1. Budget impact (BI); 2. Cost-effectiveness (CE); 3. Use; 4. Facilitating access for patients by improving CE

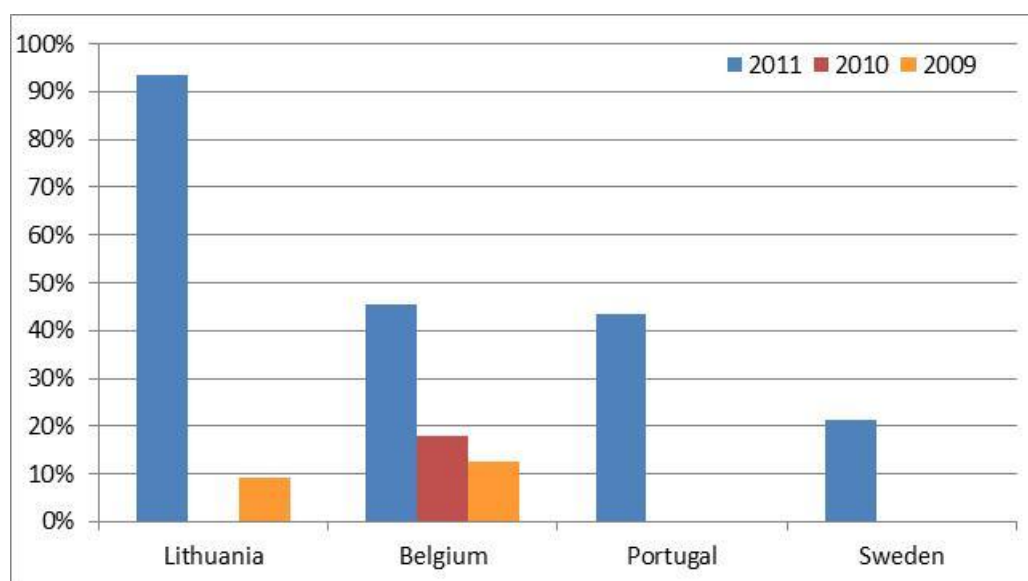
Source: The authors from the EMINet survey.

6.1.2 Implementation of MEAs in EU Member States

In Figure 6.1 and Figure 6.2 an attempt is made to provide two generic but complementary indicators of the prevalence of MEAs in some MS. Figure 6.1 shows that the percentage of MEAs across newly introduced compounds (ATC-5 level) was 93% in Lithuania, followed by Belgium (45%), Portugal (43%), and Sweden (21%) in 2011. Data for Belgium indicate that this percentage has increased quite significantly over time from 12.5% in 2009 to 18% in 2010 and 45 in 2011.

6.1.3 Prevalence of MEAs in EU Member States

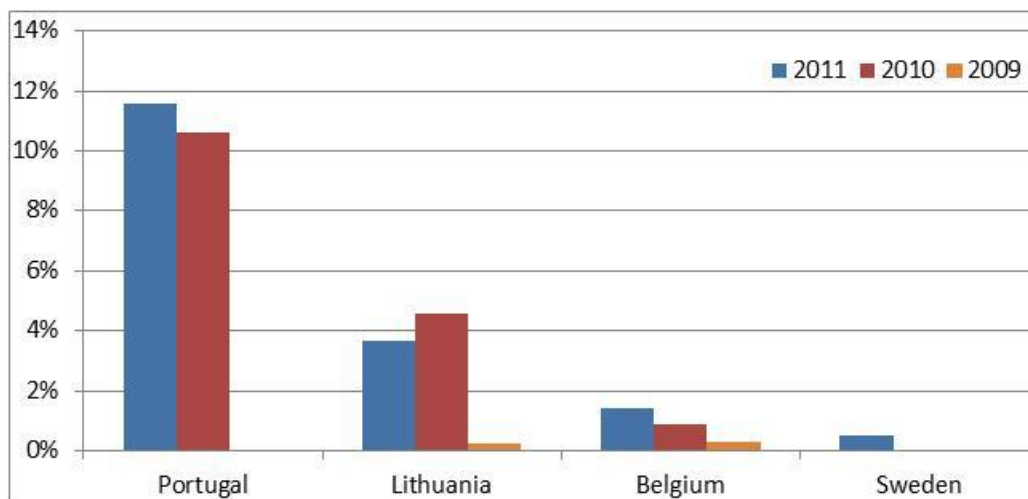
Figure 6.1: Percentage of MEAs across active compounds (ATC-5) on the positive list



Note: Drugs on the positive list are counted at ATC-5 level. If more than one agreement was available for a particular active compound, this was counted as one. For Portugal and for Sweden only data for 2011 were available.

Figure 6.2 shows the percentage of MEAs across active compounds in the positive list (ATC-level 5). These data suggest that in 2011 Portugal had the highest percentage (12%) of MEAs in its positive list, followed Lithuania (3.6%), Belgium (1.4%), and Sweden (0.5%).

Figure 6.2: Percentage of MEAs across newly introduced compounds (ATC-5)



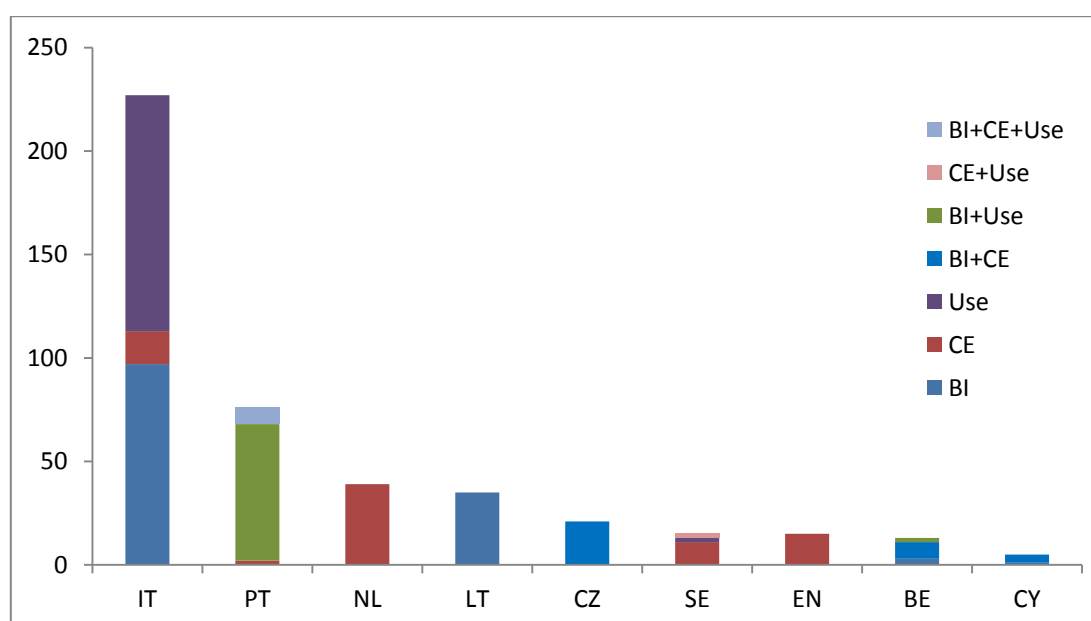
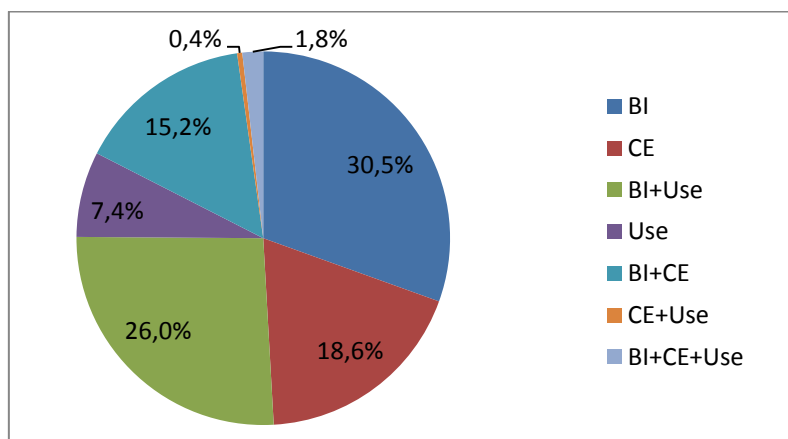
Note: New drugs are counted at ATC-5 level. If more than one agreement was available for a particular active compound, this was counted as one. For Portugal, only data for 2011 and 2010 were available while for Sweden only data for 2011.

Main objectives

Findings from survey 2 show that three-quarters (73.5%) of all the agreements in the study countries aimed to address budget impact, either alone (30.5%) or in combination with use (26.0%), cost effectiveness (15.2%), or both (1.8%) (

Figure 6.3). At country level, two main trends seem to emerge. In some countries, Portugal, Lithuania, the Czech Republic, and Belgium there was a strong focus on budget impact. In Italy about 43% of all agreements focus on budget impact but improving use of medicines emerges as the main objective overall. While in others, Sweden, the Netherlands and the UK, cost effectiveness seems to be the driving force when deciding to engage in a MEA.

Figure 6.3: Objectives Member States are trying to achieve through MEAs overall and at country level



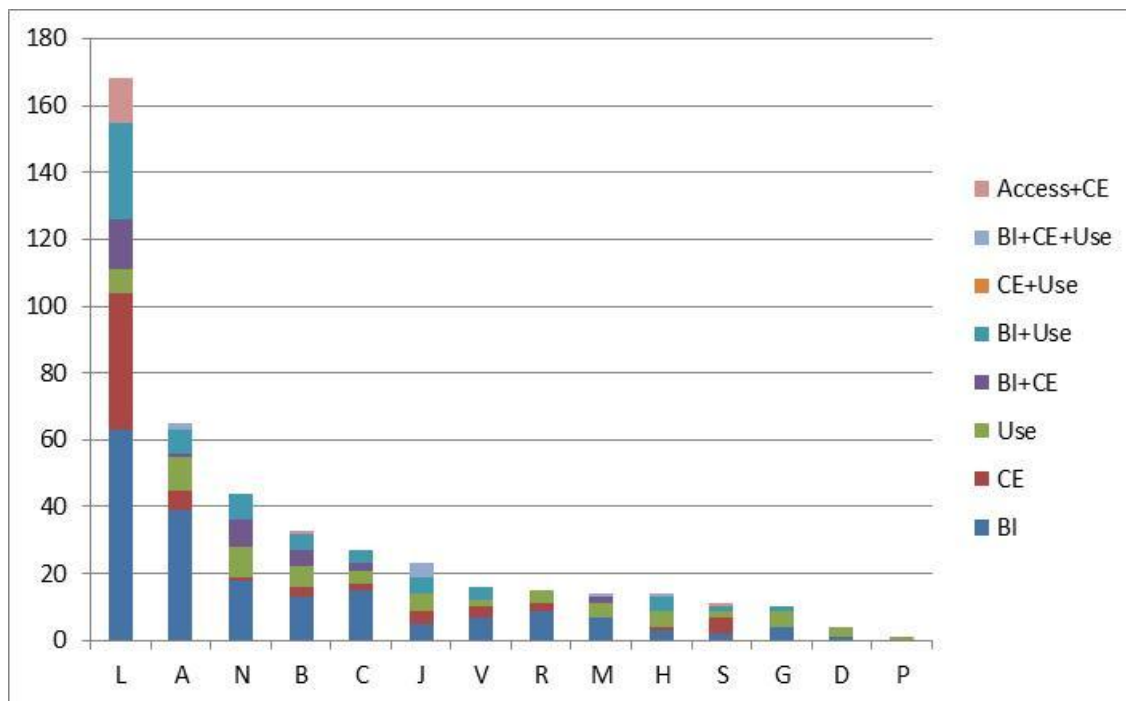
Legend: BI: Limit budget impact, CE: Address uncertainties regarding the cost-effectiveness, Use: Monitor use in clinical practice, Access+CE: Improve patient access and cost-effectiveness. BE: Belgium, CY: Cyprus, CZ: Czech Republic, EN: England, IT: Italy, LT: Lithuania, MT: Malta, NL: Netherlands, PT: Portugal, SE: Sweden

As shown in

Figure 6.4 the objectives countries are trying to achieve in different disease areas seem to be distributed across different disease areas proportionally to the number of agreement in each objective group and the number of agreement per ATC-group. The only objective which appears to be disproportionately represented among oncological and immune-modulating treatments is cost-effectiveness. This is not surprising as these types of drugs

are very often linked with high degree of uncertainty in relation to their effectiveness in real life resulting in cost-effectiveness estimates with large confidence intervals. Hence, there is need to collect additional evidence in order to obtain more precise estimates.

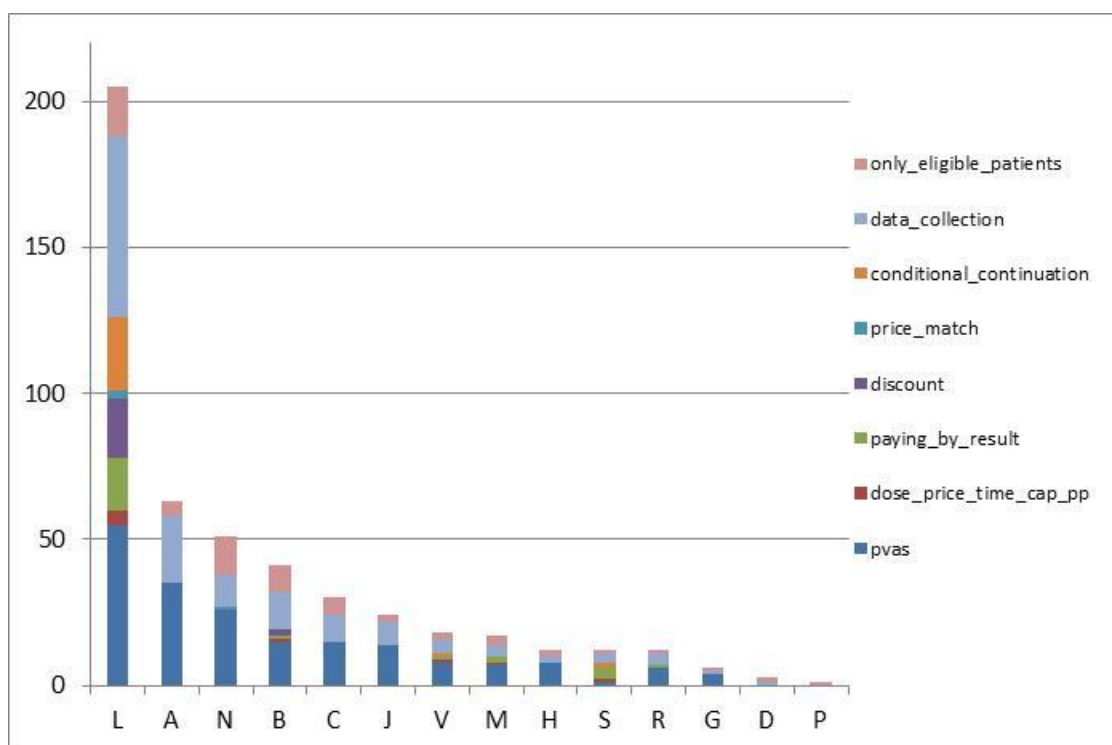
Figure 6.4: Objectives Member States are trying to achieve in different disease areas



Legend: A: Alimentary tract and metabolism; B: Blood and blood forming organs; C: Cardiovascular system; D: Dermatologicals; G: Genito urinary system and sex hormones; H: Systemic hormonal preparations, excl. sex hormones and insulins; J: Anti-infectives for systemic use; L: Antineoplastic and immuno-modulating agents; M: Musculo-skeletal system; N: Nervous system; R: Respiratory system; S: Sensory organs; V: Various; ATC_Mix: There was one case in Italy where a particular AIFA-note contained medicines from different ATC-groups. ATC-index 2011.

Figure 6.5 presents the distribution of instruments across different disease groups. Similar to the objectives, the distribution seems to be proportional to the overall use of a particular instrument and to the number of agreement in each disease group. As one would expect, data collection, conditional treatment continuation, payment by result, and discounts seem to be over-represented in the oncological and immune-modulating treatment group which can be explained the fact that uncertainty around the treatment effectiveness is one of the main concerns in this therapeutic group and that these instruments are very suitable to tackle this issue.

Figure 6.5: Instruments Member States are using to address their objectives in different disease areas



Legend: A: Alimentary tract and metabolism; B: Blood and blood forming organs; C: Cardiovascular system; D: Dermatologicals; G: Genito urinary system and sex hormones; H: Systemic hormonal preparations, excl. sex hormones and insulins; J: Anti-infectives for systemic use; L: Antineoplastic and immuno-modulating agents; M: Musculo-skeletal system; N: Nervous system; R: Respiratory system; S: Sensory organs; V: Various; ATC_Mix: There was one case in Italy where a particular AIFA-note contained medicines from different ATC-groups. ATC-index 2011.

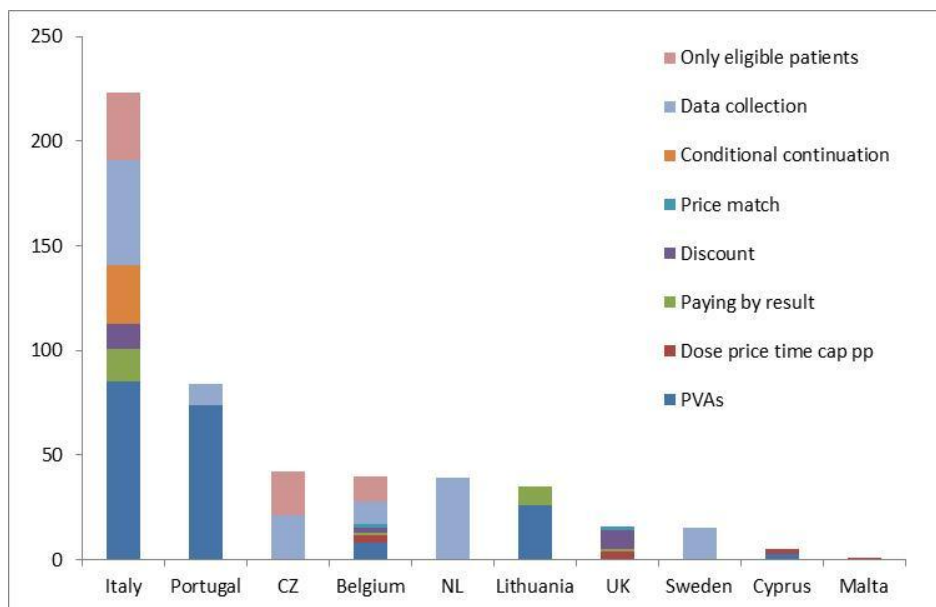
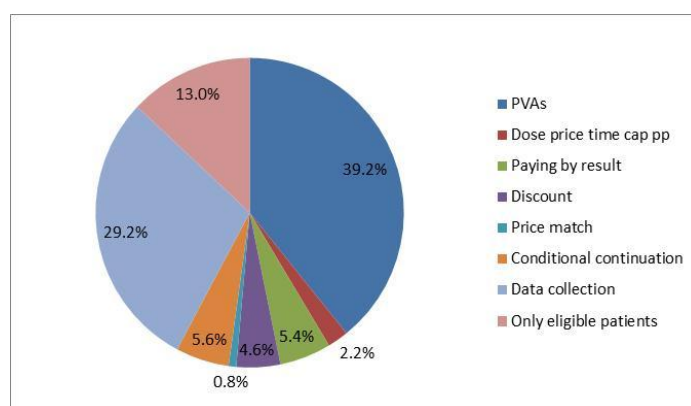
Notes: There is no one to one correspondence between the instruments used and the number of agreement as every agreement generally uses more than one instrument to achieve its objectives.

6.1.4 Common elements of MEAs

As shown in

Figure 6.6 the most common features of MEA across countries were PVAs (39%), followed by requirement for data collection (29.5%), and limited access to eligible patients (13.1%). PVAs are widely used in Italy, Portugal, and Lithuania; while data collection is a common requirement in Italy, the Netherlands, the Czech Republic and Sweden. Further, Italy, the Czech Republic and Belgium, limit access of certain medicines to eligible patients in an attempt to manage budget impact and use.

Figure 6.6: Common elements of MEAs overall and at country level



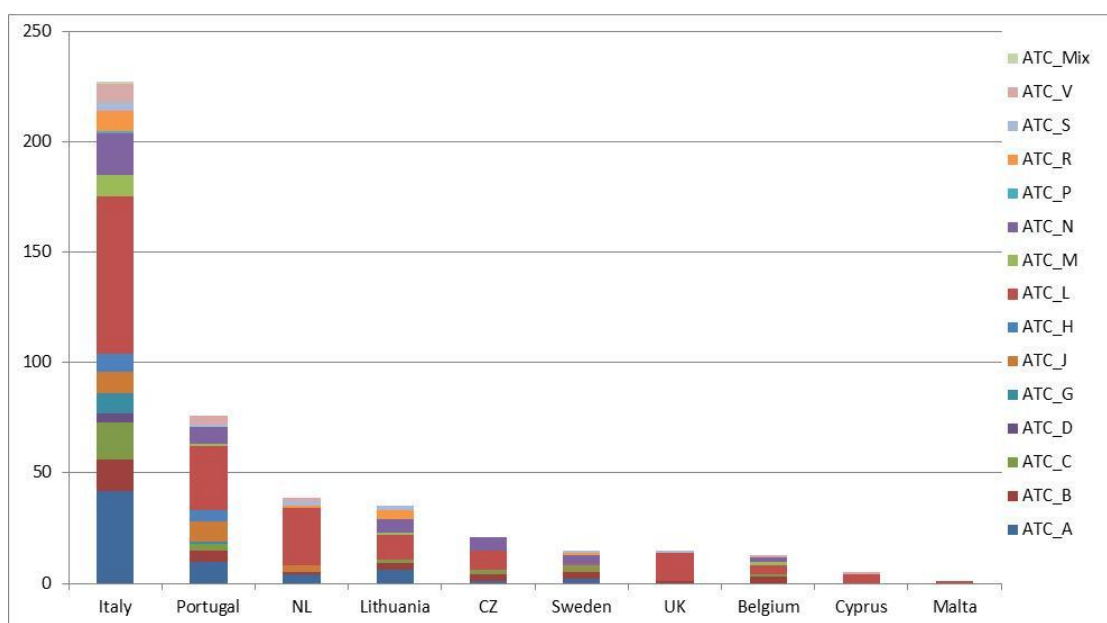
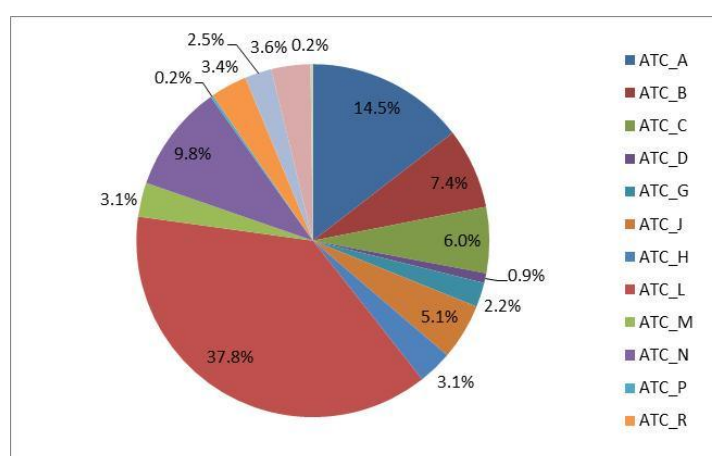
Legend: Only eligible patients: There are specific requirements in place to access treatment; Data collection: collection of additional evidence to inform the final reimbursement decision and/or monitor use in clinical practice; Conditional continuation: Conditional treatment continuation, only for patient responding to the treatment; Price match: Price match with comparator product; Paying by result: reimbursement or discount for non-responder patients; Discount: General discount on all doses or initial discount or free first doses; Dose

price patient cap pp: Cap on the number of doses or price or treatment time on a per patient basis; PVAs: Price-volume agreements.

6.1.5 Disease focus

In terms of therapeutic groups, Figure 6.7 shows that antineoplastic and immune-modulating agents represented 37.3% of all the MEAs implemented in the study countries, followed by alimentary tract and metabolism 14.7% and nervous system 10%. All member states apart from Sweden (only one MEA for ATC-L vs. 3 MEA for both ATC-B and ATC-N) the greatest proportion of agreement involved ATC-L drugs.

Figure 6.7: Disease focus of MEAs by country



Legend: A: Alimentary tract and metabolism; B: Blood and blood forming organs; C: Cardiovascular system; D: Dermatologicals; G: Genito urinary system and sex hormones; H: Systemic hormonal preparations, excl. sex hormones and insulins; J: Anti-infectives for systemic use; L: Antineoplastic and immuno-modulating agents; M: Musculo-skeletal system; N: Nervous system; R: Respiratory system; S: Sensory organs; V: Various;

ATC_Mix: There was one case in Italy where a particular AIFA-note contained medicines from different ATC-groups. ATC-index 2011.

6.1.6 Most common drugs part of a MEA

Results showed that some drugs were often part of a MEA in different countries. Table 6.2 shows that insulins were very often part of MEA in Italy and Portugal, while vidagliptin and vidagliptin + metformin were part of nine agreements in Italy, two therapeutic plans restricting patient eligibility and provider of care in Italy and in six PVAs in Portugal. Vidagliptin was part of six PVAs and two monitoring registries for different indications in Italy. Cetuximab was part of paying by result and conditional treatment continuation for two different indications in Italy, a CED in the Netherlands, and a discount agreement in the UK.

Table 6.2: Most frequent drugs part of MEAs in the study countries

Brand	INN	ATC	No. MEAs	No. countries	Instruments used
Avastin	bevacizumab	L01XC07	7	2	Italy - Four discount + monitoring registry for four different indications: breast cancer, colorectal cancer, non-small-cell lung carcinoma, renal cell cancer Netherlands - Three CED for three different indications: breast cancer, for non-small-cell lung carcinoma, for renal cell cancer
Erbitux	cetuximab	L01XC06	6	4	Italy - Payment by result + monitoring registry for head and neck cancer - Risk sharing + monitoring registry for colorectal cancer Netherlands - Three CED for three different indications: metastatic colorectal cancer, metastatic squamous cell carcinoma, locally advanced squamous cell carcinoma UK - Discount for metastatic colorectal cancer
Nplate	romiplostim	B02BX04	6	5	Czech Republic

Brand	INN	ATC	No. MEAs	No. countries	Instruments used
					<ul style="list-style-type: none"> - Data collection, reimbursement limited in time, only eligible patient, access limited to specialised health care centres Italy <ul style="list-style-type: none"> - Monitoring Registry - PVA Portugal <ul style="list-style-type: none"> - PVA Sweden <ul style="list-style-type: none"> - CED UK <ul style="list-style-type: none"> - Discount
Vidaza	azacitidine	L01BC07	5	5	Czech Republic <ul style="list-style-type: none"> - Data collection, reimbursement limited in time, only eligible patient, access limited to specialised health care centres Italy <ul style="list-style-type: none"> - Discount + monitoring registry Netherlands <ul style="list-style-type: none"> - CED Portugal <ul style="list-style-type: none"> - PVA UK <ul style="list-style-type: none"> - Discount
Velcade	bortezomib	L01XX32	5	3	Italy <ul style="list-style-type: none"> - Monitoring registry for Amyloidosis; refractory/relapsed multiple myeloma in association with dexamethasone - Monitoring registry for the pre-treated multiple myeloma - Discount + monitoring registry for non-treated multiple myeloma in association with melphalan and prednisone Netherlands <ul style="list-style-type: none"> - CED for multiple myeloma UK <ul style="list-style-type: none"> - paying by result for multiple myeloma
Votrient	pazopanib	L01XE11	6	6	Czech Republic <ul style="list-style-type: none"> - Data collection, reimbursement limited in time, only eligible patient, access limited to specialised health care centres

Brand	INN	ATC	No. MEAs	No. countries	Instruments used
					Italy - Payment by Results + monitoring registry Portugal - PVA Netherlands - CED Sweden - CED UK - Discount + expected value rebate (only implemented if expected results are not shown in an ongoing trial)
Januvia, Xelevia, Tesavel,	sitagliptin	A10BH0 1	4	2	Italy - PVA - Monitoring registry - Therapeutic plan Lithuania - Expenditure cap
Janumet, Efficib, Velmetia	metformin+ sitagliptin	A10BD0 7	3	1	Italy - PVA - Monitoring registry - Therapeutic plan
Yondelis	trabectedin	L01CX01	5	5	Czech Republic - Data collection, reimbursement limited in time, only eligible patient, access limited to specialised health care centres Italy - Payment by results + monitoring registry Malta - Dose cap Portugal - PVA UK - Dose cap
Prolia	denosumab	M05BX04	4	3	Belgium - Data collection, reimbursement limited in time, study, only eligible patients Italy - PVA - Monitoring registry Lithuania - Payment by result
Revolade	eltrombopag	B02BX05	4	4	Czech Republic

Brand	INN	ATC	No. MEAs	No. countries	Instruments used
					<ul style="list-style-type: none"> - Data collection, reimbursement limited in time, only eligible patient, access limited to specialised health care centres Italy <ul style="list-style-type: none"> - Monitoring registry - PVA Sweden <ul style="list-style-type: none"> - CED
Iressa	gefitinib	L01XE02	4	4	Czech Republic <ul style="list-style-type: none"> - Data collection, reimbursement limited in time, only eligible patient, access limited to specialised health care centres Italy <ul style="list-style-type: none"> - Paying by result + monitoring registry Lithuania <ul style="list-style-type: none"> - Paying by result UK <ul style="list-style-type: none"> - Price cap
Lucentis	ranibizumab	S01LA04	4	4	Italy <ul style="list-style-type: none"> - Payment by results + monitoring registry Netherlands <ul style="list-style-type: none"> - CED Portugal <ul style="list-style-type: none"> - PVA UK <ul style="list-style-type: none"> - Discount
Mabthera	rituximab	L01XC02	4	2	Italy <ul style="list-style-type: none"> - Two monitoring registries for two different indications: B-cell (CD20+) non-Hodgkin's lymphoma in association with polychemotherapy and non-Hodgkin's lymphoma and chronic lymphocytic leukaemia Netherlands <ul style="list-style-type: none"> - Two CED for two different indications: non-Hodgkin's lymphoma and rheumatoid arthritis
Torisel	temsirolimus	L01XE09	4	4	Belgium <ul style="list-style-type: none"> - Expenditure cap Italy <ul style="list-style-type: none"> - paying by result + monitoring registry

Brand	INN	ATC	No. MEAs	No. countries	Instruments used
					Netherlands - CED Portugal - PVA
Roactemra	tocilizumab	L04AC07	4	3	Italy - Monitoring Registry - PVA Netherlands - CED Portugal - PVA
Revlimid	lenalidomide	L04AX04	4	3	Italy - Discount + monitoring registry for multiple myeloma - Monitoring registry for syndrome myelodysplastic; mantle cell lymphoma; Diffuse large B-cell lymphomas; amyloidosis Portugal - PVA for multiple myeloma UK - Dose cap for multiple myeloma

Most of the most popular drugs for MEA were for the treatment of anti-neoplastic diseases (ATC-L: 11) and immune-modulating diseases followed by metabolic drugs (ATC-A: 4), blood and blood forming organs (ATC-B: 2), sensory organ (ATC-S: 1), and musculoskeletal treatments (ATC-M: 1).

6.1.7 Features of MEAs in EU Member States

6.1.8 Existence of a legal framework and legislation

Most countries have a legal framework in place (8 out of 13, Table 6.3) as well as legislation in place (7 out of 13, Table 6.4). There is no legal framework in Cyprus, Malta, Portugal Sweden, and in the UK. In Portugal, MEAs are based on the reimbursement legislation while in the UK PAS proposals are made within the terms set out in the 2009 Pharmaceutical Price Regulation Scheme (PPRS), a voluntary agreement negotiated between the UK Government and the Association of the British Pharmaceutical Industry (ABPI).

Table 6.3: Member States where a legal framework for MEAs is in place

Country	Legal framework
Belgium	Yes. In the reimbursement procedure of 180 days, a final decision is taken by the CRM (Commission for Reimbursement of Medicines) at day 150. There are three conditions in the decision that can lead to a MEA. Currently, the applicant can introduce a motion for reimbursement by convention and the procedure stops for a maximum of 120 days. During this period, negotiations on conditions/text agreements take place between the applicant, the insurers, the health minister and the pharmaceutical industry. At the end of the negotiation period, a contract is signed between NIHDI and the applicant with the agreement of the Minister of Social Affairs and the Minister of Budget.
France	The company and the committee in charge of pricing sign a contract
Lithuania	Order of Ministry of Health N v-634
Norway	There is a general legal framework, and separate contracts for each pharmaceutical.
Italy	Yes. The official decision concerning the type of MEA is made publicly available by AIFA.
Slovakia	Act No. 363/2011 which is coming into force on 1.12.2011
Netherlands	Up to 2011, the CED was part of a policy rule for budgeting of hospitals. From 2012 onwards the CED requirement is linked to the healthcare benefit scheme decision-making. The legal framework is that the MoH is legally entitled to exclude interventions that are not cost-effective.
Czech Republic	The MAH applies for the conditional reimbursement in case that the clinical efficiency and cost effectiveness data are not sufficient for permanent reimbursement. Can be utilized only in "very innovative products (VILP)".

Table 6.4: Member states where a legislation for MEAs is in place

Country	Legalisation
Belgium	<p>Yes. The Law on Compulsory Health Insurance (July 7, 1994).</p> <p>Art 35bis § 7 - If the CRM (Commission for Reimbursement of Medicines) considers the proposed basis for reimbursement disproportionate to the assessment of the criteria mentioned in § 2 or if the CRM is of the opinion that including the medicine in the list of reimbursable medicines is linked with uncertainties on a budgetary level, the Commission, or the applicant can propose to the Minister to establish an agreement with the Institute [...], providing with compensation rules for the compulsory health and disability insurance.</p> <p>Royal Decree on Procedures, Time Limits and Conditions (December 21, 2001).</p> <p>Art 81 and following, as modified by the RD of February 11, 2010.</p>
Czech Republic	Sec 39d and 39b of the Act on Public health insurance No 48/1997 Coll.
France	No special legislation for MEAs, however, the law does allow for the price to be set according to the expected volume of sales.
Lithuania	Order of Ministry of Health N v-634
Norway	Yes, in the general legislation on Pharmaceuticals, there is a possibility to use MEA. But there is no obligation.

Portugal	Yes, there is a specific national legislation regarding reimbursement/financing, that includes legal framework for the MEA. Decree-Law nr. 48-A/2010, 13th May, article nr. 6 out-patient, Decree-Law nr. 195/2006, article nr. 5 in-patient medicines
Slovakia	Act No. 363/2011 which is coming into force on 1.12.2011

Note: No explicit legislation for MEAs is available in Cyprus, Italy, Malta, Sweden, and the UK.

To gain more insights in the voluntary and non-voluntary nature of MEAs, MS were asked to comment on whether MEAs in their constituencies represent a voluntary or a non-voluntary form of agreement. Six out of twelve countries replied. Belgium, Italy, Portugal, and the UK reported that MEAs are voluntary agreements in their countries. Lithuania reported that expenditure caps and price volume agreements are obligatory in Lithuania while pay back agreements are voluntary. This definition does not really apply to Sweden as in this case, MEA are not strictly speaking an agreement but more of an unilateral request and condition for obtaining reimbursement expressed by TLV. The manufacturer can decide whether to accept or reject the agreement proposed by TLV but in the case he does not accept it, reimbursement will not be continued.

6.1.9 Average duration

The average duration of MEAs varies between Member States, ranging from one year in Belgium (renewable) to up to four years in the Netherlands or for an indefinite period of time subject to review (France, Malta, UK).

6.1.10 Instruments used

The most common instruments attached to MEAs in EU MS are: sales and expenditure databases (198), patient registries (119), studies (64), and online systems for reimbursement (11)⁸. Sales and expenditure registries are essential for PVAs agreements and therefore widely used in Italy (85), Portugal (76), Lithuania (35), and Sweden (2). Patient registries are particularly common in Italy (78), followed by the Czech Republic (21), Belgium (13), and Sweden (7). It is important to notice that the type of data collected through these registries was in most cases not specified. While it is known that Italy collects data on patients eligibility, duration of treatment, epidemiological data, treatment cost, and adverse effect (De Nigro 2011), it is not always clear which type of data other countries collect at patient level (for example a country could simply collect data on the number of doses received by each patient in the frame of a does capping scheme but not collect any other useful data on patient outcomes) and most importantly what they use is made this data and whether or

⁸ Please note that more than one instrument might be used for the same MEA and that not all the agreements were linked to instrument (or at least it was not reported)

not they are used to inform decision-making regarding reimbursement. Economic and impact studies are linked to MEAs in the Netherlands (39), Portugal (10), and Sweden (8), Belgium (7). Finally, the UK reports using online systems provided by the manufacturer for administrative purposes (and it seems sensible to think that probably most other countries have similar systems in place as well).

6.1.11 Stakeholder in charge of MEAs functioning and control

The main stakeholders involved are payers, drug assessment agencies, and physicians. Payers (e.g. NIHDI in Belgium), drug assessment agencies (e.g. AIFA in Italy, TLV in Sweden) or the Department of Health (UK) are responsible for negotiating the agreement with the manufacturer, or assessing⁹ (UK) the offer made by manufacturer, while physicians are responsible for filling in the patient registries usually in collaboration with other stakeholders (e.g. monitoring registries in Italy are managed by AIFA, an advisor physician from the National Health Insurer controls the implementation of MEAs in Belgium). Payers or drug reimbursement agencies might require manufacturers to submit additional evidence on drug effectiveness to obtain permanent reimbursement in which case companies are responsible for patient data collection. More often companies are required to submit regular information to payers on sales and expenditure as part of PVAs or budget impact studies.

6.1.12 Financial and administrative burden

Only a few countries provided information on the administrative burden of MEAs. Countries who provided information mostly did so by providing the number of staff working on MEAs. Although this is informative, it is not clear whether this staff is working full-time on MEA implementation or if MEA is just one of their duties. Another issue in estimating the resources needed to develop and implement MEAs is the number of different stakeholders involved. Italy for example reports that about ten people are working on MEAs within AIFA. However, in order to estimate the actual financial and administrative burden, the time

⁹ In the UK, pharmaceutical companies decide whether they wish to make a proposal, and the Department of Health confirms whether the proposal meets the criteria set out in the PPRS. So, in the UK, the process is an assessment not a negotiation.

physicians spend filling in the monitoring registries should also be included as well as the time local NHS authorities spent in administrative procedures to receive reimbursement for non-responders.

In Portugal, the number of people involved in MEAs ranges from two to four depending on whether an economic study is involved. If the agreement only involves monitoring sales and expenditure, then two internal technicians, a pharmacist and an economist are required. If an economic evaluation is required then an expert economist and a physician are also involved in addition to the two internal technicians.

In the UK, the financial and administrative burden of each agreement is assessed as part of the NICE appraisal. In order to be approved the administrative and financial burden needs to be proportionate to the benefits of the scheme.

In addition to the financial and administrative resources needed at the implementation stage, the resources needed to conclude a MEA should not be neglected. In Belgium for example, five members of staff in the National Institute of Health and Disability Insurance (NIHDI) are involved during the 120-day negotiation procedure. Up to four meetings of 2-3 hours are needed before the agreement is concluded (the latest agreements took 2 to 3 meetings which seems to suggest that as a country acquires experience in concluding these agreements, negotiation times can be reduced). These meetings include also external representatives from health insurance companies, the pharmaceutical industry, and a delegation of the Minister of Social Affairs and Budget.

6.1.13 Administrative requirements

The question about the specific administrative requirements of each MEAs model was interpreted in different ways among MS. Partly also due to the different MEAs models used in MS, some countries described the administrative requirements to conclude a MEA (e.g. contractual specifications), while others specified the conditions for their implementation (e.g. regular supply of sales data by the manufacturer) and others illustrated the conditions manufacturers need to meet for obtaining permanent reimbursement.

In terms of contractual specifications Belgium requires inclusion of price, compensatory measures for budgetary risk, reporting modalities, and other legal requirements in the each MEA contract. Regarding implementation conditions to be met, France, Lithuania, and

Portugal require the regular submission of sales data by the manufacturer, while four of the seven Italian MEAs require the creation of a patient registry for data collection sponsored by the manufacturer. To obtain permanent reimbursement after conditional reimbursement through MEA comes to an end, manufacturers need to provide Czech, Dutch, Portuguese (only for some CED schemes) and Swedish authorities of the evidence (usually on cost-effectiveness or use) initially requested by the agency. The Portuguese National Authority of Medicines and Health Product (IFARMED), the Czech State Institute for Drug Control (SUKL) and the Dental and Pharmaceutical Benefits Agency (TLV) specified their keen interest in making decisions based on evidence from their own healthcare setting. The UK presented an overview of the PAS process from its onset as part of the NICE technology appraisal to its lifetime until the next NICE review of the drug. At this stage, the manufacturer can decide to continue offering the scheme, propose its modification, withdraw it (but not before the first review of the relevant NICE guidance), or make alternative pricing arrangements with the DH.

6.1.14 Regional differences in MEAs implementation

According to information from Belgium, Italy, and Sweden, there are no regional differences in the implementation of national MEAs. Although these countries have a decentralised health care system, MEAs are subject to national decision and as such MEAs become immediately available in all regions or counties after they are approved at national level.

6.2 Stakeholder input: Competent authorities

Information presented in this section is based on material retrieved from official presentations and seminars, e.g. the 2nd Annual Risk-Sharing World, April 2011 (Webinar). Further insights were obtained from personal communication with Member State and sickness fund representatives via email correspondence, telephone communication, interviews conducted during two meetings of the EU working group on MEA in Rome on November 14th 2001 and May 21st 2012 and additional material received subsequently.

6.2.1 Belgium

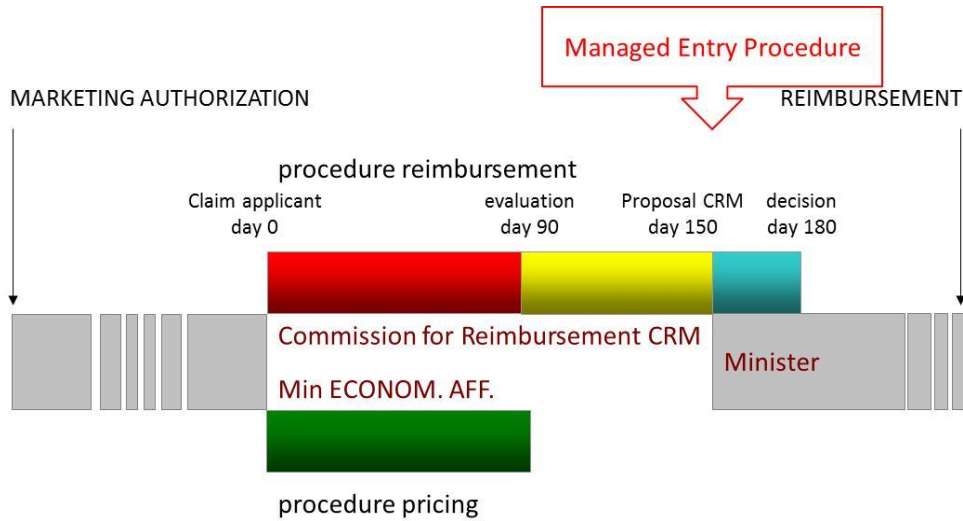
The rationale for introducing MEAs in Belgium is to address unmet medical need. For this reason, MEAs include only medicines which are either expected to bring additional therapeutic value, orphan drugs, or for extension of existing therapeutic indications when an unmet therapeutic or social need exists. The specific objectives pursued are to provide patients access to promising therapies and to provide an additional option for pharmaceutical companies to access the market. Reimbursement through a MEA is limited in time.

MEAs are exclusively introduced on initiative of the Minister following the procedures, time limits, and conditions outlined in the article 81 and following of the Royal Decree as modified in February 2010. There are three situations when a MEA may come into play, on the request of the pharmaceutical company after a negative motion, if there is no motion for reimbursement by the Commission for Reimbursement of Medicines (CRM), or on the request of the CRM itself after a negative motion for reimbursement. On the 150th day of the reimbursement the CRM releases its final proposition. In case of negative decision by the Commission the applicant can apply for reimbursement through a MEA, alternatively the Commission may suggest reimbursement through a MEA issued by the Minister.

In any case, the time clock is stopped and a 120 days' negotiation process between the applicant, the pharmaceutical industry board, health insurers, the NIHDI, the Minister of Social Affairs and the Minister of Budget starts. If negotiations are successful, a MEA is signed between the NIHDI and the applicant with the agreement of the Minister of Social Affairs and the Minister of Budget. Figure 6.8 shows the main steps of the reimbursement

process in Belgium from marketing authorisation to the final reimbursement decision (Van der Meersch 2012).

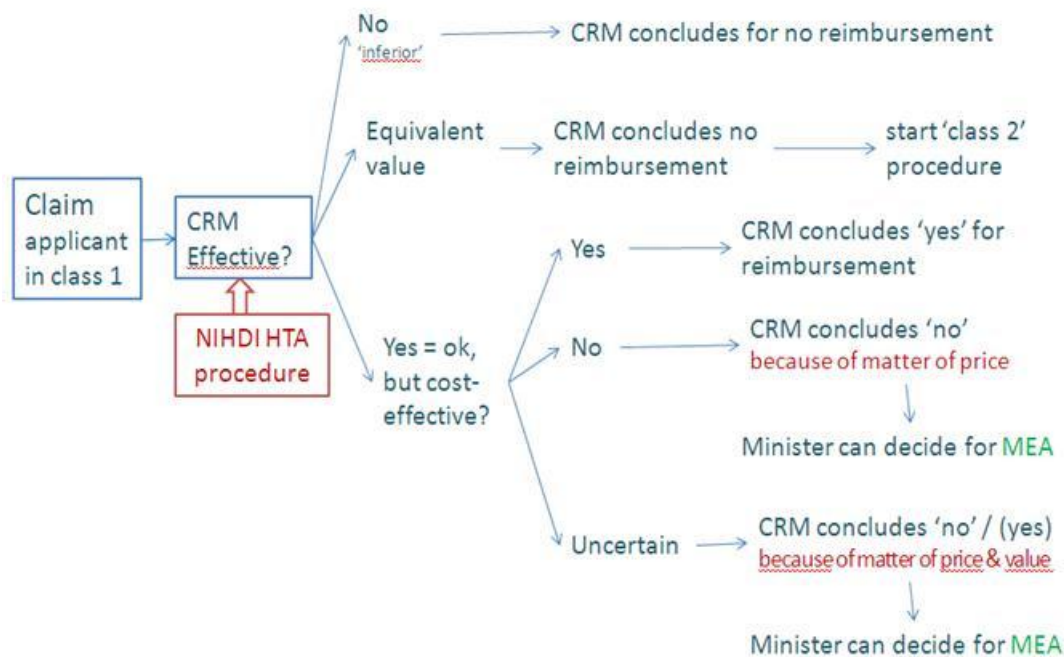
Figure 6.8: Reimbursement procedure in Belgium



Source: (Van der Meersch 2012).

In order to ask for reimbursement through a MEA, there needs to be some evidence to support the applicant claim that the drug is effective but because it was either not cost-effective or there was uncertainty around it, the CRM issued either a negative recommendation, no recommendation, or a recommendation for reimbursement through MEAs. As outlined in Figure 6.9, a MEA may be concluded to manage the risk of high budget impact due to the high cost of the drug and/or the uncertainty around its effectiveness, cost-effectiveness or expected volume of use.

Figure 6.9: Reimbursement decisions in Belgium according to the value of a drug



Source: (Van der Meersch 2012)

In Belgium, available options to address price issues through MEAs include the following financial instruments: off-list discounts, PVAs, compensation mechanisms for the price of other drugs from the same applicant, and budget caps. If the issue is price and value, then a combination of financial and non-financial instruments is used. The latter include requests for additional data collection and risk-sharing.

Since the first MEA was introduced in April 2010, 37 negotiations for MEAs have taken place, of these 19 MEAs have been positively concluded, 15 negotiations resulted in no MEA, and 3 are still pending. In addition to that one MEA which was concluded according to the old legislation. Of these 37 negotiations, 22 were for drugs of potential added value (15 positive, 1 on-going, 6 negative), six for orphan drugs (1 positive, 1 on-going, 4 negative), and ten for new indications (4 positive, 1 on-going, 5 negative).

Reasons for failure included the dissatisfaction of the applicant about the agreement (e.g. because of uncertainty about the price after MEA ends), uncertainty about which additional evidence is needed, or because no agreement was reached on the budgetary conditions of reimbursement by MEA such as the financial compensations to be paid by the applicant.

Further, other issues related to uncertainty are loss of orphan status in the future and re-evaluation of the risk/benefit ratio by the EMA.

Challenges remain even for positively concluded agreement and include the workload involved in negotiating the agreement, the difficulty for the Minister to refuse negotiating and thus conclude with a negative proposal, the decision on which type of information is needed to answer the initial questions, the limited timeframe of three years to collect data and address all open questions, the limited availability of epidemiological data at national level, and the challenge of evaluating the on-going clinical study at the end of the MEA (after one, two or maximum three years). In addition to the practical implementation challenges it is important to consider what will happen after an MEA has come to an end, was enough information obtained to answer key questions. Further issues include the lack of price transparency arising from off-list discounts and the fact that by allowing de facto to by-pass the CRM decision through a MEA, the impact of their decisions might be undermined.

Despite the issues involved with implementing MEAs, their implementation features several positive aspects for the Belgian healthcare system: first, the availability of a clear framework outlining legal aspects and timelines, the availability of a template for MEAs, and the intensive negotiation process which allows for flexible solutions; second, the transparency of the process in terms of procedures and knowledge about the existence of MEAs. The latter, however, is limited by the lack of a publicly available list of all agreements (information on MEA is only available on request) and by the lack of publicly available details of the MEA. Finally, it offers a financial safeguard for health insurers in terms of managing budget impact in the short future and for pharmaceutical companies the fact that listed prices are not affected.

6.2.2 Czech Republic

Since 2008, The State Institute of Drug Control (SÚKL) is responsible for pricing and reimbursement decisions in the Czech Republic. Clinical-effectiveness, cost-effectiveness, and budget impact are taken into consideration for reimbursement decisions. The Czech pharmaceutical system is characterised by value-based reimbursement rather than value-based pricing (Kotrba 2011).

Uncertainty concerning clinical and/or cost-effectiveness of new drugs is addressed through conditional reimbursement while uncertainty regarding its budget impact is managed through restricted use by specialised health centres (approx. 14 in the country).

Reimbursement of approximately 80 per cent of all drugs in the positive list is linked to some form of conditionality such as restricted access to particular patient subgroups and budget caps. All highly innovative drugs are subject to conditional reimbursement and demonstrating innovativeness of new drugs is crucial to obtain reimbursement. Another crucial element for obtaining reimbursement is that the drug has been previously accepted for reimbursement in at least two reference basket countries¹⁰. However, this is usually not an issue given the very large number of new drugs reimbursed in France.

Highly innovative medicines are defined as new medicines addressing very serious diseases (as defined in the ministerial decree no. 376/2011 Coll.¹¹) for which unmet medical need exists either because no treatment was previously available or because available treatments were insufficiently effective or presented important side effects. In cases where not enough information on treatment effectiveness in real clinical settings and its cost effectiveness is available, temporary conditional reimbursement is used.

Since December 2011, temporary reimbursement is granted for a minimum of two years renewable for another year (before December 2011 agreements were concluded for a minimum 1 year renewable on an annual basis for up to 3 years). To renew an agreement, the manufacturer needs to submit a request to SÚKL. Extension is granted if insufficient data on the drugs innovativeness have been collected to take a final reimbursement decision.

By concluding a temporary conditional reimbursement with SÚKL the manufacturer commits to set up a registry to collect information on the clinical effectiveness of the new drug, treatment costs, and use. Registries are managed in collaboration with the specialised

¹⁰ Belgium, Denmark, Finland, France, the Netherlands, Ireland, Italy, Latvia, Lithuania, Hungary, Poland, Portugal, Greece, Slovakia, Slovenia, Spain, Sweden, and the UK.

¹¹ Diseases demanding permanent or long-lasting hospitalization, diseases leading to often recurring hospitalizations for the period of several years or leading to invalidity or diseases that result in permanent serious damage of health, full or almost full loss of sight, hearing, speech or motion, or diseases that shorten life expectancy of more than 20%.

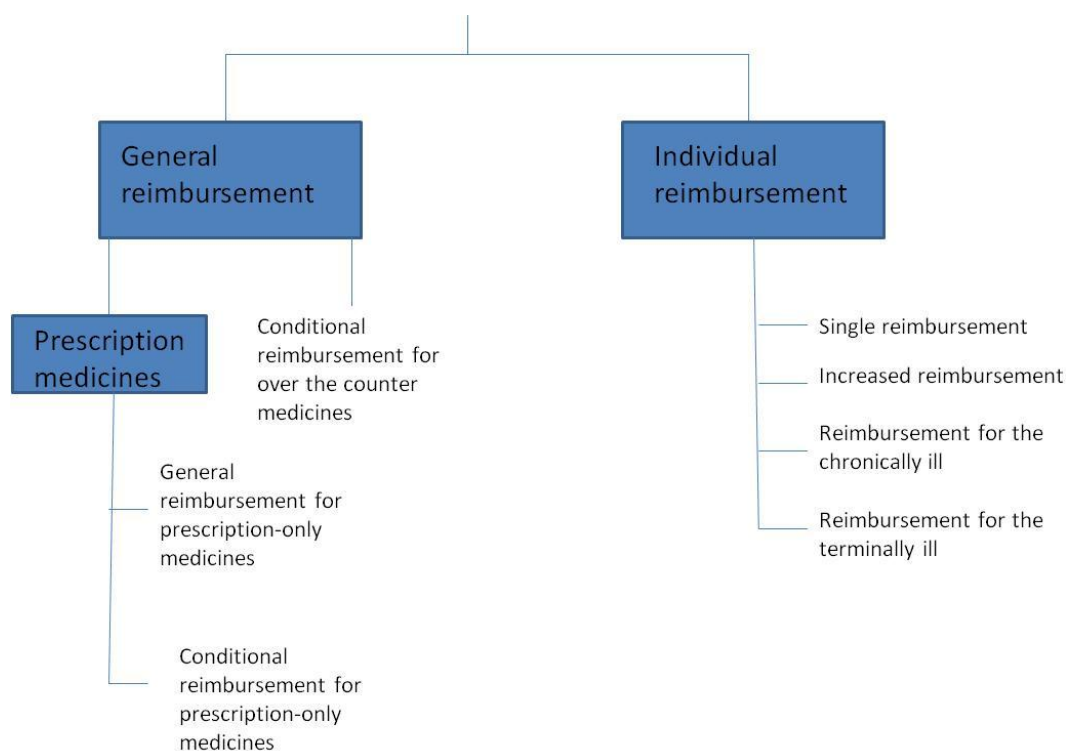
health centres where drugs are made available to patients. Centres need to have a specific contract with payers and are required to collect information on patient treatment and outcomes. This information will enable to manufacturer to submit evidence on budget impact and cost-effectiveness when an agreement comes to an end, which will provide the basis for SÚKL final reimbursement decision.

If the drug is found not be cost-effective, reimbursement is terminated. On the other hand, for drugs, which are found to be effective but with positive budget impact, the law allows for the conclusion of other types of MEAs (e.g. PVAs, dose capping, reimbursement for non-responders, etc.). These agreements can be used for any drugs, they are not limited to highly innovative ones. However, given the legislation allowing for these types of agreement has only been available since December 2011, such agreements have not yet been implemented (Katzerová 2012; Kotrba 2011).

6.2.3 Denmark

In Denmark, reimbursement of a particular medicine can be achieved as either general reimbursement or individual reimbursement that are both divided into subcategories as illustrated in Figure 6.10.

Figure 6.10: The Danish drug reimbursement system



Source: Based on information from the Danish Health and Medicines Authority website (Danish Health and Medicines Authority 2011).

Most drugs in Denmark are reimbursed as part of general reimbursement - positively listed drugs. Single reimbursement is a possibility for drugs without general reimbursement, but requires an application from a doctor. Reimbursement of prescription drugs in the general reimbursement group may be attached to specific conditions such as belonging to a particular disease or patient sub-group (Lægemiddelstyrelsen [The Danish Health and Medicines Authority] 2012).

Conditional reimbursement is used in Denmark to deal with high cost drugs and drugs with significant budget impact when the criteria are fulfilled; while single reimbursement is used when the criteria for general or conditional reimbursement are not fulfilled. In addition, reimbursement decisions are reassessed regularly in Denmark. Priority for reassessment is established based on the primary care and particularly general practice importance of a particular medicine, the availability of new evidence-based recommendations, and high costs and/or use for patients and regions (Danish Health and Medicines Authority 2012).

Although MEAs are not formally part of the Danish public reimbursement system, there have been a few cases where MEAs have been implemented in Denmark (Møldrup 2005). However, these cases have been very limited as there was no agreement with the National Health Service (NHS) and the main target were patients (Engraff 2011).

In comparison to other MEAs implemented in other EU countries, particularly the discount or free-doses agreement implemented in the UK which aim to lower the price to improve the cost-effectiveness of new drugs and to obtain a positive recommendation by NICE, Valsartan (Diovan®) already enjoyed general reimbursement when this agreement was launched by the manufacturer. Vardenafil on the other hand did not benefit and still does not benefit from general reimbursement although it was part of the individual reimbursement possibility at the time. This means that these two MEAs were not intended to achieve inclusion in the Danish positive list but rather to gain a competitive advantage in a crowded market leveraging on the “no cure no pay” formula. A similar agreement is implemented in Germany for the treatment of osteoporosis with zoledronic acid (Aclasta®). The manufacturer offered to reimburse the costs of the drug for patients experiencing a fracture while under treatment in exchange for the insurer switching osteoporosis treatment from competitor products to Aclasta® (Hogan & Hartson 2008).

Denmark has limited experience with MEAs but the experience of countries currently implementing MEAs will be part of further Danish considerations to meet possible MEA proposals from companies to obtain reimbursement.

6.2.4 France

France uses a common approach for all MEAs that is based on a framework agreement between LEEM (*Les Entreprises du médicament* - Pharmaceutical Industry Trade Association)

and CEPS (*Comité Economique Des Produits De Santé* - Healthcare Products Pricing Committee). This framework covers all MEAs based on financial results, but does not cover those based on clinical results (whose number is very limited).

There are four main types of MEA for pharmaceutical products in France: PVAs, agreement on daily cost of treatment, study requirement, and risk-sharing agreements. It is also possible to combine different types of agreement, a price-volume agreement and a study requirement agreement for example.

Price-volume agreements

PVAs are the most frequently used, indeed nearly all innovative drugs entering the French market are part of such an agreement. The aim is to limit treatment to the target treatment population by defining, for each drug, a tiered repayment structure for different levels of sales. At the end of an agreed period of time, repayments are converted into a price cut. Although it is not possible to ensure that use will be limited to the approved indication/s, PVAs are an instrument for limiting budget impact due to non-approved use.

Examples of PVAs include an oncology medicine whose name could not be disclosed due to a confidentiality clause in the contract (Espin, Rovira, and Garcia 2010). The main objective of this agreement, which will be in effect from 2010 to 2015, is overall budget control.

Two other examples implemented in 2008 involved Naglazyme (treatment for mucopolysaccharide type VI disease) and Soliris (for paroxysmal nocturnal haemoglobinuria) (Espin, Rovira, and Garcia 2010). In both cases, an agreement on prices was reached up to a fixed maximum budget ceiling, which required the companies to supply the medicine, without restrictions, to all patients who might benefit from it while also paying back to national health insurance any turnover made above the maximum budget ceiling. These agreements are in force until 2013.

Daily cost of treatment

A similar type of agreement focuses on daily cost of treatment rather than yearly sales level. The aim of this type of agreement is to ensure that the actual treatment cost per patient remains the same as the forecasted one. In practice, a target of daily cost of treatment is set based either on the range of doses or on posology. If the range of doses or posology used in

clinical practice differs from the one used to establish the selling price, the daily cost of treatment is revised.

Study requirement

In a limited number of cases, a specific study on the real-life use of a new drug might be requested to the manufacturer in an attempt to limit budget impact due to higher than forecasted use. These agreements are generally used for drugs which have shown to bring additional benefit but for which there still some element of uncertainty on the payer side. At the end of the study period, the price can be revised on the basis of the new evidence collected.

Risk-sharing agreements

In contrast to the previous types of agreement, which do not involve measurement of clinical outcomes, risk-sharing agreements (RSAs) in the French context involve assessment of real-life effectiveness. This type of agreement has so far been used in a very limited number of cases, probably five or six agreements (including for medicines used for the treatment of diabetes or mental illness but there is no relationship between the pathology and the likelihood of concluding such an agreement), which have received an *Amélioration du Service Médical Rendu*¹² (ASMR) V, but, which have claimed that they (may) have improvements which cannot be seen from the clinical evidence provided. Very specific conditions need to hold for such an agreement to be concluded: first, the benefit must be such that it could not be proven during pre-licensing clinical trials and only real-life evaluation will be able to prove evidence on its actual effectiveness; second, the claimed benefit must represent a clear advantage; and third, the company must be willing to bear the financial risk if the medicine fails. For reimbursement to be extended after the end of the trial period, the proposed study must unequivocally demonstrate that the claimed benefit exists and is considerable. In concluding such an agreement, the authorities are giving the manufacturer the benefit of the doubt, but the onus is on the manufacturer to

¹² Improvement of Medical Benefit (*Amélioration de Service Médical Rendu*, ASMR) refers to the additional therapeutic benefit versus current standards. This is measured on a I-V scale where I represents a major, II an important, III a moderate, IV a minor clinical improvement, and V no clinical improvement.

prove in a real-life setting that better than currently available results can be obtained. If this is the case, the negotiated price remains, if not, a price reduction is unavoidable.

Examples of RSA which have been completed include an agreement for risperidone (Risperdal®) an antipsychotic drug for schizophrenia, a risk-sharing agreements for a class of diabetes drugs, glitazones, and three other risk-sharing agreements for type 2 diabetes drugs (Renaudin 2010). This health outcomes-based agreement that falls under the category of conditional reimbursement price and takes into account the results of clinical or observational studies established for the period 2006-2013. In this agreement, consensus was reached that the reimbursement price would only be maintained if the medicine achieved a higher ASMR rating depending on the results of observational/clinical studies (Espin, Rovira, and Garcia 2010). If the results of those studies are negative, the company is required to pay back the difference for past utilisation and apply a price reduction on future sales. In this case, the main objective is to generate additional evidence on which price and/or reimbursement should be established.

Scale of implementation of the different types of agreement

The vast majority of MEAs in France are price-volume agreements, followed by daily cost of treatment, study requirement, and RSA. There also seems to be some relationship between price levels and the probability of contracting a PVA as the introduction of new high cost drugs almost always leads to the conclusion of such an agreement. Concerning implementation responsibilities, CEPS monitors the performance of all price-volume and daily cost of treatment contracts on an annual basis (aggregate saving results are published in CEPS' annual report (CEPS 2011)) while social security is responsible for collecting paybacks, should agreed-upon volumes be exceeded. Data for evaluating the agreements are supplied by manufacturers (sales and volume data), commercial sources such as the IMS (sales and volume data), and sickness funds (daily cost of treatment). When multiple sources for the same information exist, these are cross-checked to ensure validity of the data.

Policy options for patients to access drugs which have been excluded from reimbursement

There are no policy options to make drugs which have been excluded from reimbursement available. However, this is largely explained by the relative generosity of the French positive list in comparison to other European countries.

Future developments

PVAs are very well established in France and will always be a core element of the French reimbursement system. They will continue to be a popular way of controlling price and volume in the future, also because the cost of monitoring each scheme is low and the payback (in case of exceeding target volumes) is immediate. Agreements on study requirement are just beginning but they are very likely to grow particularly after the new reimbursement law, which was approved at the end of 2011 but has not yet been implemented, will be introduced. As part of the new law, two evaluations will be conducted before a reimbursement decision will be taken. Two different committees will be responsible to evaluate the product from a medical perspective (as it is already done) and from an economic perspective (new). These reforms are likely to increase the number of request for real-life study to companies and authorities are currently improving their ability to ask for very specific studies.

In principle, expanding implementation of RSAs is desirable on the condition that there will be agreed-upon clinical benchmarks to be measured, therefore, alluding to some type of performance based agreement (if introduced, their use should be expected to remain limited). Requirements for evidence will also need to be produced focusing on specific metrics. This is already part of the framework agreement between CEPS and industry, which will currently be under re-negotiation and will possibly be concluded by the end of 2012.

Study requirements also do have a future in France, particularly in what concerns real-life studies and the ability to conduct economic analysis and economic evaluations; this is already foreseen in the legislation and leveraging this in the near future, is a priority.

6.2.5 Germany

Little control over prices of innovative medicines prior to the reform in 2011 led to tremendous increase in expenditure on prices of new medicines in Germany. The introduction of the new system of early assessment (effective 2012) (Der Bundestag 2010) is

trying to change the situation towards a value-based pricing model by setting the price of new medicines according to the added value of the drug. Aside from the challenges of implementing such reform (e.g. how is additional benefit to be translated into different price level?) it does not address the issue of drug performance in real-life. The latter can only be achieved post-marketing.

From a literature perspective, fifteen MEAs have been identified; five of these are disease management programmes, four outcome-guarantee agreements, three PVAs, one utilisation cap, one cost capping, and one discount scheme (Rutten, Uyl-de Groot, and Vulto 2009; Anonym 2008; Senior 2009; Hogan & Hartson 2008; Pugatch, Healy, and Chu 2010).

This information is most likely incomplete (and some of the agreements might have in the meantime come to an end) given the lack of information and transparency on the subject and the decentralised nature of these agreements, which take place at sickness fund level. Of interest are a small number of what were defined as “disease management programmes”. One example is the compliance programme for the rheumatoid arthritis and psoriasis injectable drug etanercept (Enbrel). In 2008, the manufacturer (Wyeth) agreed to develop and finance a programme to increase patient compliance among BKK (the third largest sickness fund in Germany) patients (Senior 2009). The programme, whose cost is estimated to be EUR500 per patient per year, includes homecare visits by a nurse, a telephone-line for support, and promotion of patient communication (Senior 2009). Considering the very low-compliance rates of injection drugs and the high price for etanercept, it must still be profitable for the manufacturer to invest considerable resources in keeping patients on treatment.

Interviewees from the sickness funds pointed that managed entry of new drugs (as a process and in comparison to the conclusion of drug specific agreements) in Germany is currently addressed mainly by recent legal approaches surrounding AMNOG (Der Bundestag 2010), therefore, this is not organised at sickness fund level but at the statutory health care level. Despite many positive aspects of these recent reforms, Germany is far behind in horizon scanning activities as implemented by Italy and Sweden.

Interviewees were rather critical with respect to sickness fund-specific solutions, as adding nothing of substance, and mentioned that the most prominent example is the case of insulin analogues, for which several or most sickness funds have discount contracts in place. There

was agreement that such discount contracts were not necessary due to a negative assessment of cost-effectiveness by IQWiG at the price proposed by the manufacturer. However, because one of the smaller sickness funds made a discount agreement which ensured cost of insulin analogues at the level of human insulins, all other sickness funds had to follow suit due to the logic of competition. The key point is that the other sickness funds did not conclude rebate contracts for insulin analogues because they thought these drugs constitute a valuable addition to therapeutic options. Rather, these contracts were mainly concluded because this first rebate contract practically forced them to keep up with the rest.

MEAs over and above the AMNOG provisions seem to be limited to a few isolated cases in Germany. The main reason for this is probably the lack of incentives for sickness funds and manufacturers. If a drug is approved for general reimbursement by G-BA (subsequent to assessment by IQWiG), then all the sickness funds are mandated to reimburse it; so the manufacturer does not have an incentive to engage in such an agreement. On the other hand, if the drug is not approved for general reimbursement, the sickness funds are by law not allowed to reimburse it. Further, sickness funds tend to be suspicious of this type of agreement because they fear that once it comes to an end and a number of patients is already on treatment, the manufacturer might either not be willing to continue providing the drug as part of a MEA or the conditions of it will be less favourable in comparison to when the drug was first introduced. The need for good negotiation skills and the uneven balance of these between industry and sickness funds is another element of caution from a payer's perspective.

Initially sickness funds were not allowed to enter into contracts with pharmaceutical companies. The law was then adapted in 2003 to allow for the introduction of discount agreements (rebate contracts) (Bundesministerium der Justiz). Section 8 this article (§ 130a) directly concerns discount agreements. The wording explicitly mentions the possibility to take into account volume-based agreements, allowing for pay-back agreements in case of over-shooting a predefined target, and agreements for "measurably successful therapy".

The future of managing the introduction of new drugs in Germany will probably be limited to the implementation of the new AMNOG law. Although this is a speculation, it is sensible to expect that whatever the outcome of the new elections next year will be, no revolutions

would take place but rather different levels of efforts (depending on the elected party) in implementing the new AMNOG law.

The idea of updating reimbursement decisions as new evidence becomes available is in principle good; however, it requires a framework to assess the value of the drug and such an exercise touches on a highly sensitive topic in Germany which is attaching specific values to life.

Another issue with such system is fear on the sickness fund's side that prices might increase and resistance on the industry side for fear that prices might decrease as new evidence becomes available.

6.2.6 Italy

The Italian drug reimbursement landscape (Figure 6.11) is characterised by the following reimbursement options: no reimbursement, unconditional reimbursement or reimbursement in the frame of a managed entry agreement (MEA). Within a MEA context various instruments such as price-volume agreements (PVAs), cost-sharing, budget cap, monitoring registries, payment by results, risk-sharing, therapeutic plans, and "AIFA notes" are used to manage budget impact, uncertainty around clinical- and cost-effectiveness, and use.

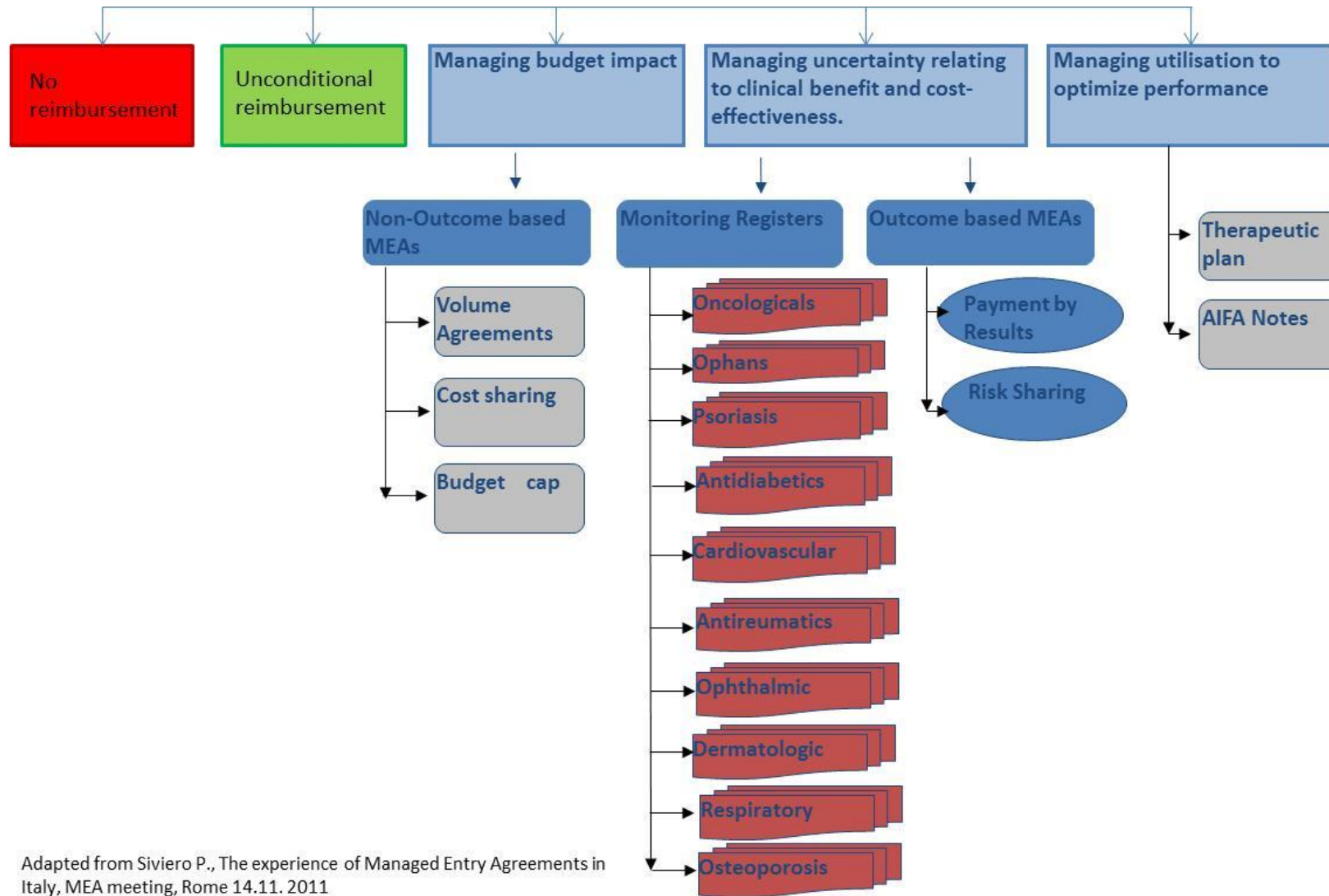
One of the most important instruments for MEAs in the Italian context is drug-monitoring registries. These registries aim to assess and track patient eligibility, evaluate utilisation in clinical practice, collect epidemiological data including data on the safety profile and collect additional information which was missing at the first evaluation stage. This should guarantee appropriate use of medicines according to its therapeutic indication while providing important information on the tolerability of a new drug and prescribing appropriateness.

As of December 2011, 78 therapeutic indications (corresponding to 66 active compounds) were part of the Italian monitoring registry scheme, broken down into 30 for anti-neoplastic drugs, 14 for orphan drugs, 1 project for the treatment of psoriasis, 1 for a cardiovascular drug, 2 for ophthalmic drugs, 2 for rheumatoid arthritis drugs, 2 for diabetes drugs, 2 for dermatological drugs, 2 for respiratory drugs, 1 for an osteoporosis drug, and 2 specific projects for multiple sclerosis and attention deficit & hyperactivity disorder (ADHD).

Of the 78 therapeutic indications part of a monitoring registry, 28 are also part of a conditional reimbursement agreement such as cost-sharing (12 indications), risk-sharing (discount scheme) (2 indications) or payment by result (14 indications) (results from survey 2). Figure 6.12 illustrates how these three different models are implemented. All three models include a health outcome element in the form of evaluation of the treatment efficacy and continuation of treatment conditional on a positive response to the drug. The main differences lie in the financial arrangements. Cost sharing applies a general discount to all eligible patients at the beginning of treatment whereas both risk sharing and payment by result use a payback mechanism to compensate for the treatment costs of non-responders. In the case of risk sharing a discount is calculated and paid back by the manufacturer to the NHS while for payment by result the full cost of treatment for non-responders is reimbursed to the NHS. In terms of implementation, the system of applying an initial discount to all eligible patients used in the cost-sharing scheme is simpler to administer than the system of reimbursement for non-responders used in the risk sharing and payback scheme.

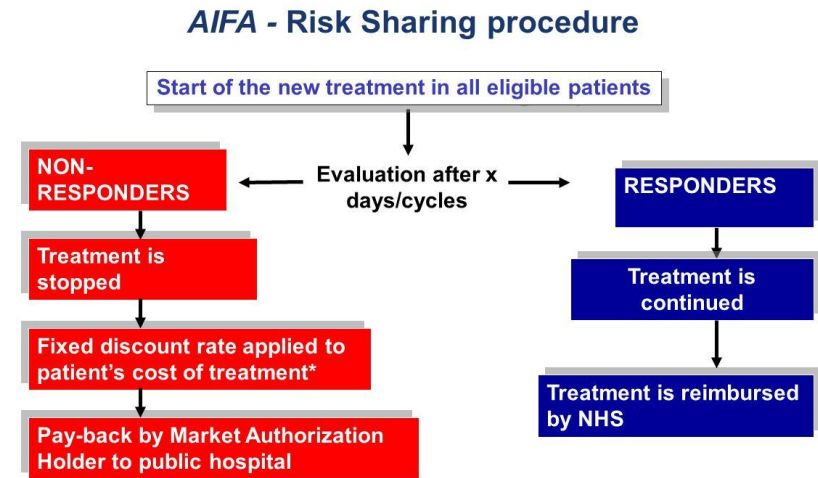
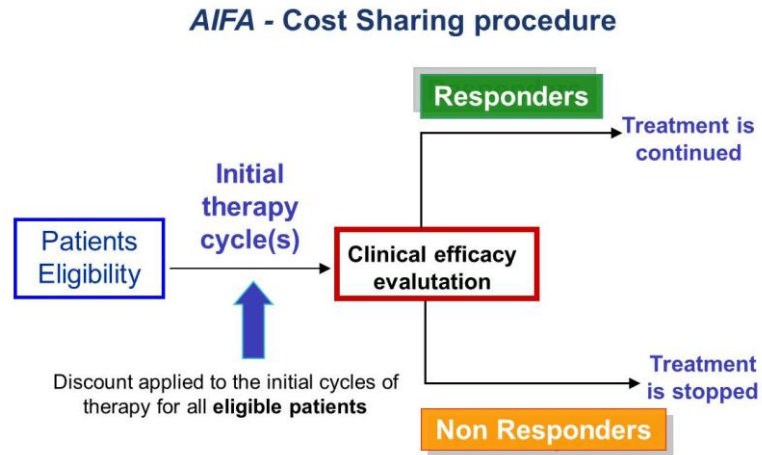
In terms of outcomes, 8 monitoring registries (7 for oncological drugs and 1 for a cardiovascular drug) have now been closed. Based on the data collected, a report has been published on the use of Ivabrandine in clinical practice (Tomino et al. 2010). Results include the epidemiological characterisation of patients with angina with contra-indication or intolerance to beta-blockers, identification of causes for non-administration, evaluation of the drug effectiveness in clinical practice and definition of the safety and tolerability profile of the new drug. A second report has been published on the use of diabetic drugs (Tomino et al. 2011). The data collected have enabled to identify reasons for treatment interruption, to collect information on adverse drug reaction, off-label use, patients' clinical profile by active principle, treatment switch, and to analyse the therapeutic effects of different treatments.

Figure 6.11 The Italian reimbursement landscape and the application of MEAs

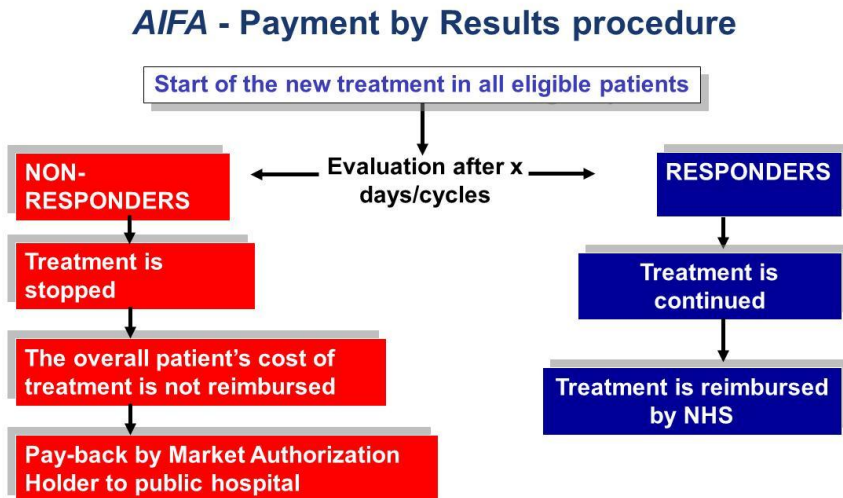


Adapted from Siviero P., The experience of Managed Entry Agreements in Italy, MEA meeting, Rome 14.11. 2011

Figure 6.12 Italian models of MEAs between pharmaceutical companies and the NHS



* predefined n. of initial packages



Source: (Siviero 2011)

6.2.7 Latvia

The National Health Service of Latvia is responsible for making decisions about inclusion of pharmaceuticals in the positive list and these are based on clinical and economic criteria. The main therapeutic criteria for a pharmaceutical to be reimbursed are (a) the relative therapeutic value of a new product based on the evidence level from published clinical trials; the relevance to the way the disease is managed and international guidelines for the treatment of the disease; (b) the place in the treatment pathway of the disease (e.g. first/second-line treatment, specific patient group); and (c) the relevance of the dosage, pharmaceutical form and pack size to the treatment course. The main economic criteria for a pharmaceutical to be reimbursed are a justified price, based on comparison with other available treatments and prices in other Baltic states and certain EU Member States; evidence on cost-effectiveness data and expected budget impact.

There are three main reimbursement options, general reimbursement, which is linked with reimbursement rates of either 100%, 75%, or 50% depending on the severity of the disease; prescribing limited to specialists or specialised centres; and limited reimbursement for certain patient groups which are likely to benefit more.

In terms of ways to manage entry of new expensive drugs, within the limited reimbursement budget there are few possibilities to introduce even new cost-effective expensive medicines. If there is uncertainty regarding cost-effectiveness and/or budget impact of a new product, most probably it will not be included in the positive list. However, the manufacturer can submit a new application for reimbursement when new evidence is available.

For certain expensive products in the positive list, there are agreements in place between the NHS and the manufacturer concerning the number of treated patients per year. As part of these agreements, manufacturer pays either part of the expenses for each patient or the full treatment cost for certain number of patients.

As part of legislation changes introduced in January 2013, the NHS can now conclude other types of agreement with manufacturer, including financial agreements, payment for performance, etc.

Thinking at future sustainable options to introduce new drugs, long term agreements, especially performance-related, could be a temporary solution in case of uncertain cost-effectiveness and/or budget impact, while more evidence is gathered by manufacturer regarding effectiveness and cost-effectiveness of the product. Patient databases are essential prerequisite of collecting effectiveness data, and these databases are rather underdeveloped in Latvia. However, the additional human resources needed for managing these agreements might render the introduction of these agreements cost-ineffective. In the end, it appears as if the most viable solution for Latvia to manage the budget impact of expensive, yet cost-effective medicines is through financial agreements.

6.2.8 Lithuania

The National Health Insurance Fund (NHIF) is responsible for medicines reimbursement in Lithuania together with the Minister of Health. There are two groups of reimbursed drugs, list A includes 250 reimbursed INN and eligibility is based on diagnosis while list B reimburses 56 INN and eligibility is restricted to vulnerable groups. Decisions on reimbursement are taken by the reimbursement committee together with the obligatory health insurance council, and the Health Minister. There are three reimbursement criteria, first therapeutic value, second pharmacoeconomic value, and third budget impact for the NHIF.

Drugs demonstrating added therapeutic value and negative impact on the NHIF budget are included in reimbursement list A or B while drugs showing added therapeutic value but positive budget impact are put on a waiting list. If a drug shows low therapeutic and pharmacoeconomic value it is excluded from reimbursement.

For drugs, which demonstrated added value but positive budget impact and are therefore put on the waiting list there are two options to obtain reimbursement, either to engage in a PVA or in a pay-back agreement. If expenditure exceeds the pre-agreed threshold pharmaceutical companies must refund all or part of the difference. There is a third type of MEA which is used for medicines already reimbursed as part of list A or B whose expenditure was more than LTL 1 million (EUR 0.3 million) in the previous year and more than 1 percent of total expenditure for drug reimbursement for ambulatory care.

As of December 2011, there were 35 MEAs, focusing mainly on antineoplastic and immunomodulating drugs (ATC-L: 11), followed by alimentary tract and metabolism drugs (ATC-A: 6) and neurological drugs (ATC-N: 6). Nine are subject to a payback agreement, six are PVAs, twenty are expenditure caps for drugs which exceeded expenditure (results from survey 2).

These agreements are administered by the NHIF under the Ministry of Health. From 2008, such schemes are obligatory for all new pharmaceuticals that will have a positive budget impact compared with current treatment approaches for the target patient population.

The minimum duration for an MEA agreement in Lithuania is three years (Garuoliene 2012).

6.2.6 Poland

In an attempt to limit public expenditure on drugs while extending the drug reimbursement list, MEAs have been introduced in Poland. Before the new pharmaceutical law came into force in January 2012, not all MEAs were translated into legal contracts and most are implemented as „gentlemen’s agreements”. However, there were some binding MEAs which include dose-capping, patient-capping, rebates, and free samples.

Since January 2012, the new law on drug reimbursement provides the legal basis for implementing MEAs, which have so far been implemented in a rather informal and confidential way. There are various changes which will affect MEAs. For example, according to the new law, the President of the National health Fund (NHF) will be responsible for monitoring the results of the reimbursement decision that contained the risk-sharing instruments.

The new law foresees MEAs to involve the following characteristics (Article 11, paragraph 5): (1) making the size of the applicant's income dependent on health outcomes generated by the drug; (2) making the official manufacturer price dependent on the applicant’s assurance to supply the drug at a reduced price determined in negotiations; (3) making the official manufacturer price dependent on the size of the sales of the drug; (4) making the official manufacturer price dependent on the partial repayment of the reimbursed amount to the public payer; (5) arrangement of other conditions improving access to healthcare services or reducing the cost of these services (Wilk 2012). These descriptions correspond can be linked to following MEA models: (1) payment by result, (2) discounts, (3) PVAs, (4) payback agreements, and (5) other.

Two further changes introduced by the reimbursement reform are relevant to MEAs. The first is the establishment of an Economic Commission within the Ministry of Health with responsibility for pricing, negotiating with applicants, fixing official retail prices, and defining risk-sharing instruments.

The second is the replacement of the Consultative Council in AHTAPol¹³ with a Transparency Council, which will be responsible for reimbursement decisions and for defining the relative conditions such as reimbursement levels, internal reference pricing, drug programmes, and risk-sharing instruments.

In terms of measuring the performance of these agreements, there are currently two committees, one for ultra-orphan products and one on rheumatoid arthritis, which ultimately decide on patient eligibility based on clinical effectiveness. The work of these committees is indirectly assisted by 50 or so registries, which are currently in place in as many disease areas (Adamski 2011).

Despite the fact that the new law provides a legal framework for implementing MEAs, important implementation challenges remain. First, although provision is made for certain types of MEAs to be implemented, MEAs templates for the design of such agreements are available; second, there are no executive regulations so far; third, it is not clear whether AHTAPol will assess these agreements; and fourth, there are high expectations on industry who is meant to present solutions applied in other countries and to propose models to be implemented in Poland (Wilk 2012; Brzezińska 2012).

6.2.9 The Netherlands

In the Netherlands, the Health Minister decides on drug reimbursement based on advice from the Health Insurance Board (CVZ). There are three types of decision the Health Minister may take: to reimburse the drug as part of the basic insurance package, not to

¹³ The Agency for Health Technology Assessment in Poland (AHTAPol) is the Polish agency responsible for assessing the cost-effectiveness of pharmaceutical and non-pharmaceutical products introduced in Poland and to make recommendations to the Health Minister. For out-patient drugs, AHTAPol may recommend that a new drug is reimbursed either unconditionally, conditionally, or not reimbursed. Depending on which of the reimbursement lists the drug is assigned to, different reimbursement rates apply. For in-patient drugs there are additional options such as the drug being listed as part the National Health Fund (NHF) therapeutic programmes (such programmes make special budgets available for financing innovative and high cost drugs) or as part of individual agreement for oncology treatment.

reimburse or to conditionally reimburse a new drug. Conditionality refers to the eligible patients and who can provide it (e.g. authorised physicians or prior authorisation must be obtained from the health insurance company).

Despite the steady growth of total pharmaceutical expenditure in the Netherlands, expenditure on hospital drugs has increased sharply in the past years. Increasing costs for hospital drugs together with tight hospital budgets (hospitals need to cover the medicines costs with their allocated budget), have led to geographical inequities in access (given that not all the hospitals can afford to pay for these expensive drugs).

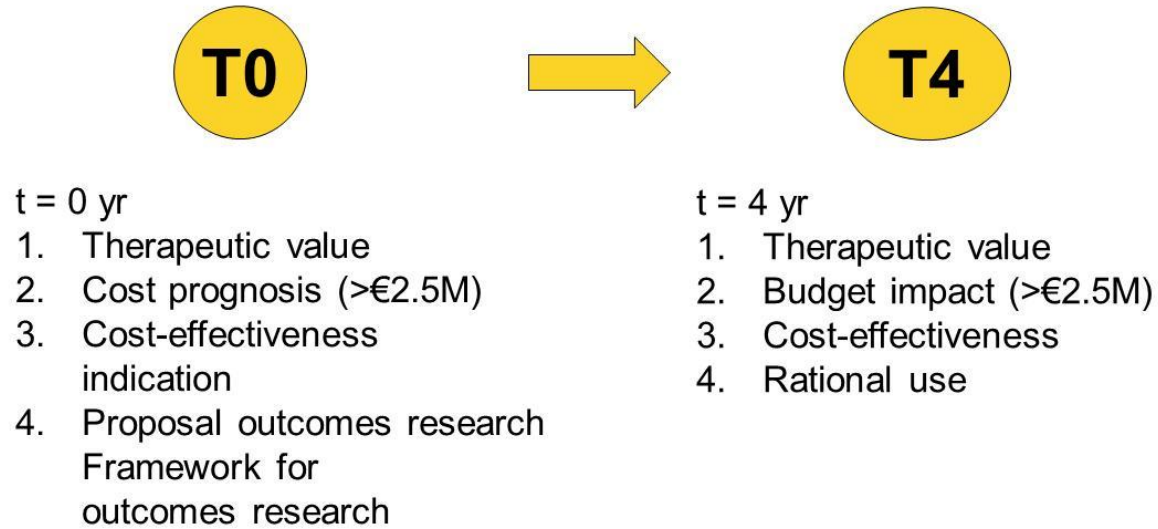
In an attempt to address issues in access to expensive drugs, the Government introduced a policy for hospital drugs (2006-2011) whereby it covers 80% of the cost of expensive drugs (budget impact > 2.5 million) and 100% for orphan drugs.

However, coverage comes with certain conditions; it is temporary (4 years) and conditional on the design of a study to collect additional evidence on the drug effectiveness in clinical practice. At the end of the four year funding period, if the results of the study demonstrate that the drug is cost-effective funding will continue and this time unconditionally (Figure 6.13).

As of November 2011, 45 expensive hospital drugs (including 10 orphan drugs) are part of coverage with evidence development in the Netherlands. The final coverage decisions are expected in December 2011.

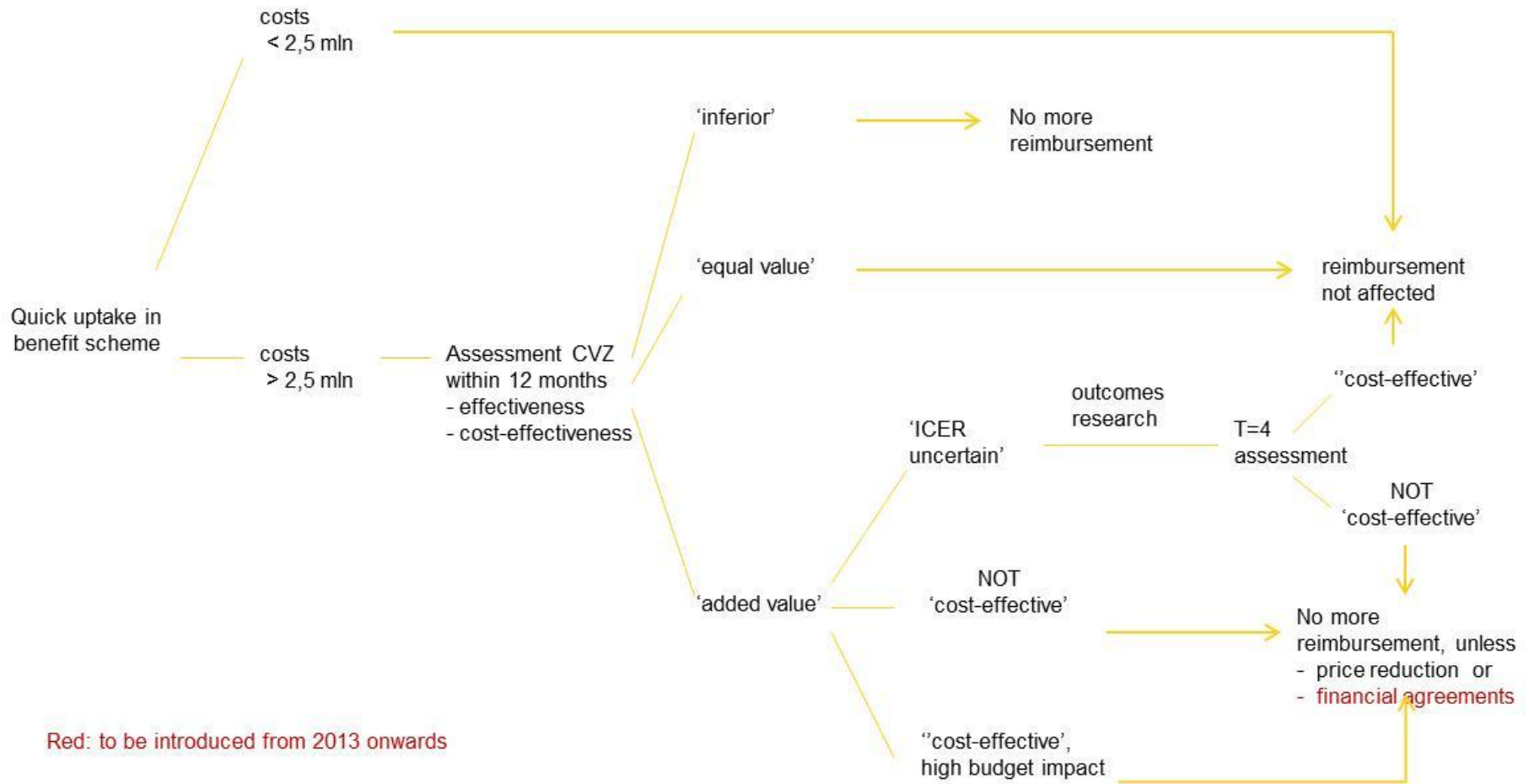
This system is expected to change from 2012 onwards as it will transit to healthcare benefit scheme decision-making. Further developments include the introduction of financial based agreements and outcome-based agreements in 2013 (Figure 6.14).

Figure 6.13 Coverage with evidence development as part of the expensive hospital drug policy in the Netherlands



Source: (Kooijman 2011)

Figure 6.14 The Netherlands: Conditional reimbursement for expensive hospital drugs from 2012 onwards



Source: (Kooijman 2011)

6.2.10 Portugal

In Portugal, health technology assessment (HTA) has been used since 1998 as an instrument to support evidence-based reimbursement decisions for out-patient drugs and since 2007 for hospital drugs. Reimbursement decisions include reimbursed or not reimbursed. Reimbursed drugs are assigned to different reimbursement groups depending on whether they are essential, non-essential medicines, or new pharmaceutical whose therapeutic value has not been proven yet (Teixeira and Vieira 2008). Essential medicines are further divided depending on the type of illness they treat (chronic vs. serious illness). Each reimbursement group is linked to a different reimbursement rate.

The main sources of uncertainty identified during the HTA assessment in Portugal are budget impact and uncertainty around relative effectiveness and/ or cost-effectiveness of a new drug. In an attempt to address these challenges, Portugal introduced price-volume agreements (PVA) and coverage with evidence development (CED) agreements. As of November 2011, there were 73 PVAs and 10 CED agreements in Portugal.

The legal basis to introduce MEAs for out-patient medicines is provided by the Decree-Law nr. 48-A/2010 while the Decree-Law nr. 195/2006 provides the legal framework for MEAs in-patient-medicines.

PVAs aim to limit budget impact and to restrict drug use to the approved therapeutic indications and target patient population. After defining the eligible patient population, an annual budget limit for the NHS is set. If this budget threshold is breached, manufacturers need to reimburse the difference to the NHS. The initial agreement terminates after 2 years at which stage the therapeutic added value and cost-effectiveness of the drug is re-evaluated. If the drug is found to provide added therapeutic value and to be cost-effective, a new budget limit may be set and the agreement may be extended for another 2-year period.

CED agreements are implemented to address uncertainty about relative effectiveness and cost-effectiveness. These agreement offer temporary coverage, which can become be extended or become permanent if the manufacturer provides additional data supporting the drug's effectiveness at the end of the 2-year conditional reimbursement period. When the initial agreement period expires, the drug's therapeutic added value and cost-

effectiveness is re-evaluated and coverage decision updated. CED can be used in combination with a PVA if there is uncertainty about both effectiveness and budget impact.

The Portuguese experience with MEAs has highlighted several challenges mainly related to the availability of sound data for decision making. Challenges include the definition of the population of patients who could benefit from the drug, paucity of clinical evidence particularly for rare diseases and orphan drugs and the challenges in conducting CE studies given the small patient numbers, inconsistencies between different data sources, evidence from other countries which is not transferable to Portugal, and the time required to generate additional evidence. Further challenges are more specific to hospital medicines and include complaints from manufacturers about the legal mandate to define PVAs for medicines with value-added therapeutic and cheaper than therapeutic alternatives, difficulties in establishing which medicines need to be evaluated and which not (the evaluation requirement was introduced in 2007 and applies to all agreement introduced thereafter but not to those introduced before 2007), and difficulties in evaluating indications. Finally, as the number of agreement increases so does the number of people to be monitored thus posing significant challenges from a logistical perspective.

6.2.11 Slovakia

The reimbursement system in Slovakia is defined in the legislation and is in line with EU legislation. The Ministry of Health of the Slovak Republic (MoH) is responsible for pricing and reimbursement. An advisory body – so called „Categorization committee (CC)“ is established by the Minister of Health. The main task of CC is to evaluate applications for reimbursement of new pharmaceuticals, applications for the change of indication restrictions, prescription restrictions and health insurance companies reimbursements, based on clinical evidence and cost-effectiveness with a focus on safety and positive influence on population health status. After evaluation by CC, the expert elaborates the opinions for the MoH, which subsequently decides on it. Criteria according which applications are evaluated are clearly defined in relevant norms regarding drugs reimbursement. These norms also describe processes and procedures regarding communication with the applicant or participant in the proceedings. The main focus is transparency and objectivity of decisions made and also there is possibility for the participant to object or appeal against the decision. The whole process is transparent and

decisions are published online. Composition of the advisory body (CC) is defined in the Law and includes representative from all relevant sectors, physicians, health insurance companies, and the MoH.

Criteria for reimbursement of new drugs or changing indications and prescription restrictions are defined in relevant legislative acts and include clinical, social or pharmacoeconomic criteria. The price of a drug cannot exceed the average of 3 lowest prices from among all prices of drugs officially set in other EU member states. Drugs for inpatient healthcare are procured by means of tenders. Decree 365/2009 on drugs and medical devices, which can be procured by health insurance companies, stipulates which drugs can be centrally procured.

There are several ways to set reimbursements on the basis of the above mentioned criteria. Drugs can be included in the positive list without limitations, with conditions or for a limited time period (e.g. 24 months).

The legislation also defines the criteria for introducing orphan drugs. As mentioned before two of the most important criteria are pharmacoeconomic aspects and cost effectiveness. Slovakia is one of 2 EU countries, which has QALY directly defined in the Law. The value of such indicator is one of the most important after pharmacoeconomic aspects.

The basic principle of state health policy in the field of drugs is to ensure the most modern, quality and safe pharmacotherapy, the use of which is medically reasonable and leads to the improved health status of population or saving lives. This state function must be fulfilled alongside with another state function - providing sustainability of public finance. For this reason, the MoH does not take into consideration only clinical or social aspect in its assessments of new drugs but also considers pharmacoeconomic aspects.

6.2.12 Spain

In Spain MEAs are concluded at the regional level. PVAs agreements are usually applied to single new products where the negotiated price is conditioned by the expected number of units sold. Four performance-based agreements were identified in the literature, one in Catalonia (gefitinib) and three in a hospital in Granada, Andalusia (ambrisentan, pegfilgrastim, somatropin).

The pilot programme for gefitinib (Iressa®) in Catalonia started in 2011 with the duration of one year. Depending on the results of the pilot it is foreseen that the payment-by-performance formula could progressively be extended to other drugs starting from 2012 (Generalitat de Catalunya 2011).

All the three payment for performance agreements in Granada were initiated because of concerns around the high price of the drugs. Accordingly, the price of ambrisentan (Volbris®) (Gaceta Médica 2011), pegfilgrastim (Neulasta®) and growth hormone somatropin (Norditropin®) is dependent on the effectiveness of the drug. A technical committee (formed of a doctor, an industry representative, the hospital manager, a representative of the hospital pharmacy department, and representative of the Andalusian School of Public Health) is responsible for monitoring the functioning, control and monitoring of the agreements and the annual cost for running these agreements totals to approximately 1% of the annual drug cost (about EUR 15,000 per drug). The most important cost component is data collection.

In 2011, the regional HTA body AETSA recommended that in areas where there is uncertainty about Soliris® (eculizumab)'s efficacy in terms of health-related outcomes (in this case reduction of thrombosis rates) an agreement based on shared risks should be concluded with the manufacturer (AETSA 2011).

There are no conditions to encourage the hospital to engage a MEA. In every hospital, it is the pharmacist (director) who decides how to manage the available budget. Some of hospitals engage in confidential agreements, while others make information publicly available.

6.2.13 Sweden

The Swedish Dental and Pharmaceutical Benefits Agency (TLV) is responsible to assess the cost-effectiveness of all new out-patients medicines introduced in the Swedish healthcare market. Since a couple of years, as part of a pilot project, TLV is also reviewing some hospital medicines although lacking of a mandate of making decisions in this area, thus its recommendations are not binding. All the data from Sweden presented in this report refer to those drugs for which TLV decides on reimbursement (i.e. out-patient drugs).

After reviewing all the available evidence, TLV makes one of the following three recommendations based on three principles: the principle of human value, the need and solidarity principle and the cost-effectiveness principle.

1. To unconditionally reimburse the drug (no restrictions on indications or patient eligibility)
2. To conditionally reimburse the drug (with restrictions on indications or patient eligibility)
3. Not to reimburse the drug

Conditionality refers to three main situations:

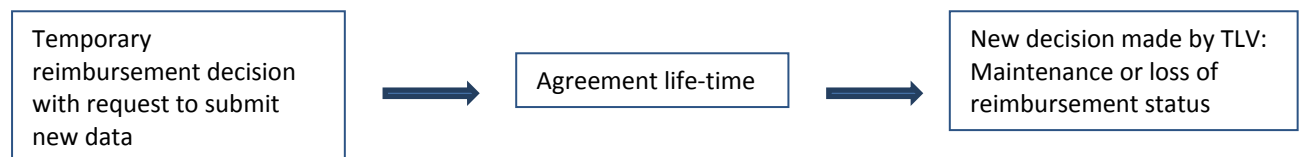
- a) Reimbursement is limited to specific indications, and/or level of severity of a particular condition, and/or specific patients subgroups, there is no requirement for the manufacturer to submit additional data;
- b) Similar to a) but with the requirement for the manufacturer to submit additional data;
- c) There are no limitations on indications, and/or level of disease severity, and/or patient eligibility but there is a requirement for the manufacturer to submit additional data.

Conditional reimbursement without submission of additional data is a definitive decision with the aim of limiting coverage to those patients who are going to benefit the most from treatment. Differently, conditional reimbursement with data collection is a temporary coverage decision, which enables patients to access a new drug and at the same time gives the manufacturer the opportunity of collecting real world data on the effectiveness of the drug with the aim of resubmitting the cost-effectiveness model. The updated model should allow TLV to make a final decision.

Most MEAs in Sweden fall in the second category of conditional reimbursement. Drugs in this group are recommended for use in specific patient sub-groups (those in which the drug is most cost-effective). In addition to coverage being limited to eligible patients, for certain drugs, TLV may request the manufacturer to collect additional data based on clinical practice and to re-submit the cost-effectiveness model. As of November 2011, there were 15 MEAs in Sweden. All these MEAs agreements were coverage with evidence development, there are no financial agreements. These agreements are initiated by TLV, which requires

the manufacturer to submit additional evidence in order to obtain definitive coverage after the initial period of conditional coverage. In fact there is no real formal agreement between the manufacturer and TLV. TLV requires the manufacturer to accept specific reimbursement conditions and in certain cases requests additional data and manufacturer's acceptance of these conditions is the requirement to obtain reimbursement.

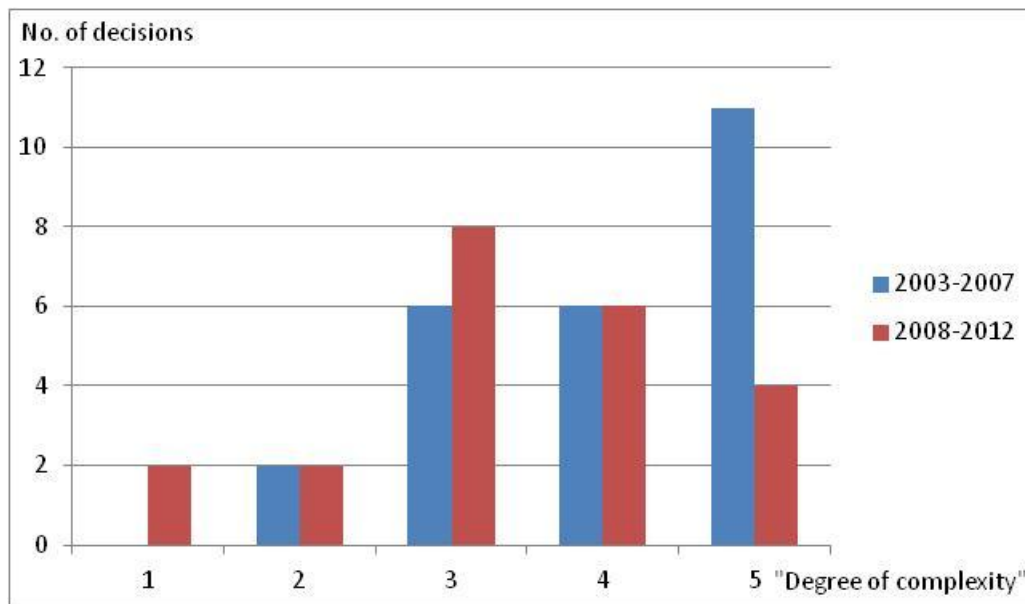
Swedish model of coverage with evidence development:



The type of risk addressed by MEA varies, the main focus is on cost-effectiveness and use in real-life including compliance with prescribing restrictions but some agreements also look at long term effects on morbidity and mortality or risk of stroke for example.

Data on the number of decision by the decision's degree of complexity presented suggests a trend towards less complex decisions. The number of decisions including presentation of evidence on effect and a non-interventional study decreased from 11 to 4 between 2003-2007 and 2008-2012. In 2003-2007 there were no decisions based on the number of patients treated and sales volume while in 2008-2012 two such decisions were made. This type of decision is relatively simple to implement given the ready availability of the data required while non-interventional study requires the collection of a number of additional data which would have otherwise not been collected.

Figure 6.15: Conditional reimbursement decisions in Sweden



Notes: 1: number of patients, sales volume; 2: treatment duration; 3: patient characteristics; 4: effect RCT + new health economic model; 5: effect, non-interventional study (Arnberg 2012).

6.2.14 UK - England and Wales

The National Institute for Health and Clinical Excellence (NICE) is responsible for assessing the clinical and cost-effectiveness of medicines, medical devices, diagnostic techniques, surgical procedures and health promotion activities. NICE can be asked to review a drug, device, technology or intervention for a number of reasons, for example, when availability varies across the country. This may be due to different local prescribing practices, funding policies or confusion or uncertainty over its value. After reviewing available clinical and economic evidence, NICE makes a recommendation over the use of the technology:

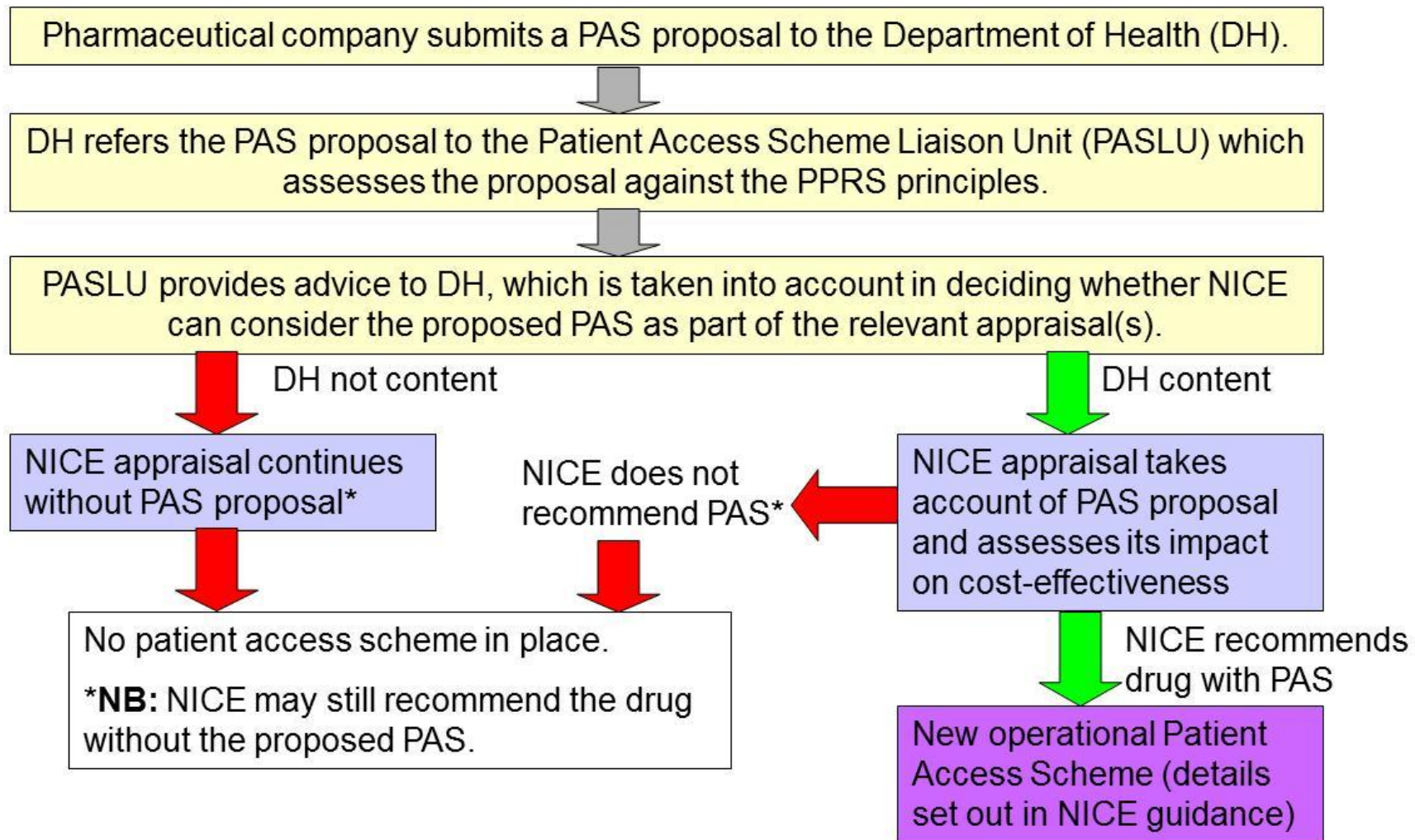
1. Recommended
2. Optimised: the technology is recommended for more restricted patient group than the one prescribed by the marketing authorisation
3. Only in research
4. Not recommended

The NHS in England is legally obliged to provide funding for treatments and drugs recommended by NICE technology appraisal guidance. It is important to note that NICE appraisal guidance does not, however, constitute a reimbursement decision for a medicine.

Where NICE guidance does not recommend a drug, NHS clinicians remain able to prescribe the product, subject to local decisions about funding.

Patient access schemes (PAS) are arrangements within the 2009 Pharmaceutical Price Regulation Scheme (PPRS – the current UK pricing scheme for branded medicines), which may be considered to be a form of MEA. To be classified as a PAS, a scheme must feature in positive NICE guidance. PAS can be associated with both ‘full’ and optimised recommendations (categories 1 and 2 above). The 2009 Pharmaceutical Price Regulation Scheme (PPRS) first introduced the concept of PAS by making provisions and outlining the principles for the development and implementation of PAS. Prior to that, a few arrangements that can be considered to be MEAs had been implemented in the UK (notably the Multiple Sclerosis Risk Sharing Scheme) but in the absence a formal regulatory framework. After the implementation of the 2009 PPRS, the DH commissioned NICE to set up the Patient Access Scheme Liaison Unit (PASLU) with the mandate of advising the DH on PAS proposals submitted by manufacturers. Figure 6.16 provides a simplified representation of the process through which a PAS is developed. As indicated in the figure, PAS are always proposed by the manufacturer. The proposed PAS may be accepted as part of the NICE appraisal process conditional on the approval of both DH and a positive recommendation by NICE. This process applies to all PAS proposals. The main impact of PAS in the UK so far has been to facilitate patient access to some drugs that might not otherwise have been recommended by NICE due to low cost-effectiveness or uncertainty about costs (e.g. where treatment duration is uncertain). Apart from the Multiple Sclerosis Risk-Sharing Scheme (which preceded the PAS arrangements and is not classified as a PAS), which explicitly aims to generate additional evidence on the effectiveness and cost-effectiveness of interferon-beta, there is no emphasis on generating additional evidence mainly because evidence showed that such arrangements can be very burdensome for health staff to manage.

Figure 6.16 PAS proposal process (simplified)



Source: (Bowden 2011)

Generally, NICE-approved PAS do not involve data collection because they are not meant to generate additional evidence since these drugs have already received a positive recommendation by NICE. On the contrary, these schemes were the pre-condition for NICE to recommend the drug because they enabled to improve the cost-effectiveness by e.g. lowering the drug price through discounts.

However, as described above, pharmaceutical companies may offer schemes or discounts to the local NHS outside NICE appraisals as long as these do not contravene any aspect of the PPRS, and some local schemes are offered for drugs which have either not been reviewed or have received a negative recommendation by NICE (NHS Devon 2011). For example, Erlotinib (Tarceva®) for the maintenance treatment of non-small cell lung cancer, advanced or metastatic, was rejected by NICE on cost-effectiveness grounds (National Institute for Health and Clinical Excellence 2011) but is available to NHS Devon patients through local arrangements¹⁴. Eligibility criteria set by NHS Devon include: the patient being stable disease after platinum-based first-line chemotherapy and the availability of individual funding before prescribing (obtainable upon completion of an Individual Funding Panel Request and following positive response by the Panel). Funding decisions for drugs, which have not been reviewed by NICE are made by local NHS organisations. Degarelix (Firmagon®) for advanced hormone dependent prostate cancer has currently not been reviewed by NICE and is available in the NHS Devon through local arrangements (NHS Devon 2011). NHS Devon criteria for patient eligibility include being an adult male patient with advanced hormone dependent prostate cancer, availability of individual funding before prescribing (obtainable by completing an Individual Funding Panel Request and following positive response by the Panel), approval by the panel. Further, according to the Peninsula Health Technology Commissioning Group (PHTCG)¹⁵, degarelix will not be routinely commissioned for this indication. The NHS Devon local arrangement for Firmagon®

¹⁴ Erlotinib as an alternative treatment to docetaxel for patients with non-small-cell lung cancer (NSCLC) who have already tried one chemotherapy regimen but it has not worked is available to all eligible NHS patients under a NICE-approved PAS (National Institute for Health and Clinical Excellence 2010).

¹⁵ The Peninsula Health Technology Commissioning Group is a collaborative decision making group with delegated decision making from the four Primary Care Trusts in the South West Peninsula - NHS Devon, NHS Plymouth, Torbay Care Trust and NHS Cornwall and Isles of Scilly (NHS Devon 2011).

(degarelix) is a 5 year agreement which aims to remove the financial barrier to degarelix within primary care by paying a 30% discount to the PCT based on primary care spend (NHS Devon 2011). Further, agreements between local NHS organizations and manufacturers may be initiated (e.g. Lipitor, North Staffordshire health authority, Pfizer with the participation of Academia to ensure robustness and independency of data collection and analysis (Chapman et al. 2003; Chapman et al. 2004)).

In addition to fully recommending, not recommending or recommending limited access to a new drug, NICE may also recommend its use in research only (“only in research” recommendation (OIR)). It has been suggested that this recommendation could be used as a “polite no” by NICE (Chalkidou, Hoy, and Littlejohns 2007). It is debatable whether OIR recommendations should be considered as MEAs, some authors have classified them as a form of coverage with evidence development (Carlson et al. 2010; Carbonneil, Quentin, and Lee-Robin 2009), while others have excluded them from the definition of MEAs (Staffinski 2010). If we consider a MEA as a two-party agreement between payers and manufacturers then OIR should not be considered as MEAs due to the absence of such a formal agreement. However, there are examples where a drug, which was recommended as OIR has later been recommended by NICE after submission of new evidence by the manufacturer. In 2000, docetaxel as an option for the adjuvant treatment of women with early-node positive breast cancer was recommended as OIR. In 2006, after submission of additional evidence by the sponsor, it received a positive recommendation (Scottish Medicines Consortium 2011). Irinotecan and oxaliplatin for the treatment of advanced colorectal cancer had also been initially recommended as OIR but received a positive recommendation in 2003 thanks to the availability of new evidence generated as part of clinical trial (Chalkidou, Hoy, and Littlejohns 2007).

The aim of PAS in England is to manage uncertainty and to improve patient access to cost-effective innovative drugs. There are concerns about administrative burdens for the NHS and the industry and this was also the reason for focussing on financially-based PAS mainly involving discounts, rebates or dose capping without requiring additional monitoring such as an outcome-guarantee agreement requires. The PPRS includes the option of outcome-based agreements, but these are considered only in exceptional circumstances, and there is only

one operational PAS, which includes an outcome-based element (for bortezomib (Velcade) in the treatment of multiple myeloma).

The introduction of the new value-based pricing system in January 2014 will lead to major changes in the pricing landscape for branded medicines in the UK. The main change is the move from a price regulation system based on controlling manufacturers' profits to a system of value-based pricing (VBP), though the intention is that VBP will focus primarily on new active substances, at least in the short term. It is possible that this new system could make PAS redundant as the prices of new drugs will be based on their value, which in turn implies understanding how a drug works in practice and what (clinical) benefits it delivers along the disease trajectory. However, no decision has yet been made on whether there might be a role for some type of PAS or 'PAS-like' arrangements in the new arrangements for pricing branded medicines.

6.2.15 Overview of Member States perspective on MEAs contribution

This section presents results of an email survey conducted in June-July 2012 and asking Member States to share their views on the most important contribution of MEAs.

Results from Table 6.5 show that access to new therapies which might have otherwise not been accepted for reimbursement or not been recommended by NICE in the UK, limiting budget impact, and managing uncertainties related to cost-effectiveness and use at the point of decision-making are seen as key contributions of MEAs according to MS.

Table 6.5: Member States perspectives on the most important aspects of MEAs as they are currently implemented in each country

Belgium
<i>Patients</i>
<u>Access to promising new therapies</u>
<i>Health payers (NHDI)</i>
<u>Financial safeguards</u> in terms of budget management and control
<i>Manufacturer</i>
Access to the market with a list price = financial guarantees

Italy

MEAs aim at guaranteeing access to medicines for patients and budget sustainability at the same time.

Lithuania

The most important contribution of MEAs in Lithuania is to manage budget impact for the NHIF. In addition to that, MEAs can be very important managing uncertainty relating to clinical or cost-effectiveness.

Portugal

The most important contribution of MEAs is to provide a legal framework in which INFARMED can provide access to medicines that in other way would not be provided, because of the uncertainty related to their effectiveness and cost-effectiveness.

Therefore the main benefit is to provide a mechanism of access/reimbursement that addresses the uncertainty and at the same time maximises an adequate and effective use of the medicine and limits the budget impact generated by his use.

Sweden

The most important contribution of MEAs, as they are used today in Sweden, is that they can alleviate some of the uncertainties regarding cost-effectiveness at the point of decision (e.g. will the product be used by the “correct” patients? Will the outcomes in real practice be in line with the assumptions?).

UK

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) includes the option for pharmaceutical companies to propose Patient Access Schemes (PAS), which are national level arrangements to improve the cost-effectiveness of a medicine being considered as part of a NICE technology appraisal. PAS have proven a useful tool within the 2009 PPRS in facilitating patient access to some medicines that might not otherwise have been recommended by NICE. (Though it is important to note that NICE appraisal guidance does not constitute a reimbursement decision. Where NICE does not recommend a drug, NHS clinicians remain able to prescribe the product, subject to local decisions about funding).

Source: EMINet survey

6.3 Stakeholder input: Manufacturers

The research-based manufacturers' position on MEAs is captured in this section and is based on an internal survey conducted by EFPIA among its members, the results of which were subsequently communicated for inclusion in this study. This section reflects, as a consequence, EFPIA's positions on behalf of the manufacturers it represents.

EFPIA's position is based on the right for manufacturers to freely set drug prices based on their value, and on the payer's right to assess the drug and decide whether the price asked by the manufacturer represents "value for money".

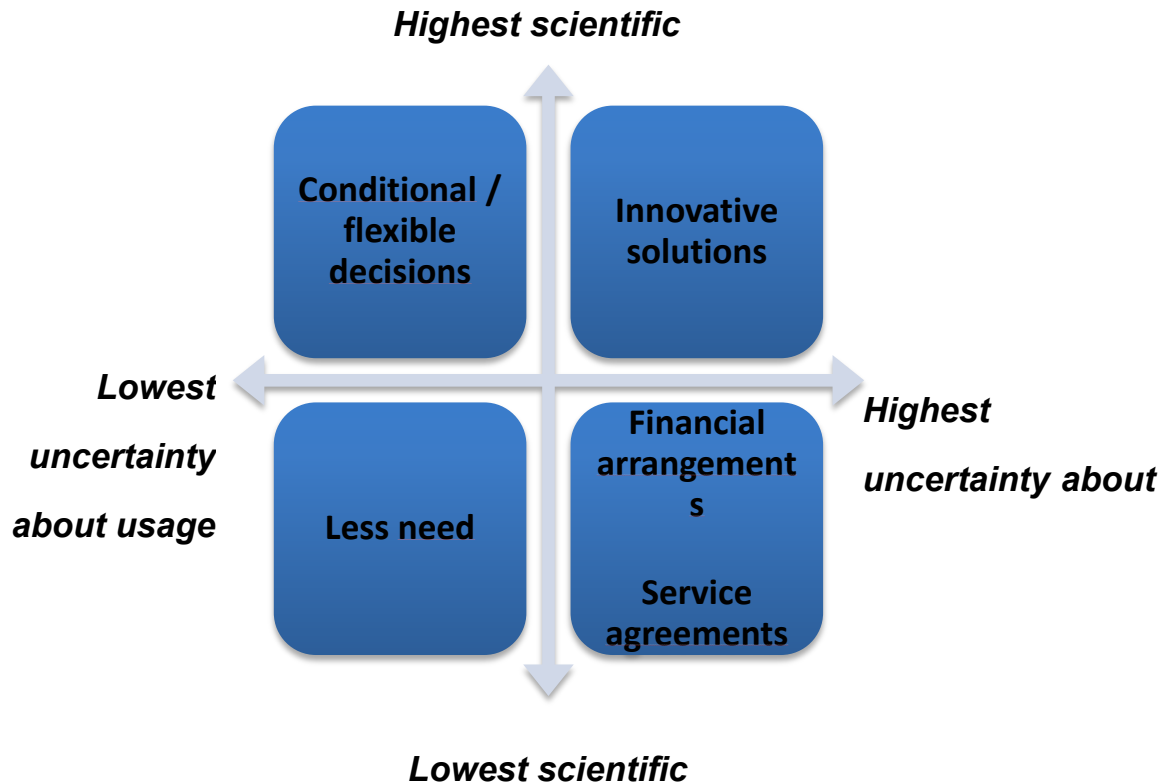
In reality there can be considerable uncertainty over a product's performance in real life at the time of launch and EFPIA sees higher than normal levels of uncertainty, especially where a more significant budget impact is expected, as the motivation which should drive the introduction of these schemes. Used in this way, contractual agreements are perceived as a useful instrument to improve patient access to new medicines. Contractual agreements that do not consider the value of a particular product (whether based on an assessment of clinical added value or including economic evaluation, such as cost-effectiveness) are considered as not justified by EFPIA. This includes schemes that are more about "risk-shifting" than true "risk-sharing", price-volume agreements, claw-back policies or budget caps that do not incorporate the notion of value.

Further, because the available evidence at the time a new drug is launched is often limited to data from RCTs, the value of a newly-launched product may not be fully demonstrated yet. In this respect, specific areas of uncertainty may include the patient sub-groups who are most likely to benefit from the drug, whether surrogate parameters used in clinical trials will be validated in post-launch studies, and uncertainty around the transferability of clinical trial results to real-life situation within a specific healthcare system.

EFPIA recognises the existence of different types of uncertainty which include scientific uncertainty (e.g. risk-benefit may change over the life-cycle, effectiveness in real life, which patients will benefit the most and who will respond), financial uncertainty (e.g. number of doses required per treatment, duration of treatment, need for treatment combinations, need for supportive care, aggregate budget impact), utilisation uncertainty (e.g. are health care providers and prescribers able to target the patients in which the product is found "of

value”? Will patients adhere to treatment?). For many new medicines there is limited uncertainty, and hence no need for agreements from EFPIA’s point of view. In other cases agreements can ensure “value for money” (figure 6.17).

Figure 6.17: EFPIA’s perspective on the situations where MEAs may be applied



The duration of the agreement should be set in relation to the uncertainty to be addressed, particularly if data on long-term efficacy/effectiveness is sought (e.g. on disease progression).

Where agreements seek to collect additional evidence on the value “in real life” through registries, observational studies and similar schemes, it is desirable that also the pharmaceutical company has access to data – without jeopardising data privacy.

MEAs and differential pricing

Contractual agreements have also been suggested as a mechanism for improving access to medicines in Europe. Public policy makers have discussed how “discounting” could be used

to reflect affordability across countries. Pharmaceutical companies are today effectively discouraged from price differentiation due to international reference pricing and parallel trade. To work in practice, such patient access agreements must be protected from extra-territorial effects and the inherent conflict between transparency and efficiency needs to be addressed. The 2008 OECD report of global pricing policies suggests that contractual B2B-solutions on price and usage (=volume) are the natural evolution of value-based pricing. It also states that the confidentiality of agreements is a cornerstone for successful contracting. Contractual agreements are still in their infancy in Europe and approaches to regulate these, such as inclusion in a possible revision of the Transparency Directive, would be counter-productive from EFPIA's perspective. Nevertheless, EFPIA thinks that there are principles in the Directive which should apply to these agreements, most notably the non-discrimination towards foreign companies. Another issue that the European Commission has identified, and that EFPIA appreciates, relates to what happens after the expiry of contracts.

EFPIA suggests that the EU discussion should aim to seek agreement on terms (taxonomy) and good principles for contractual agreements.

Managed entry agreements - Principles

Harmonisation of MEAs would be counter-productive in EFPIA's view. At the same time, EFPIA believes there are general conditions that will greatly enhance a scheme's success and ensure that ultimately the patients who will most benefit from the new drug will access it; these conditions are outlined below. First, there should be flexibility in, and clarity about, the circumstances under which a scheme might apply. A particular type of agreement cannot be applied indiscriminately to all products. Second, to facilitate the undertaking of further outcomes studies and to minimise their additional cost, payers and healthcare bodies should improve the provision of data and should cooperate with industry to develop and maintain efficient data-collection systems. Third, for the agreement lifetime not to become a protracted series of price/reimbursement renegotiations, there needs to be a clear agreement on what is going to be measured and a clear assignment of responsibilities on how this is going to be achieved (required outcomes, specified time period for subsequent review of the reimbursement agreements, criteria, data collection capabilities, volume targets, etc.). Fourth, schemes should not lead to ever higher hurdles in terms of value expectation and burden of data provision. Fifth, payers should accept evidence from

different sources, e.g. both phase IV clinical studies and observational/epidemiological studies. Sixth, data requirements should remain proportional to the agreed target outcomes to be demonstrated, the timeframes set, and considerations around the costs vs. benefits of additional data. Clear understanding between payers and manufacturers on quantifying uncertainty, defining a “confidence interval” for the demonstration of target outcomes, and accepting residual margins of uncertainty (which are almost inevitable in real-life use) are key to address these concerns. Seventh, payers/healthcare authorities should ensure that the appropriate infrastructure and expertise is in place to enable schemes to be properly conducted and evaluated. Eighth, there should not be any ad hoc cost-containment mechanisms applicable to a medicine in addition to the scheme. Finally, information on MEAs should be accessible to the public with certain elements of such agreements covered by confidentiality rules that enable manufacturers to make the best offer. A climate of mutual trust and understanding based on the acceptance that some of the contractual details are covered by confidentiality obligations will ultimately lead to better outcomes for the negotiating parties because it offers the highest degree of willingness to put the best possible offer on the table.

Conclusions

EFPIA believes the following three key objectives should be achieved through a discussion on MEAs. First, the identification of concrete success factors (including health policy, legal, regulatory and political factors) for contractual schemes, looking at existing examples and define the general conditions needed to ensure schemes are clear, fair and achieve effective and timely access for patients. Second, to explore ways in which existing data collection systems at national and European level can be further leveraged in Europe. Third, to identify pricing and reimbursement system hurdles to access, in particular with regards to the impact of international price referencing.

6.4 Stakeholder input: Patient representatives

Interviews with six representatives from Belgium, Italy, Sweden and the UK were conducted in April-May 2012. Three of these patient representatives are active in the area of cancer diseases, one in the area of immune disorders, while Cittadinanza Attiva is a consumer organisation promoting civic participation and protection of consumer's rights in Italy and in Europe. The views presented in the sections that follow reflect those of the interviewees and are also reflective of the setting or the country where the interviewees and their organisations are operating.

6.4.1 Representative of Myeloma UK

The interviewee was very well familiar with the concept of MEAs. Indeed Myeloma UK pioneered the concept of patient access scheme (PAS) with bortezomib (Velcade). The bortezomib scheme was the first of NICE's PAS and set the scene for subsequent schemes as a means to gain access to new medicines where the QALY/ICER was above the accepted threshold.

Myeloma UK knew the drug would bring benefits to myeloma patients and that it underperformed in the appraisal because of the uncertainty surrounding the data due to the fact of the companion crossover design of the pivotal clinical trial.

Given the uncertainty with the data, the ideal solution was to share the risk caused by the uncertainty between the NHS and the manufacturer. Myeloma UK worked with the drug company and the Department of Health to find a solution to make bortezomib available to NHS patients. While the drug company worked on the details and the technicalities of the scheme, Myeloma UK was absolutely instrumental to make this happen.

The risk-share scheme is essentially a money back guarantee. If patients do not reach a partial response or better, treatment is stopped and the NHS reimbursed for the cost of the drug. If patients receive a partial response or better after four cycles, treatment continues to a maximum of eight cycles with the NHS bearing the full cost.

In clinical practice, many more patients than projected achieved a partial response due to the fact that the drug is always given in combination with the steroid dexamethasone plus or minus cyclophosphamide. These additional drugs, although very cheap, increase response rates from about 30% to 60%.

The manufacturer is responsible for auditing and collecting the data on how the scheme is working but it was a slow process in the beginning because some health staff would not fill out the required form to obtain reimbursement for non-respondent patients. It took some time before the scheme was efficiently monitored and implemented.

Benefits

In terms of benefits for patients and manufacturers, PAS can bring advantages to patients because often they apply to drugs which would not otherwise fall within NICE's cost-effectiveness criteria and therefore would be unlikely to receive a positive recommendation by NICE. Further, PAS offer a way to manufacturer to provide a discount without changing list prices (and there are not many other mechanisms available) and improve the cost-effectiveness of the drug.

However, PAS should be limited to the short-term and that they should not become a long-term solution for industry to access the market.

In the long term manufacturers should deliver a better value proposition to obtain inclusion in positive reimbursement lists through for example more creative pricing mechanisms which reflect value and innovation. Drug companies will need to work harder and produce more robust evidence in order to justify the price. Through such requirements, the appetite for patient access schemes will eventually decrease and PAS will be very much seen as exception rather the norm.

Eligibility criteria

Regarding fairness or restrictiveness of eligibility criteria, it is hard to generalise as they need to be seen in the context of the drug, disease, the appraisal and what the most appropriate benchmark for the scheme is. If there is uncertainty about the effectiveness of the drug for example, then a response-scheme is suitable. With lenalidomide there was less uncertainty about the effectiveness instead the price was too high. In this context, putting a cap to the number of doses per patient was probably the simplest and most straightforward solution.

Monitoring requirements

One of the major flaws in the UK is that nobody really concentrates on efficiency. No-one collects data on how, for example, NICE appraisals work in practice. This means that there is no evidence of the cost-effectiveness of for instance bortezomib or lenalidomide in clinical practice because no one collects this information. Collecting data on treatment performance is critical and it should be captured in an outcome registry which can be used to understand how the drug performs and is used in clinical practice.

Evaluation process

Myeloma UK has not been really involved in the evaluation process. Part of the reason is because this is a more administrative type of process. What is really important to patients is accepting to stop treatment because according to NICE guidance they did not obtain a sufficient response to treatment. In the eyes of patients, this is just penny-pinching but in reality a doctor would never keep treating a patient with a drug if the patient was not responding. However, because this happens in the frame of NICE guidance, patients perceive it is as a non-justified cost-saving measure not allowing their doctor to continue treatment.

This suspicion on patients' side goes back to communication problems between patients and doctors. Evidence from patient satisfaction surveys in the UK shows that what patients are most upset about is poor communication with their physicians. Better communication and better management of expectations (in general this should be not limited to communication about PAS) could help making patients accept NICE guidance stopping criteria.

Mutual benefits for all the parties involved

There are most definitely benefits for patients and drug manufacturers. Patients benefit from accessing medicines, which would have otherwise probably been rejected by NICE because of low cost-effectiveness; while the benefit for manufacturers is to receive a positive NICE recommendation for their drug. For the NHS the balance might be more unfavourable because of the administrative burden of managing the schemes.

Further, there are also 2 pregnancy prevention schemes that accompany two common treatments for myeloma, so in any given clinic you have 4 types of schemes being

implemented only for myeloma PAS. This additional workload for hospital pharmacists and doctors goes without counting that 20% of the patients will be on clinical trials. All this linked back to the communication issues mentioned before because the administrative requirements of these schemes draw time away from doctors and other clinical staff (in particular hospital pharmacy staff) to communicate with patients.

MEAs as the way forward for introducing new and expensive drugs

No. The existence of PAS is due to the failures with the current pricing and drug evaluation process. If these failures did not exist, there would be no need for PAS, individual funding requests, and cancer drug fund. Their existence is a clear sign of the existing issues with the current system. The introduction of value-based-pricing (VBP), which is meant to address these issues, will make PAS redundant and eventually led to their disappearing.

6.4.2 Representative of a Swedish patient representative organisation

The concept of MEAs was new to the interviewee. For this reason, the interview focussed on options to enable access to high cost-drugs, which have been rejected by TLV in Sweden.

As a matter of fact there is mainly one option, which is funding through the County Council (CC). This generally happens for expensive drugs, targeted at a small patient group, when there is lack of alternative treatment options.

However, reimbursement at CC level leads to disparities in access across the country because not all CC are likely to grant special reimbursement. The process of obtaining reimbursement from the CC can be initiated by an individual patient or a group of patients who lobby the CC for reimbursement, by the CC itself if they think TLV rejected a drug which should be available to patients, but the most common way in which this process is stated is probably on request of the doctor responsible for treatment to the CC. Funding decision are taken by a special medicine committee in each CC.

An example of a drug which was rejected by TLV and which received reimbursement through the CC (the interviewee had no information about how many CC reimbursed it) is velaglucerase alfa (VPRIV) for the treatment of a rare inherited disorder called Gaucher's disease. This drug fulfilled the general CC criteria for reimbursement: it is an expensive drug, it is directed to a small patient population, and has no available treatment alternatives. For this reasons, the County Council accepted to fund the drug.

However, use of lapatinib (Tyverb®) for second line treatment of a very difficult breast cancer, was refused by the CC (the interviewee does not exclude that some CC may have been able to pay for it) because alternative medicines were available.

6.4.3 Representative of multiple sclerosis (MS) patients in the UK

The interviewee was familiar with the concept of MEAs. Overall patients benefit from PAS as it enables them to access new and expensive drugs, which might otherwise not have been available to them. However, in order to ensure this, it is crucial that access is not limited to clinical trial participants.

Eligibility criteria will always be there whether as part of a PAS or NICE positive recommendation with conditions. The MS Society accepts that as long as the criteria are wide enough to enable all patients who can benefit from the drug to access it. Further, it is important to adapt such criteria as new evidence of clinical benefit emerges.

It is important to collect additional data on drug use and effectiveness in clinical practice and the healthcare system should be willing to bear the additional workload and resources needed to collect them. However, because resources are limited, it is essential that data collection is balanced against the benefits it can bring to avoid misplacing resources which could have otherwise been employed to enable patient access to treatment.

This patient representative organisation has never really performed an evaluation of PAS in the UK.

The issue with the evaluation of the risk-sharing scheme for beta interferon and glatiramer acetate for multiple sclerosis (MS) is that not enough time was planned for the evaluation of this scheme. In fact, the conclusion reached at the end of the first evaluation was that more time is needed to provide a definitive answer on the performance of these drugs.

One important issue with this scheme is that even if and when a conclusion on the effectiveness of these drugs is reached, it will be very difficult to ask patients who do not classify as having a positive response according to the scheme criteria to stop treatment. Many patients are already on treatment and the evaluation of the drug performance is made difficult by the very nature of the disease. There is a grey area where it is difficult to establish whether the treatment is actually bringing a benefit to the patient. In addition to that views on treatment performance are likely to be different between patients and NICE.

Patients might think the drug is beneficial to them but from a NICE perspective these benefits are not necessarily sufficient to make the drug cost-effective. A possible solution to address the peculiarities of MS through a MEA is to develop a performance based scheme whereby the manufacturer reimburses treatment costs for patients who do not achieve a pre-agreed response level.

PAS do offer mutual benefits to the involved parties as they enable patients to access drugs and manufacturers to obtain positive NICE recommendation and therefore increase their sales. Overall, the English experience with PAS is positive. For the MS Society the main underlying problem is access to treatment. Due to local prescribing practices and difficulties in establishing whether a patient meets NICE criteria, access to MS drugs differs substantially across England.

PAS could be a possible way forward for introducing new and expensive drugs as they represent a win-win situation for all the parties involved.

Whether value-based pricing (VBP) will make PAS redundant or not depends on what VBP is meant to be. If VBP is only about adding a few additional factors into NICE's appraisals probably not. However, if it is about introducing a price negotiation platform and the issue is price, then negotiation as part of VBP would make the need for PAS redundant as the discount which would otherwise been granted as part of a PAS could be arranged at the negotiation stage. However, if the issue is poor evidence, then a system of VBP would not solve existing issues and PAS, which include collection of additional evidence would still be needed.

6.4.4 Representative from European multiple sclerosis (MS) platform

The interviewee was familiar with the concept of managed entry agreements (MEAs). Indeed, the European MS platform supported the MS Society in the UK campaigning for the interferon scheme in the UK and helped them to overcome NICE's first negative reaction towards this new drug group.

Any initiative to improve access is most welcome to patients and if negotiations between payers and manufacturers are stopped or delayed because of uncertainty issues, MEAs represent the second best solution to unconditional reimbursement. However, there is also

a danger for payer to continue funding a drug, which is not cost-effective if no clear conclusion is reached on the effectiveness of the drug at the end of the MEA study period.

MEAs should be linked with the DG-Sanco Joint Action Patient Registries Initiative (PARENT), which would allow to bring together a large amount of data across Europe. Further, opportunities should be sought to link MEAs with post-marketing data collection.

Patients benefit of improved access through MEAs, while manufacturer have chance to obtain reimbursement and therefore recover investment in R&D. The advantages for payers seem to be more limited based on the UK experience with MS scheme. An important issue, which needs to be considered for the successful implementation of MEA, is whether they are implemented as initially agreed. For example if healthcare provider receive reimbursement for unsuccessful treatment outcome.

MEAs can definitely represent a solution for introducing new and expensive drugs if there is uncertainty about their effectiveness. However, this also raises issues in regards to how drugs are evaluated in HTA. For the interferon scheme in the UK, there is no clear evidence of the drug effectiveness on scientific grounds to date but substantial anecdotal evidence of the benefits for patients (“I would not be able to work if was not taking this drug”) exists. Apart from the specific issues involved with the evaluation of this scheme, broader issues common to the evaluation of all drugs remain. First of all, it is difficult to capture quality of life in the quality adjusted life year (QALY) indicator used in HTA. Second, patients are not sufficiently involved in setting the criteria of about the outcome measure, which will be used to evaluate the drug.

Whether there will still be a place for MEAs in the era of value-based pricing (VBP) really depends on how VBP is going to be implemented. Issues around the right comparator drug for example are likely to remain. An important aspect to consider when issues about the financing of new and expensive drugs are discussed is the concept of holistic budgeting. This concept entails moving away from single drug budget to a more holistic budgeting approach. For example, if a drug enables a patient to avoid early retirement and stay in the workforce, it is reasonable that the pension fund would contribute to the treatment costs because in the end it will enable to save pension funds.

6.4.5 Representative of melanoma in Belgium

The interviewee was familiar with the concept of managed entry agreements (MEAs). While it is not possible to generalise, MEAs is an instrument and as such it can be used and abused.

It is difficult to express an opinion on eligibility criteria in Belgium, since patients are presented with the final decision and there we have no information on the elements which fed into the decision-making process. Monitoring requirements.

Monitoring the drug effectiveness can be a controversial issue. Patients want real life data to see if results from Phase-3 clinical trials actually apply to all patients. However, some patients also fear that the drug might be taken away if the study does not show that the drug is effective.

This patient representative organisation has so far never been involved in an evaluation of MEAs.

There is no “yes” or “no” answer in terms of mutual benefits for all actors involved; it really depends on how this instrument (MEA) is used. One important issue for patients is the lack of knowledge about MEAs, about available options in terms of agreements, and experiences in implementing MEAs (from a patient, health service, and manufacturer perspective). One positive element is definitely access, however there are also threats linked with the use of diagnostic tools and how these tools are going to be evaluated. If the same manufacturer owns the drug and the diagnostic tool there are serious issues in terms of monopoly power.

Another issue is the threat that MEAs might draw away attention from the real issue. For example, several oncologists and patients are not convinced about the recommended dosing and regime, of the monoclonal antibody ipilimumab (Yervoy). This immunotherapy is very expensive even for cancer therapy standards. Concentrating on how to make the drug available as part a MEA, may distract from the real issue which is to collect more evidence to improve dosing, regime, and use.

MEA is an instrument, it is not a solution, and in order to make it work patients need to be informed about best practices, the process of developing MEA needs to be transparent, and most importantly it needs to include patients.

MEAs as the way forward for introducing new and expensive drugs

At the moment there are few alternatives to MEA. However, for MEA to succeed cultural differences between countries, particularly in the way they perceive risk, need to be taken into consideration. The very transparent Anglo-Saxon model might not work in a country like Belgium for example. Regarding how VBP would change the landscape of MEA, there would most probably still be the need for them, particularly as most countries think a system of VBP is unaffordable and would therefore not help in making very expensive drugs more affordable.

6.4.6 Representative of Cittadinanza Attiva in Italy

The interviewee was familiar with the concept of managed entry agreement (MEAs).

MEAs represent an innovative formula to introduce new medicines in a fast and transparent way, from this perspective they certainly bring benefits for patients. However, one issue with MEA is that patients are not involved in the decision-making process regarding eligibility criteria.

In terms of monitoring treatment, the interviewee would welcome more registries. Data collection is essential to confirm the data submitted by the manufacturer and to support (and if relevant in the light of the new evidence to update) reimbursement decisions.

Cittadinanza Attiva has never conducted an evaluation of MEAs in Italy.

MEAs can offer mutual benefits to all the parties involved. Patients benefit of faster access to innovative treatments while the manufacturer, by taking responsibility for the outcome of its drugs, can improve its image in the eyes of the public, gains credibility for its products, and raise its reputation.

MEAs can definitely represent the way forward for introducing expensive innovative drugs especially because there are not many other alternatives available. In cases where there are doubts about the effectiveness of a new drug, a MEA it is a worthwhile investment despite the additional resources needed to develop it. Even in the context of value-based pricing there will be always the need for MEA because it does not solve the problem of paucity of evidence at pricing and reimbursement level.

6.4.7 Summary of patient representative experiences with MEAs

All apart from one of the patient representatives interviewed was familiar with the concept of MEA. Indeed some of them had been involved in promoting and facilitating the development of MEA (e.g. Myeloma UK and MS Society UK with the support of the European MS platform).

There is general agreement that MEA bring advantages to patients in terms of access to treatment and to manufacturers in terms of reimbursement. Some interviewees acknowledged the possible disadvantages for those implementing the schemes such as doctor and pharmacists.

Most interviewees think that there is still need for MEAs even in an era of VBP because of the many remaining issues (e.g. challenges in choosing the appropriate comparator product, lack of evidence at the time of pricing and reimbursement, etc.).

Concerns include the lack of transparency surrounding MEA, the limited involvement of patients in designing the schemes and defining the relevant outcome measures.

7 Discussion

Despite the diversity in the different models of MEAs implemented across EU Member States, all these agreements are introduced in an attempt to address one or more of three objectives: first, to limit budget impact, second, to address uncertainties regarding clinical effectiveness and cost-effectiveness and/or in a specific context (e.g. validate cost-effectiveness information from another country with local data), and third to manage utilisation to optimise performance.

The following paragraphs will discuss the instruments used by EU Member States in an attempt to achieve these objectives. Some of the instruments used have application in more than one area, for example, conditional treatment continuation or limitation of reimbursement to specific patient sub-groups contribute to both managing budget impact (through reduced utilisation) and managing utilisation to optimise performance (by limiting reimbursement to the patient sub-groups who are likely to benefit the most).

7.1 Managing budget impact

Instruments to manage budget impact include PVAs, budget caps, dose caps, discounts, paying for performance, and price-match with comparator. Managing budget impact is one of the main objectives of MEAs in Belgium, the Czech Republic, France, Italy, Lithuania, Portugal, and the UK.

This is reflected in the design of MEAs in these countries which includes features of PVAs, budget caps, and a compensation mechanism in Belgium, limited access through specialised healthcare centres in the Czech Republic, widespread use of PVAs in France, PVAs, discounts and conditional treatment continuation in Italy, PVAs, payback, and expenditure cap in Lithuania, PVAs in Portugal PVAs, and discounts, dose capping, initial free doses in the UK.

Although these schemes are designed to address budget impact, without data on the target expenditure vs. the achieved expenditure, it is not possible to say whether the schemes implemented succeed in managing budget impact.

7.2 Managing uncertainty relating to clinical and/or cost-effectiveness

There are two main ways to address uncertainty relating to clinical and/or cost-effectiveness. The first is to grant reimbursement for a limited time period during which

additional evidence on the drug effectiveness will be collected and to update the reimbursement decision afterwards based on the new cost-effectiveness results. The second way is to decrease the price or to limit utilisation so that the cost-effective ratio is improved because of lower costs. However, this option does not address the underlying issue of uncertainty in cost-effectiveness.

Collection of real-life data to update the cost-effectiveness model is practiced in various countries. In the Netherlands a cost-utility analysis needs to be submitted after the initial 4-year conditional reimbursement period. A similar system is in place in Sweden where manufacturers can be asked to submit additional evidence generated through coverage with evidence development schemes. Portugal also requires submission of additional evidence to evaluate the therapeutic value and cost-effectiveness of new drugs if there is uncertainty in the original data presented by the manufacturer (or if local data on cost-effectiveness are needed).

Italy uses payment-by-result and discount or reimbursement for non-responders as a tool to address uncertainty issues. This is usually coupled with data collection as part of the monitoring registries.

The UK tends to prefer using discounts, which do not require additional data collection to improve the drug's cost-effectiveness in its patient access schemes (PAS).

7.3 Managing utilisation to optimise performance

The main strategy used to optimise utilisation is to limit prescribing and reimbursement to specific therapeutic indication and to those patients sub-groups who are most likely to benefit. The instruments used include limiting prescribing to specialised healthcare centres, use of biomarkers, and physician certification that the patient meets the eligibility requirements together with monitoring. The Czech Republic for example limits access to specific patient subgroups and to specialised healthcare centres. In Italy, patients eligibility is monitored through the registries and physician are request to certify that a patient meets the prescribing requirements in order for him to obtain the drug at the pharmacy.

Although the schemes seemed to be designed to achieve optimal utilisation performance, it is not clear in how well they are implemented in practice, i.e. if they really succeed in limiting reimbursement to specific patient sub-groups.

Based on the design and features of MEAs in Member States, overall it seems that these agreements are well equipped to achieve their objectives. However, implementation challenges are not to be excluded and only an impact analysis based on savings generated and challenges encountered in implementing MEAs (e.g. difficulties in obtaining reimbursement for non-responders from the manufacturer, feasibility of withdrawing drugs which proved not to be cost-effective) would allow establishing their actual impact.

7.4 Advantages and disadvantages of MEAs as reported in the literature

There seems to be a general agreement that MEAs can, under certain conditions, help address post-licencing uncertainty and enable patient early access to innovative treatments (Russo et al. 2010; Willis et al. 2010). However, the UK experience seems to support the view that despite offering improved access PAS have not addressed the issue of outcome uncertainty (Towse 2010). There is less agreement on whether MEAs actually offer incentives for innovation or not. On one side, it has been argued that they offer manufacturers some predictability in terms of initial price and the hope of future financial rewards (de Pouvourville 2006) thus encouraging innovation (Stafinski, McCabe, and Menon 2010; Cook, Vernon, and Manning 2008). However, post-market shift of a significant portion in the experimental phase of the product development process and uncertainty about manufacturers' future income stream (McCabe et al. 2009) might actually act as a disincentive for manufacturer. Additional disincentives have been discussed such as the risk manufacturers are required to assume in a MEA and which they may perceive as too high, potential disinvestment in disease areas with weak evidence-base, and delays in data collection and dissemination due to the small treatment population of a MEA (Trueman, Grainger, and Downs 2010).

Regarding the disadvantages, several issues have been raised such as high transaction and administrative costs (Adamski et al. 2010; Carlson, Garrison, and Sullivan 2009; Carlson et al. 2010), the introduction of additional uncertainty for manufacturers in terms of expected returns (Towse and Garrison 2010; McCabe et al. 2009) which may have the opposite effect of dis-incentivising additional data collection (Towse and Garrison 2010), the advantage competitors may take of data collected by the manufacturer (de Pouvourville 2006; Carlson, Garrison, and Sullivan 2009), and related to this the problem of free-riding. Further,

there are challenges linked to the regulation of these agreements (Towse 2010) and the transferability of results from one country to another (Towse and Garrison 2010; de Pouvourville 2006). Moreover, if MEAs become increasingly common there is a risk that manufacturers may ask a high initial price in expectation of a MEA, in the context of an HTA appraisal (Towse 2010).

In addition to this, there are a number of open questions which need to be addressed such as who should finance data collection, who should be responsible for it (and in this context it is essential that data collection is conducted by an independent party to avoid conflicts of interest), and how to streamline implementation of MEAs so as to reduce the management burden for health care staff.

7.5 Perceptions

During interviews with country representatives it became clear that what is considered to be a MEA in one Member State may not be perceived as such in another. Italy, for example, considers conditional reimbursement – through the AIFA notes - and restricted access – through the therapeutic plans - as MEAs (Figure 6.11). The same instruments are used in Denmark, however, the latter does not consider them to be MEAs. A similar situation is true for the UK, which imposes several restrictions in terms of defining patient eligibility for several drugs appraised by NICE but does not consider such restrictions as a form of MEA. Again, this raises issues in terms of classification and taxonomies as they both pre-suppose a common understanding and definition of what constitutes a MEA.

The emerging opinion among patient representatives is that MEAs bring an important benefit to patients in terms of access to treatment. However, there were also some concerns on how these agreements will be implemented, in particular about the current lack of transparency in the field (notably, the UK is an exception here) and their impact on patients. Lack of transparency, especially towards patients, is particularly important in the case a drug under coverage with evidence development is found not to meet the criteria which would include it in the positive list and the health payer decides to stop conditional reimbursement. In such cases, it is essential that patients are informed from the beginning that the drug is made available for temporary reimbursement, under specific conditions, and subject to re-evaluation.

None of the patient representative groups interviewed conducted an evaluation of MEAs.

The majority of interviewees thought that MEAs can represent a possible instrument for introducing new and expensive drugs and that the need for them will remain even in an era of value-based-pricing (VBP). However, one patient representative thought that the introduction of VBP in the UK will make redundant as the drug will be priced according to the additional benefit it brings to the patient. From a UK perspective, this view may be justified by the fact that the wide majority of PAS are discount agreements negotiated during the HTA assessment. In such cases, an ideal system of VBP would price the drug at a lower level instead of arranging a discount as part of a PAS. However, in cases where the agreement involves additional data collection to address uncertainty present at the time of the first HTA assessment and the aim is to take a final reimbursement decision after the initial cost-effectiveness model is updated with real-life data, there would be still a role for MEAs.

Another observation from a participant of this working group was that if MEAs are to bring additional value, HTA should be the basis of every MEA. This is the case in some countries, particularly those countries which use coverage with evidence development to collect additional data with the objective of updating the final coverage decision based on the cost-effectiveness results of the new HTA, but not all.

7.6 Limitations

Due to the open-nature of certain questions, one should not exclude that if a country did not mention for example patient co-payments as part of the criteria to access a drug as part of a MEA, this is not actually a requirement. It could well be that this criterion was simply omitted from the description since the question did not specifically ask for it. The same issue applies to other features of MEAs like administrative requirements or burden, which was not defined.

8 SWOT analysis

Strengths of MEAs General strengths	Weaknesses of MEAs General weaknesses
<ul style="list-style-type: none"> - From a literature perspective there seems to be a general agreement that MEAs can, under certain conditions, help to address post-licencing uncertainty and enable patient early access to innovative treatments - In general, MEAs offer flexibility in dealing with new and often expensive technologies, which are characterised by significant levels of uncertainty - Different types of schemes exist in order to address different needs (budget impact, weaknesses in clinical evidence, etc.). Their potential is further amplified by the possibility to combine financial and non-financial elements in the same agreement and address different issues at the same time (e.g. budget impact and use, access and cost-effectiveness, etc.) <p><i>Agreement including a health-outcome component (e.g. CED, payment for performance)¹⁶</i></p> <ul style="list-style-type: none"> - Collection of information on drug use and effectiveness in different sub-groups of patients under real-life clinical conditions (i.e. outside a clinical trial), to update treatment guidance, reduce uncertainty and reach the final reimbursement decision (coverage with evidence development). <p><i>Pure financial agreements, no health outcome component (PVAs, price/dose capping, price-match,</i></p>	<ul style="list-style-type: none"> - There is little evidence to support the claimed benefits of MEAs and the extent to which some of the challenges involved in MEAs implementation (e.g. monitoring requirements, transaction costs,) impact on the final outcome - Frequent lack of transparency on the agreements implemented, their objectives, and evaluation of their impact is preventing cross-country learning and severely limiting the ability of patients engage with MEA processes¹⁷. - Voluntary versus non-voluntary nature of MEAs varies across Member States and this can create confusion to different stakeholders - Variability in the perception of MEAs across countries and what actually is a MEA may differ across settings <p><i>Agreement including a health-outcome component (e.g. CED, payment for performance)</i></p> <ul style="list-style-type: none"> - Despite collecting very useful data, which would enable the drug to be re-assessed and its price re-negotiated according to its impact and cost-effectiveness in real-life, few countries actually leverage on this opportunity. - Discontinuity in assessing evidence in clinical

¹⁶ May or may not include a financial component

¹⁷ Notably the UK is an exception here. NICE has a list of all the approved patient access schemes and the terms of the agreement are generally available (the exact amount of the discount is not always available)

etc.)

- Improve the cost-effectiveness of the drug through a discount offered by the manufacturer on the official price or a payback agreement for non-responders. Higher cost-effectiveness will increase the probability of the drug receiving a positive recommendation by HTA agencies.
- Evidence of savings from PVA in France

Strengths from a payer perspective: Depending on the type of agreement and its objective, it enables better control of budget impact, to increase cost-effectiveness, and to improve use of and access to medicines.

Strengths from a patient perspective: It improves access to medicines, which had been or were likely to be rejected on cost-effectiveness grounds.

Strengths from a manufacturer perspective: MEAs enable manufacturers to obtain reimbursement for drugs, which were likely to be rejected by drug reimbursement agencies. Discounts can be granted without touching list prices.

practice post-MEA implementation

Pure financial agreements, no health outcome component (PVAs, price/dose capping, price-match, etc.)

- Although these schemes are designed to address budget impact, without data on the target expenditure vs. the achieved expenditure, it is generally not possible to say whether the schemes implemented succeed in managing budget impact (notably France who publishes its savings estimates on an annual basis is an exception).

Schemes aiming to manage utilisation to optimise performance

- Although the schemes seem to be designed to achieve optimal utilisation performance, it is not clear if they really succeed in limiting reimbursement to specific patient sub-groups. PVAs for example are used in France in an attempt to limit use to the approved indication. However, the data collected does not enable to verify whether the reimbursed doses were prescribed for approved indication or not.

Weaknesses from a payer perspective:

- Additional efforts are required to make a new drug available to patients such as negotiation time, monitoring of patient response, data collection, development of registries, etc.
- Limited capacity to implement and assess evidence – especially if clinical evidence needs to be assessed- if implementation takes place at regional or hospital level.

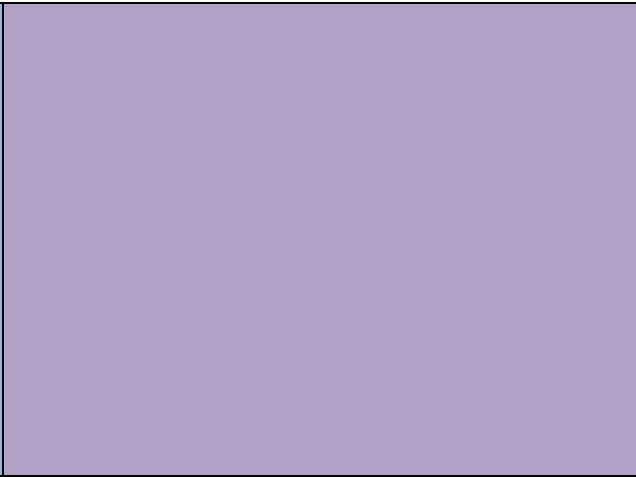
Weaknesses from a patient perspective:

- Generally limited opportunities to engage with the development of MEAs;
- Not all patient groups are aware of what MEAs

	<p>do, let alone individual types of MEAs</p> <p>Weaknesses from a manufacturer perspective:</p> <ul style="list-style-type: none"> - Concessions need to be made such as refund for non-respondent patients, discounts, collection of additional data, etc.
<p><u>Opportunities of MEAs</u></p> <p>General opportunities</p> <p><i>Coverage with evidence development</i> Potential to increase efforts with regards to re-evaluating the effectiveness of the drug at a later stage and re-negotiating the price based on the real-life effectiveness of the drug.</p> <p><i>Linking with other activities and initiatives</i></p> <p>To streamline post-marketing studies with data collection requirements as part of MEAs and adaptive licensing (EMA) in the light of reducing data the burden of data collection.</p> <p>To link data collection as part of MEAs with EU initiatives on registries. Pulling evidence from different countries will allow generating a large pool of data and increases the statistical significance of the results. In This context, registries should focus as much as possible on primary endpoints rather than secondary ones.</p> <p><i>Managed introduction of new medicines</i></p> <p>To limit the impact of introducing new drugs by integrating MEAs into a process of managed introduction of new medicines which starts from horizon scanning activities and continues all the way up to post-marketing studies and surveillance.</p> <p>Opportunities from a payer perspective: Re-evaluation of drugs and re-negotiation of the price as new evidence becomes available would enable to move towards a system of value-based pricing whereby a drug is reimbursed according to additional clinical benefits it brings to patients.</p> <p>Opportunities from a patient perspective: More</p>	<p><u>Threats of MEAs</u></p> <p>General</p> <p>Proliferation of MEAs as quick-fix ad-hoc solutions which are not integrated into a comprehensive process of managed entry of new pharmaceuticals, is likely to cause additional burden to the healthcare system and manufacturers rather than providing a viable long-term solution to manage entry of new medicines.</p> <p>Threats from a payer perspective:</p> <p>If MEA agreements proliferate without integrating with other activities and initiatives, the burden of MEAs is likely to become too high.</p> <p>As MEA become more common, there is a threat that manufacturers could start proposing higher entry prices in expectation of having to engage in a MEA.</p> <p>If opportunities to synergise across initiatives (e.g. adaptive licensing, EU initiatives on registries, etc.) and to pull together evidence from and share evidence between countries are not seized, duplication of data collection efforts will occur and evidence available to individual countries is likely to remain weak and fragmentary.</p> <p>Threats from a patient perspective: If MEAs become too burdensome for payers and manufacturers, the latters might become less willing to engage. This means that fewer instruments will be available to facilitate access to patients.</p> <p>Threats from a manufacturer perspective: If MEAs are going to add to other requirements (e.g. post-marketing data collection, surveillance) without reducing them, industry will become more and more reluctant to engage.</p>

transparency and formal opportunities to engage in the MEA process would enable patients to make use of this instrument to obtain faster access to new medicines.

Opportunities from a manufacturer perspective: Public image benefits from the willingness to take responsibility for the use of the drug in real-life. If integrated with post-marketing data collection and adaptive licensing there is the potential of reducing data collection requirements for industry.



9 Towards a new taxonomy to capture MEAs across EU Member States

9.1.1 Available taxonomies

Different systems to classify managed entry agreements (MEAs) have been proposed in the literature (Carlson et al. 2010; Klemp, Frønsdal, Facey, and on behalf of the HTAi Policy Forum 2011; Jaroslowski and Toumi 2011; Espin and Rovira 2009) in addition to country specific taxonomies (UK Department of Health and ABPI 2008; Siviero 2011) (see Appendix 7).

Although these taxonomies have different features, they can be broadly ascribed to two main classification systems: one classifying agreements based on their financial or health outcome nature while the other distinguishing them based on the objectives they are trying to achieve.

9.1.2 Key issues

The HTAi Policy Forum classifies agreements based on their objectives (HTAi 2011 framework). In that it provides substantial flexibility in classifying agreements but it does not provide any information on the instruments used to achieve these objectives or the impact of monitoring.

Leveraging from the experience developed with the EMINet survey, we developed a framework which can be used to classify MEAs in Europe. While developing its structure, at each level we have taken into account the evidence presented across countries as well as tools and instruments that are being used by policy makers in this context in order to negotiate a MEA. We have attempted to incorporate these pieces of information into a structure that can, hopefully, provide a workable framework for MEAs and the way they operate across EU Member States.

The proposed taxonomy features four levels.

The first level represents the objective a particular MEA is trying to achieve, financial or performance.

The second level focuses on what is being monitored, notably, the total cost for all patients, the total cost per patient, utilisation in real life, or evidence regarding decision uncertainty.

The instruments used for achieving these objectives are illustrated in level three (e.g. discounts, price-volume agreements, CED, outcome guarantee) while level four presents the impact of MEAs on price, reimbursement and reassessment (figure 9.5). A brief analysis by level, as presented in this section is outlined below.

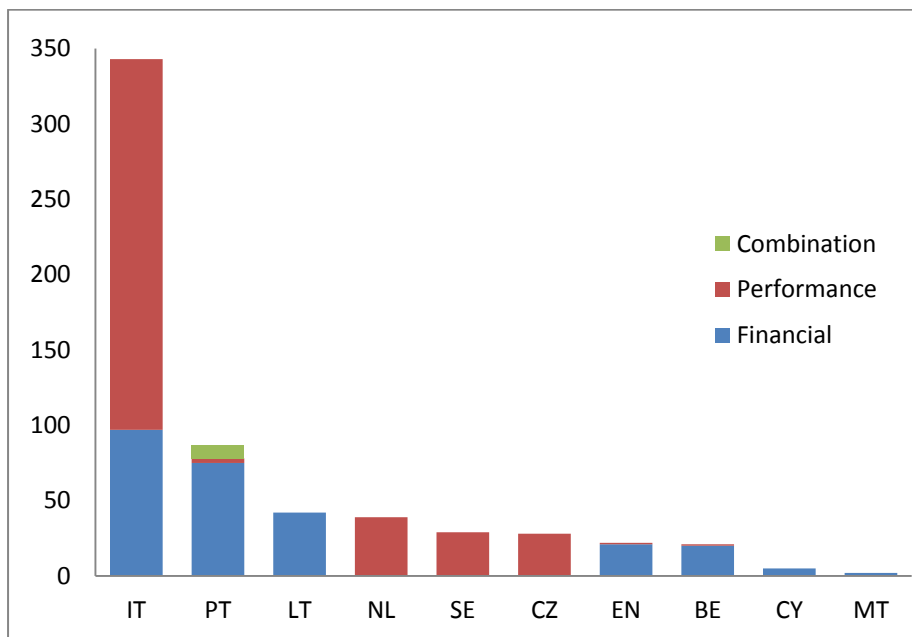
9.1.3 New taxonomy

Based on the new taxonomy proposed in the previous section and shown in Figure 9.5, all MEAs reported by Member States in the survey in the earlier parts of this report were subsequently re-classified. Whilst doing so, Member States also provided an update on the number of available schemes in their territory as of December 2012¹⁸.

Figure 9.1 shows the number of agreements or schemes based on the main objectives pursued by countries, notably financial, performance-related or a combination of the two. The figure highlights very clearly existing trends, with Portugal, Lithuania, England, Belgium, Cyprus and Malta focusing very explicitly on financial objectives while the Netherlands, Sweden, the Czech Republic focusing more on performance-related schemes. Italy has a greater number of performance-based agreements but also implements a considerable number of financial schemes.

¹⁸ The following countries provided updates on the number of their agreements as of December 2012: Belgium, Czech Republic, England, Lithuania, Malta, Portugal, and Sweden.

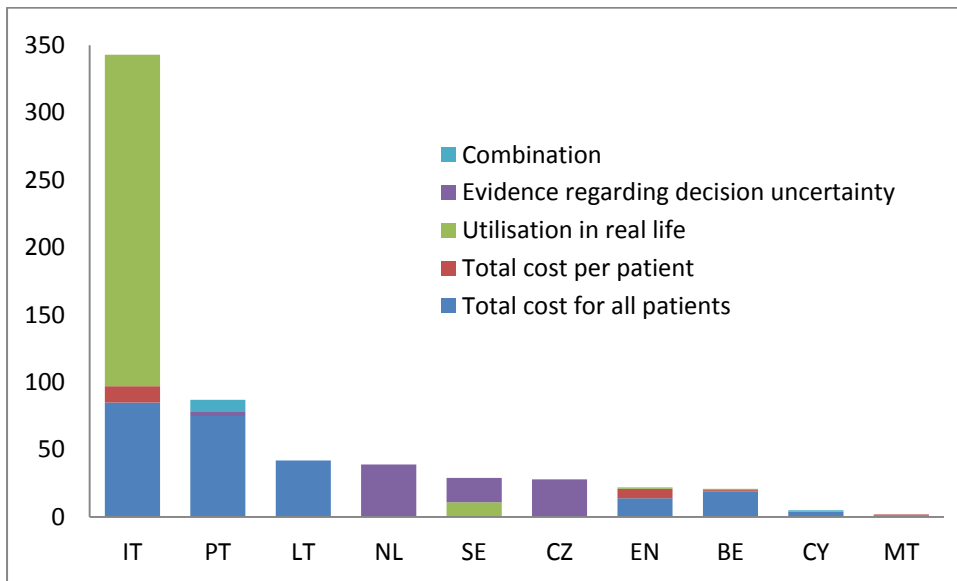
Figure 9.1: MEA analysis by means of objectives countries are trying to achieve



Notes: BE: Belgium, CY: Cyprus, CZ: Czech Republic, EN: England, IT: Italy, LT: Lithuania, MT: Malta, NL: Netherlands, PT: Portugal, SE: Sweden

When examining the relevant monitoring means (level 2 of the new taxonomy), it becomes clear that among financial schemes, a large proportion focuses on the total cost for all patients, while only a minority focuses on the total cost per patient which could be explained by the simpler implementation of schemes focusing on the total sample of patients rather than on a per patient basis (Figure 9.2). The trend for performance-based agreements varies: some countries concentrate on gathering evidence about decision uncertainty. This is prevalency in the Netherlands, the Czech Republic, and Sweden for the majority of its agreements. Italy, on the other hand, implements a number of agreements to optimise utilisation in real life. Sweden also has various agreements in place in this area.

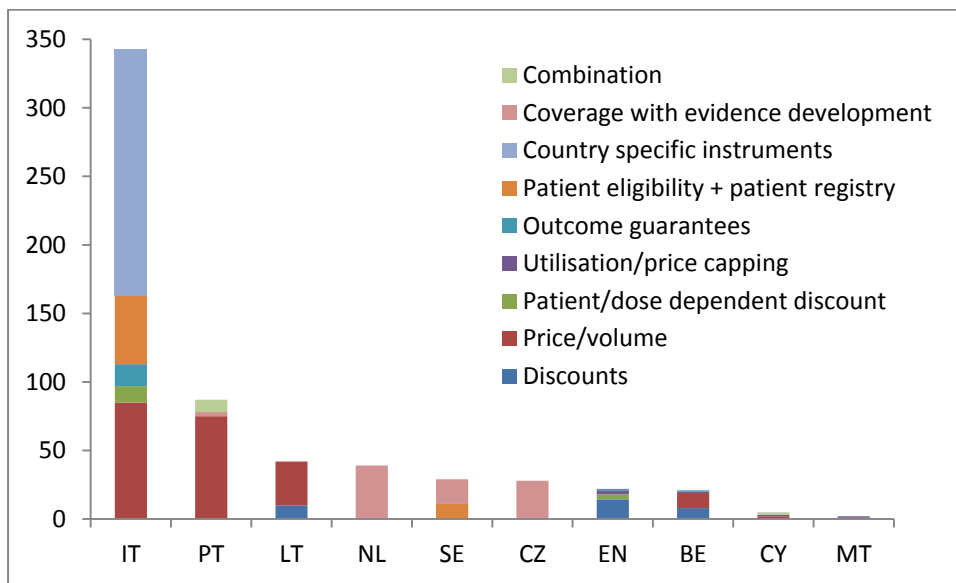
Figure 9.2: MEA analysis by monitoring means



Notes: BE: Belgium, CY: Cyprus, CZ: Czech Republic, EN: England, IT: Italy, LT: Lithuania, MT: Malta, NL: Netherlands, PT: Portugal, SE: Sweden

Moving on to the third level of the new taxonomy of MEAs (monitoring means), it appears that PVAs, followed by discounts, are the most common instrument for financial schemes while, coverage with evidence development, patient eligibility criteria linked to a registry to ensure compliance and country-specific instruments, such as AIFA notes and therapeutic groups in Italy, are the most common instruments for performance-based agreements (Figure 9.3).

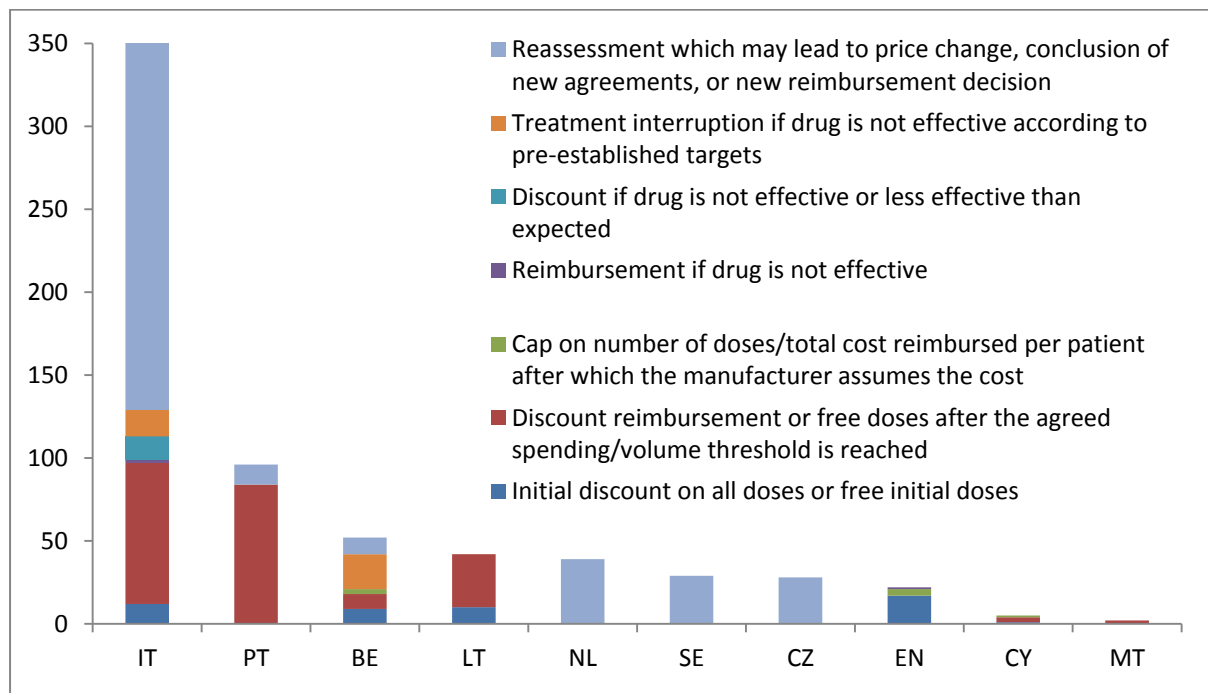
Figure 9.3: MEA analysis by type of instrument



Notes: BE: Belgium, CY: Cyprus, CZ: Czech Republic, EN: England, IT: Italy, LT: Lithuania, MT: Malta, NL: Netherlands, PT: Portugal, SE: Sweden.

The final level of the new taxonomy displays the impact of MEAs on expenditure, prices, and reassessment (Figure 9.4). As some of the MEAs implemented impact more than one area, a particular scheme may be associated with more than one area of impact. In comparison to the previous three figures there is therefore not always a 1 to 1 association between scheme and impact but sometime it may be a 1 to 2 or 1 to 3 association. The figure highlights that collection of additional evidence for reassessment is very prevalent in Italy, the Netherlands, Sweden and the Czech Republic. Discounts, reimbursement and free doses after an agreed threshold of spending has been reached, are common in Italy, Portugal, Lithuania, and to a lesser extent also in Belgium, Cyprus and Malta.

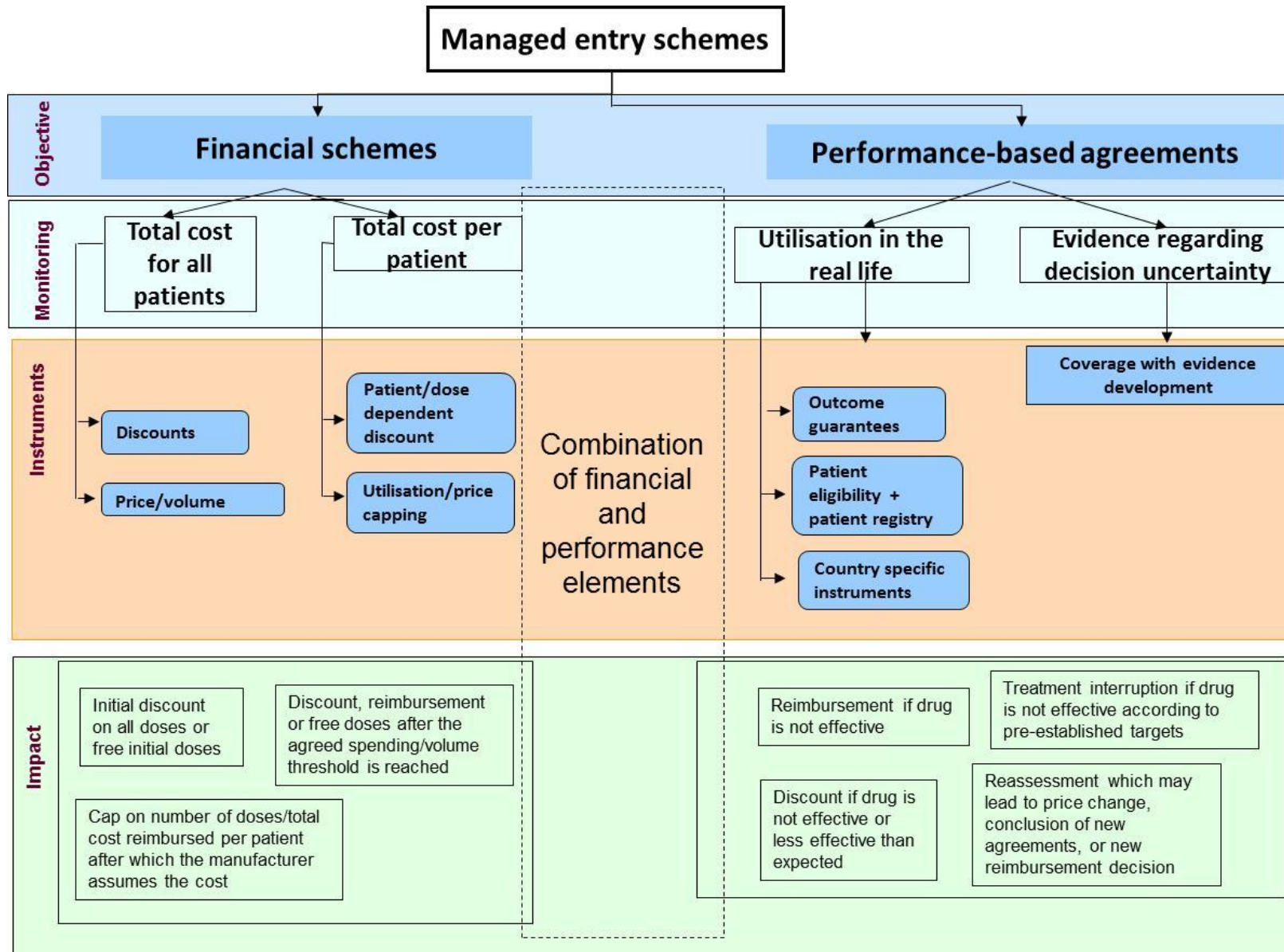
Figure 9.4: MEA analysis by impact



Notes: BE: Belgium, CY: Cyprus, CZ: Czech Republic, EN: England, IT: Italy, LT: Lithuania, MT: Malta, NL: Netherlands, PT: Portugal, SE: Sweden

In summary, by applying the proposed taxonomy to the data collected on MEAs in Europe we tested the feasibility of using the new framework in the European context and new lens of analysis which distinguishes between what the objectives are, what is being monitored, the instruments used to achieve the objectives and the impact of MEAs.

Figure 9.5: Proposed taxonomy for MEAs



10 Conclusions

European countries are using a variety of instruments to tackle uncertainty arising from lack of information about budget impact, cost-effectiveness, use in real life, and access. Despite the non-negligible number of agreements implemented, little information is available on the impact of these schemes and whether they are meeting their objectives. Moreover, the little amount of information available in the public domain is hampering cross-country learning and the ability of patients to engage in the process.

Previously proposed taxonomies do not well suit the reality at country level, where complex agreements with financial and health outcomes features are implemented. While there is scope for improvement, the taxonomy employed in this study aims to address this issue by using a more versatile classification system which on one level focuses on the objectives countries are trying to achieve through MEAs and on a second level highlights and summarises the features of the implemented agreements. Further there is the need to agree on a common definition of MEAs and to define the boundaries between a MEA and a non-MEA.

MEAs should not become a quick-fix solution to introduce expensive drugs but be integrated into a process of managed introduction of new medicines which starts from horizon scanning activities, moves to forecasting, HTA assessment, pricing and reimbursement, and continues with post-marketing studies and surveillance.

Appendices

Appendix 1: Description of each MEA used in your country

For each TYPE of MEA implemented, member states were asked to provide the following information:

1. MEA definition
2. Extensive description of MEA
3. Is there a specific legal framework for the MEA? If yes, please specify.
4. Is there a specific national legislation for the MEA? If yes, please specify.
5. Duration of the MEA
6. Specific administrative requirements
7. Notes

Appendix 2: MEA for each therapeutic indication

For each MEA implemented, member states were asked to provide the following information:

1. Branded name
2. INN
3. ATC Code
4. Therapeutic indication
5. Type of MEA (e.g. cost sharing, risk sharing, payment by result/payment for performance, price by volume, cap to expenditure, volume based agreement)
6. Starting year
7. Year of completion (if available)
8. Criteria on which MEA is based (e.g. numbers of therapeutic cycles for cost-sharing schemes; performance indicators for payment by performance schemes)
9. Tools used, if available (e.g. registry, web applications)
10. Who is in charge of MEA functioning and control (e.g. in case of price per volume agreements, who controls the volume ceiling? Or in case of a registry, who fills the forms?)
11. Objective (e.g. managing budget impact, managing uncertainty on safety, clinical and/or cost effectiveness)
12. Financial and administrative burden (e.g. number of employees, cost of the tools)
13. Notes

Appendix 3: Country responses to survey 1 and 2

Country	Responded to survey 1	Responded to survey 2	Notes
Belgium	Yes	Yes	
Cyprus	Yes	Yes	
Czech Republic	Yes	Yes	
Denmark	See notes	See notes	<p>The official response from the Danish Health and Medicine Authority (DHMA) was that MEAs are currently not implemented. The literature review identified two MEAs. Following clarification with the DHMA we concluded that, examples like the ones identified in the literature review are limited to a few cases and in all of them there was no agreement with the National Health Service (NHS) and the main target were patients.</p>
France	Yes	No	

Finland	NA	NA	MEAs are not implemented
Hungary	No	No	
Italy	Yes	Yes	
Latvia	No	No	
Lithuania	Yes	Yes	
Malta	Yes	Incomplete	
The Netherlands	Yes	Yes	
Norway	NA	NA	At the time of the survey there was no active MEA but Norway has had two MEAs in the past.
Poland	No	No	
Portugal	Yes	Yes	
Slovakia	No	No	
Spain	No	No	
Sweden	Yes	Yes	
United Kingdom	Yes	Yes	
Total respondent	11	9	

Appendix 4: Semi-structured Interview guide for drug reimbursement authorities

1. Does your country have in place any type of MEAs and if so, how are these implemented?
2. Where do MEAs fit into your reimbursement system?
3. Which type of uncertainty are you trying to address by implementing MEAs?
4. Can you provide a few examples of how evidence collected in the frame of a MEA influenced the final reimbursement decision?
5. In general, how does your country deal with:
 - Uncertainty regarding budget impact and cost-effectiveness, and
 - The introduction of high-cost drugs?

Appendix 5: Semi-structured Interview guide for industry representatives

GENERAL INFORMATION

1. Based on your experience of implementing MEAs, what is your opinion of MEAs? (Advantages, disadvantages, challenges, preferences of implementation depending on country and type, etc.)
2. Have MEAs offered predictability in terms of price and (future) financial rewards or have they rather been a disincentive in disease areas with weak evidence base?
3. What has been your members' experience in terms of the operational requirements for implementing these agreements (e.g. admin burden, monitoring performance, collection of additional data, requirement to conduct further studies, etc)?

IMPLEMENTATION

4. Which types of agreements are you currently implementing, for which therapeutic areas, and in which country?
A list of agreements in each country (with conditions attached to the agreement if possible).
5. *For each agreement:* Who proposed to introduce this drug through a MEA and what was the reason for implementing this agreement?
6. *For each agreement:* Do you think this agreement enabled your product to obtain earlier market access than without?

EXPERIENCE/OPINION

7. In general, do you think these agreements reward manufacturers for the perceived level of innovation? Do you think they could act as an incentive for future R&D investments?
8. Have MEAs offered you some predictability in terms of initial price and future financial rewards or have they rather been a disincentive in disease areas with weak evidence base due to uncertainty in terms of expected returns?
9. Could MEA offer competitive advantage to manufacturers implementing them? E.g. If more than one comparable therapy is available for a particular diagnosis, the drug linked to a MEA might become more attractive in comparison to the others?
10. Were the operational requirements for implementing these agreements (e.g. administrative burden, monitoring performance, collection of additional data, requirement to conduct further studies) manageable or too burdensome? How have manufacturers coped with these?
11. Who do you think should be in charge of additional data collection and who should pay for it? What (regulatory) framework would you like to see around additional evidence development?

12. What do you think about the statement that “MEAs cause a post-market shift in the product development process of a significant portion of the experimental phase?”
13. Has your company ever performed an evaluation of the MEAs you implemented? If so, what were the findings/lessons learned and would that be possible for you to share any relevant information?

COMMON FINAL QUESTIONS

14. Do you think MEAs can offer mutual benefits to all three parties involved, i.e. manufacturer, payer, patient? If yes, which advantages and which disadvantages do they offer and under which circumstances (e.g. particular therapeutic area, type of uncertainty, operational requirements)?
15. Do you think MEAs represent the way forward for introducing expensive innovative drugs? Why/Why not? If no, how do you think payers/health insurers ought to address uncertainty and the cost implications of introducing highly specialised medicines?

Appendix 6: Semi-structured Interview guide for patient representatives

BACKGROUND INFORMATION

As part of the EU process on corporate responsibility in the field of pharmaceuticals, one of the three work areas looks at access to medicines in Europe. Capacity building on managed entry agreements for innovative medicines is one of this platform's five projects.

http://ec.europa.eu/enterprise/sectors/healthcare/competitiveness/process_on_corporate_responsibility/platform_access/index_en.htm

After a new medicine has been approved for safety and efficacy by the European Medicine Agency, individual country's drug reimbursement agencies need to decide whether they are willing to reimburse the drug and which price they are will reimburse. Information available at this stage is often limited and this leads to uncertainty regarding the projected vs. actual use, effectiveness in clinical practice and cost-effectiveness. In turn, uncertainty can lead to delayed access to new medicines for patients. Managed entry agreements (MEAs)¹⁹ for pharmaceuticals have been introduced as an instrument to deal with this type of uncertainty by sharing the risk of introducing a new drug onto the market between payers and manufacturers. Examples include payback if the drug does not achieve the promise effect, price-volume agreements, and discount agreement (cost-effectiveness).

GENERAL INFORMATION

1. Are you familiar with MEAs for pharmaceuticals and do you know if your country is implementing any?
2. What do you think about MEAs, what advantages and/or disadvantages can they bring to patients? (E.g. early access to innovative treatments, danger of not being treated because not eligible and is this better or worse than the threat of the drug not being reimbursed at all)

¹⁹ Several terms have been used to define these agreements including risk-sharing agreements, patient access schemes (UK), coverage with evidence development, performance-based agreements, conditional reimbursement, payment-by-result, etc.

EXPERIENCE/OPINION

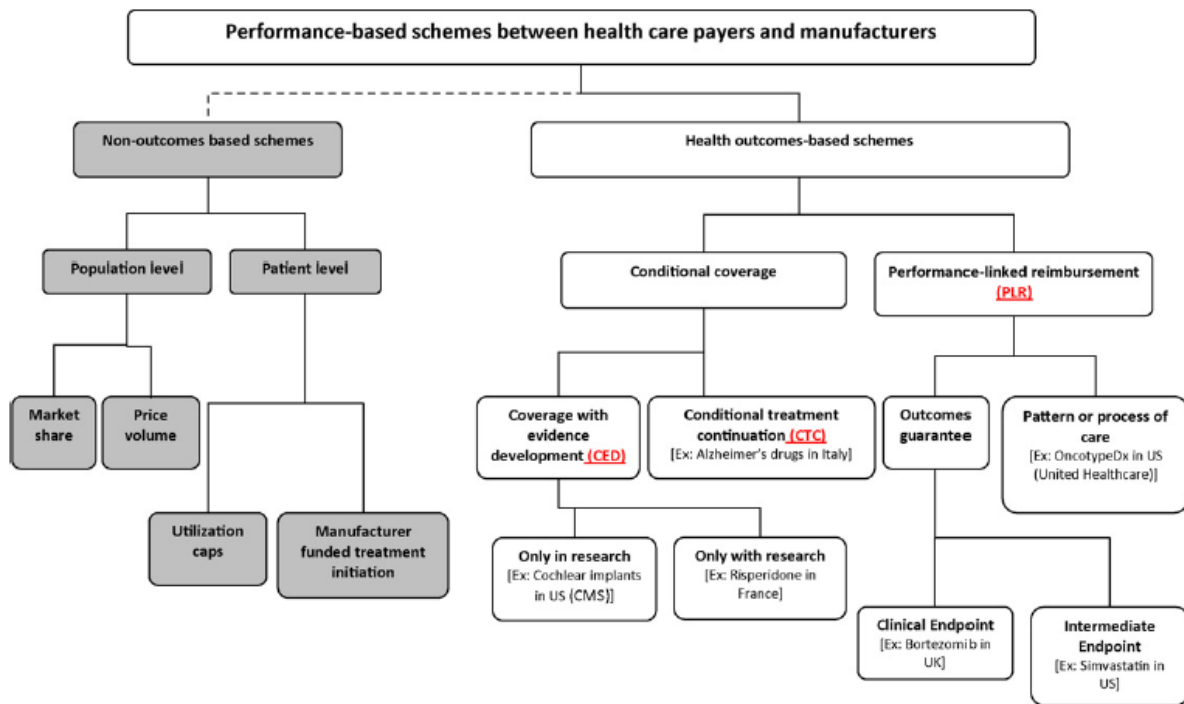
3. What do you think about eligibility criteria (both eligibility to start treatment and to continue with treatment)? Do you perceive eligibility criteria as fair (they aim to avoid treating patient in which the drug does not work) or do you perceive them as rather restrictive because they may exclude patients who could benefit from the drug (e.g. the biomarker or indicators for treatment continuation are not sensitive enough)?
4. What do you think about the requirement of certain agreements of monitoring patients? Do you perceive them rather as a contribution to generate additional evidence which will benefit other patients or would you rather not participate (and if yes why)?
5. Has your patient representative group ever performed an evaluation of the MEAs implemented in your country/disease area? If yes what were the findings and would that be possible for you to share the report?

FINAL QUESTIONS

6. Do you think MEAs can offer mutual benefits to all three parties involved, i.e. manufacturer, payer, patient? If yes, which advantages and which disadvantages do they offer and under which circumstances (e.g. particular therapeutic area, type of uncertainty, operational requirements)?
7. Do you think MEAs represent the way forward for introducing expensive innovative drugs? Why?

Appendix 7: Frameworks for MEAs

Non- outcomes vs. health outcome based taxonomy developed by Carlson *et al.* in 2010



Source: (Carlson et al. 2010)

Characterisation of MEAs according to nature of the risk they are trying to address developed Klemp *et al.* on behalf of the HTAi Policy Forum 2011

- **Managing budget impact:** management of the process of adoption to address concerns about budget impact (e.g., through capping total budget impact, discounting, limiting number of doses, free first cycle, etc.).
- **Managing uncertainty relating to clinical and/or cost-effectiveness:** management of uncertainty relating to the clinical and cost-effectiveness in the long-term, in a real-world clinical setting (e.g., through CED).
- **Managing utilization to optimize performance:** management of delivery systems to plan technology diffusion to targeted patients/ or by means of particular delivery mechanisms (e.g., limitation of technology diffusion to appropriately trained practitioners).

Source: (Klemp, Frønsdal, Facey, and on behalf of the HTAi Policy Forum 2011)

Jaroslowski and Toumi, 2011

MAA Category	Commercial Agreement	Payment for Performance Agreement	Coverage with Evidence Development
Contract type	• Discount-based contract	• Permanent risk-shifting agreement (outcomes guarantee/insurance) applied on a per-patient basis	• Provisional agreement until new, clearly specified evidence develops from a cohort of patients
Collection and analysis of patient health outcomes data by the payer	• None	• Per patient	• Cohort of patients
Timeframe of the MAA	• Permanent/not linked to final decision-making	• Permanent/not linked to final decision-making based on new robust evidence	• Temporary/provisional until new evidence allows making a final decision
Underlying concept (payer perspective)	• Reducing pharmaceutical expenditure	• Avoiding inefficient expenditure on treating patients who do not respond to a drug and who cannot be identified <i>ex ante</i> (by permanently linking the payment to drug's performance in individual patients)	• Reducing uncertainty about drug's real-life effectiveness (by linking a final HTA, reimbursement and/or pricing decision to drug's performance in a cohort of patients, during a defined test period)
Examples	• Flat price per patient (regardless of the number of doses administered) • Cost Sharing • Rebate • Discount	• Payment for performance • Pay-back for non performance	• Temporary coverage on a condition that new evidence reduces uncertainty about a pre-specified health outcome: - Real-life effectiveness - Higher efficacy in a pre-specified subpopulation of patients - Long-term effect - Improved patient's adherence - Reduction of use of health care resources (e.g. hospitalization)

Source: (Jaroslowski and Toumi 2011)

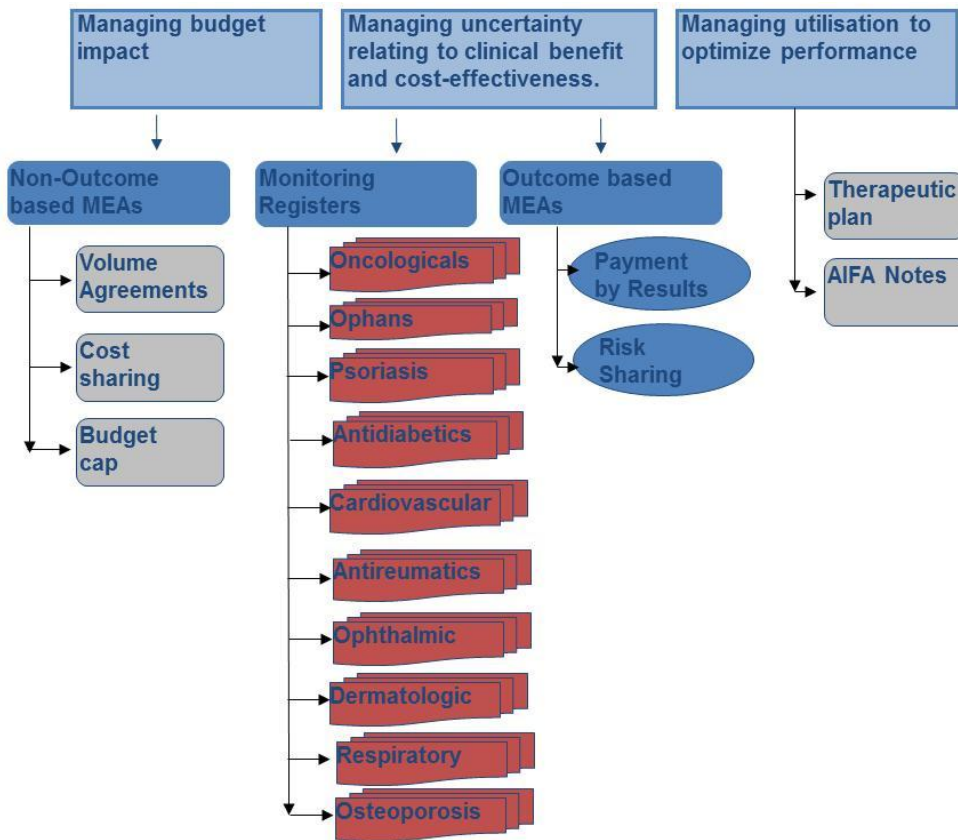
Espin and Rovira 2009 adapted from Casado *et al.* 2009

Outcome measures	Financial Measures	(IT) Erlotinib, Sorafenib, Sunitib			
	Health Outcomes	(UK) Erlotinib	(UK) Beta-interferon	(IT) Bevacizumab (UK) Premetrexed	
	Clinical Measures	(UK) Sunitinib		(UK) Ranibizumab	(IT) Ivabradine, Exenatide, Sitagliptin and Vildagliptin
		In Advance Payment	A Posteriori Payment	Prescription Limit	Conditional Reimbursement
Strategy Request					

Source: Adapted from Casado, A 2009.

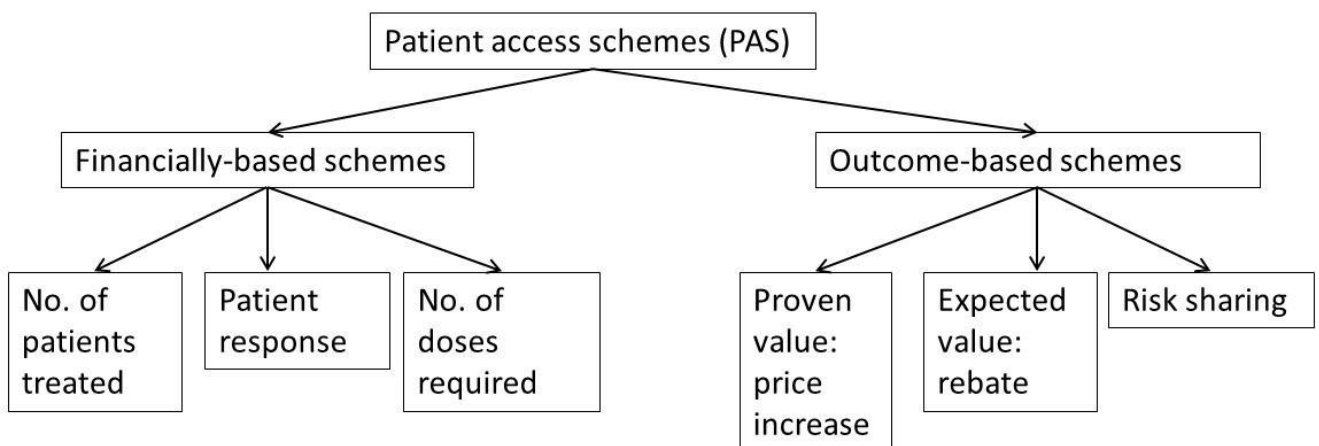
Source: (Espin and Rovira 2009) adapted from (Casado et al. 2009)

MEAs in Italy



Source: (Siviero 2011)

MEAs in the UK



Source: (UK Department of Health and ABPI 2008)

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