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Managed Entry Agreements in the context of Medicines Adaptive Pathways to Patients Final Report

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List of Acronyms

AIFA	Italian Medicines Agency
CMA	Conditional Marketing Authorisation
EMA	European Medicines Agency
HTA	Health Technology Assessment
MAPPS	Medicines Adaptive Pathways to Patients
MEA	Managed Entry Agreement
NICE	National Institute of Health and Clinical Excellence
OMP	Orphan Medicinal Product
RWE	Real World Evidence
TLV	Dental and Pharmaceutical Benefits Agency in Sweden

Executive summary

The European Federation of Pharmaceutical Industries and Associations (EFPIA) asked Charles River Associates (CRA) to undertake an interview programme to understand how managed entry agreements (MEA) have been used for products with conditional Marketing Authorisations or Market Authorisations under exceptional circumstances (which we collectively refer to as CMAs) as a proxy for Medicines Adaptive Pathways to Patients (MAPPs).

Methodology and scope

Drawing from a list of 56 products from 38 manufacturers that have received a conditional marketing authorisation or a marketing authorisation under exceptional circumstances from EMA between 2006 and June 2016, 20 EFPIA member companies were contacted representing 37 products. A parallel process was undertaken by National Institute of Health and Clinical Excellence (NICE) to understand the perspective of health technology assessment (HTA) agencies and payers. A common interview guide was used to ensure consistency between the industry and payer perspectives.

We conducted interviews on a confidential basis with 11 market access experts who have direct experience and knowledge of the products involved from seven companies (two large pharmaceutical companies, three medium size companies, two orphan medicines manufacturers). The companies interviewed were responsible for 17 products with CMA. As illustrated in

Table 1, this included 11 oncology treatments (six of which had an orphan medicinal product (OMP) designation) and six treatments in other therapeutic areas (all of which had an OMP designation).

Table 1: Types of products with conditional MA/MA under exceptional circumstances discussed during the interviews

	Oncology	Other therapeutic areas
OMP status	6 (T-LBL, aRCC, CLL, BCC ¹)	6 (MPS, Laron Syndrome, RA, Amyloidosis, Hyper-lipoproteinemia ²)
Non OMP	5 (NSCLC, mRCC, CML, BCC ³)	
Total	11	6

1 T-cell lymphoblastic lymphoma (T-LBL); Advanced Renal Cell Carcinoma (aRCC); Chronic lymphocytic leukaemia (CLL) basal cell carcinoma (BCC)

2 Mucopolysaccharidosis (MPS), rheumatoid arthritis (RA)

3 Non-small cell lung cancer (NSCLC); Metastatic renal cell carcinoma (mRCC); Chronic myeloid leukaemia (CML); Advanced Basal Cell Carcinoma (aBCC)

It is important to note that for the purpose of this study, conditional marketing authorisations have been used as a proxy for MAPPs; in the future, however, not all CMA products would necessarily qualify for MAPPs.

Key Findings

All of the interviews started with a general discussion on the use of MEAs regardless of the regulatory approval status and subsequently turned to assessing whether there were implications for the use of MEAs when products had a CMA.

General experience with MEAs

All respondents indicated that they had little experience with outcomes-based agreements and that financial agreements were much more common. It was highlighted that, given the payers' concerns revolved largely around cost and budget impact, financial agreements were the most straightforward tool. Furthermore, the administrative workload and resources needed to agree and manage financial agreements (such as simple price-volume (PV) agreements) is much lower than for more complex outcomes-based agreements, which often involve real-time individual patient follow-up and measurement of patient data.

Most respondents indicated that outcomes-based MEAs remain attractive in some circumstances even though they tend to be more complex and can involve substantial administrative burden. It was noted that some MEAs could be too administratively cumbersome for reimbursement agencies and their feasibility depends on the duration of the MEA.

Experience of MEAs with CMA products

Based on our interviews, there are relatively few cases where a product receiving conditional regulatory approval has subsequently used an outcomes-based MEA. Indeed, out of the 17 products with conditional approval or approval under exceptional circumstances which were discussed in our interviews, only nine products were reported to have been subject to some form of MEA. This included:

- Five reported cases of financial agreements (e.g. price volume agreements, utilisation cap, payback agreements)
- Four reported cases of outcomes-based agreements for oncology products (across four different countries)

We did not come across any outcome-based agreements for orphan medicines with CMA as part of our qualitative research. In fact, there was agreement amongst OMP manufacturers interviewed that given the small patient population and the administration cost involved, outcomes-based schemes for orphan drugs were not normally warranted given the cost/complexity involved in following up on individual patients. Given the level of clinical uncertainty and greater patient populations involved, oncology products (without OMP status) with CMA appear to be more likely to be subject to outcomes-based MEA.

This is broadly consistent with the literature. A 2013 comparative study of managed entry agreements applied to OMPs between 2006-2012, across seven European countries conducted in Morel et al, identifies a small number of "performance-based risk-sharing arrangements" (23) applicable to OMPs, all located in the Netherlands, Italy and Sweden. Out of these 23 "performance-based risk-sharing arrangements", seven applied to OMPs

with a CMA.⁴ These often involved conditional reimbursement based on the long term performance of the product, with a re-evaluation of clinical and cost data re-submitted by the manufacturer after a few years. These types of scheme are often less complex than the outcomes-based agreements described above as they do not involve individual real time follow-up of patients – instead companies can submit data collected from phase IV clinical trials, from patient registries (when available) or from electronic medical records.

Regarding the five products that had financial MEAs, there seemed to be little interaction between the financial deal which was negotiated and the conditional nature of the approval. All products had an OMP status, including two oncology products other rare diseases (MPS⁵, Laron Syndrome, hypolipoproteinaemia) and the agreements were primarily based on price volume agreements and overall budget caps. The financial agreements were primarily used to manage budget certainty and did not make reference to the data collected through the CMA. We did not find any evidence that the CMA influenced the nature of the deal. Overall, interview respondents did not see CMA as influencing the use of financial MEAs.

Of the 17 products with conditional approval, only four products (all oncology and non-orphan) were reported to have been subject to some form of outcomes-based agreement, primarily coverage with evidence development. All four of these products had the following characteristics:

1. Potential high patient population leading to potential high budget impact
2. Difficulty in demonstrating cost effectiveness at local level
3. Clinical trials misaligned with real-world patient care

It was noted that this is especially relevant in oncology products for which published evidence from clinical trials may not represent real-world patient care, and a substantial portion of clinical use has not been systematically evaluated. It is this uncertainty that prevents post-regulatory decision makers from making accurate assessments of the value of these treatments.⁶ It was therefore suggested that outcomes-based MEAs remain an attractive mechanism for managing reimbursement for some oncology products although it was recognised there was still limited experience with such schemes.

For the four products reported to have been subject to an outcomes-based agreement, all manufacturers indicated that they were systematically asked by the medicines regulatory agency (i.e. EMA) to collect additional data, as part of the conditions for conditional approval, either through safety studies, the development of a patient registry or retrospective studies. **Error! Reference source not found.** However, it was pointed out that these studies or registries did not necessarily match the additional specific data that national HTA agencies and payers required. As illustrated in Table 2, for three of the four

4 Morel, T., Arickx, F., Befrits, G., Siviero, P., van der Meijden, C., Xoxi, E., & Simoens, S. (2013). Reconciling uncertainty of costs and outcomes with the need for access to orphan medicinal products: a comparative study of managed entry agreements across seven European countries. *Orphanet Journal of Rare Diseases*, 8(1), 1.

5 Mucopolysaccharidoses (MPS)

6 Mullins, C. D., Montgomery, R., & Tunis, S. (2010). Uncertainty in assessing value of oncology treatments. *The Oncologist*, 15 (Supplement 1), 58-64.

products, there were important differences between the data requested by regulators and the evidence requested by payers for products with conditional marketing authorisation subject to outcomes- based MEAs analysed here.

Table 2: Data requested by regulators vs payers for products with conditional MA/MA under exceptional circumstances subject to outcomes-based MEAs

Product	Therapy area	CMA	Data request by EMA	Type of MEA	Payer data requested
Product 1	Oncology mRCC	Conditional Approval	Review of Phase III data	Conditional reimbursement (Czech Republic)	Not specified
Product 2	Oncology NSCLC	Conditional Approval	Information on patient population for proof of epidemiology-eligible patient population. Phase IV trial was conducted.	Conditional reimbursement (Poland)	Local clinical & epidemiological data (to support the reimbursement application- (e.g. drawing data from electronic medical records).
Product 3	Oncology CML	Conditional Approval	A larger study on specific patients sub population previously treated with one or more tyrosine-kinase inhibitors	Conditional reimbursement (Sweden)	TLV asked to obtain a health economic analysis, i.e. estimates of costs and benefits that apply under different assumptions about the duration of treatment. e.g. cost per day. The analysis could take into account data requested by EMA.
Product 4	Oncology BCC	Conditional Approval	Additional safety study in specific patients sub population	Combination of discounts & payment-by-result (Italy)	Concerns on the safety and efficacy were aligned with EMA request – payer requested additional safety data for specific sub populations

Drawing on our interviews, we identified four countries (Sweden, Italy, Poland and the Czech Republic) where outcomes-based MEAs were concluded for products with conditional marketing authorisation. All of these countries require different forms of evidence development. However, the form of the agreement and the use of the additional evidence collection varied from country to country. There were three different forms:

- *Conditional coverage with evidence development* (Sweden) whereby products are granted reimbursement for certain indications or patient subgroups or certain product lines, whilst additional evidence on the drug effectiveness is collected to update the reimbursement decision and expand coverage.

- *Conditional reimbursement in the form of limited time coverage restrictions* (e.g. Poland and the Czech Republic) on the use and access of certain high-cost innovative medicines whereby reimbursement is limited in time (2-3 years) until additional evidence is considered and reimbursement restrictions are lifted.
- A combination of *discounts, payment-by-result and conditional treatment continuation* to improve cost-effectiveness (Italy) whereby additional patient data for some products are used to establish automatic discounts based on the number of patients.

We summarise the experience with outcomes-based agreements in Table 3 below.

Table 3: Experience with outcomes-based agreements for products with conditional MA/MA under exceptional circumstances

	Conditional coverage with evidence development (Sweden)	Limited time coverage restrictions (Poland and Czech Republic)	Combination of discounts & payment-by-result (Italy)
What worked well?	<ul style="list-style-type: none"> • CED allowed earlier reimbursement for selected types of patients - CED was facilitated by the presence of CMA. • Real World Evidence (RWE) data collected and submitted to EMA as part of post-approval commitment helped address payers' data requests. 	<ul style="list-style-type: none"> • Payers are keen to understand the clinical data and cost effectiveness and to consider how product is used in real life and some of this information is collected in the context of the CMA process. • Earlier patient access to the new compound while additional RWE data are collected 	<ul style="list-style-type: none"> • Italy has a wide range of well-established registries and the AIFA has also developed its own IT infrastructure linked to clinical treatment centres to collect its own data. • RWE collected via the registries is useful in case of re-evaluations. It may also help with product differentiation versus upcoming competitors, especially for products subject to CMA.
Challenges	<ul style="list-style-type: none"> • New process requiring more data at an earlier stage makes it difficult for the manufacturer to meet the request, while EMA submission is still on going. • There is no possibility for the price to be re-discussed following positive results. 	<ul style="list-style-type: none"> • Collecting additional data for payer purposes (as part of MEA) remain a challenge where infrastructure is currently underdeveloped. • Currently, some payers do not have the necessary expertise to analyse these complex RWE data. 	<ul style="list-style-type: none"> • RWE data collection remains a challenge and does not systematically correspond to the data expected by AIFA. • Need robust data collection mechanisms – deals remain vulnerable to problems in IT systems
Key success factors/ recommendations	<ul style="list-style-type: none"> • Flexibility from the payer side regarding the sources and types of data/information that companies can provide to demonstrate cost effectiveness (e.g. survival needs, longer term analysis, etc.) 	<ul style="list-style-type: none"> • Greater alignment between the EMA's and Payer's data requirements regarding eligible patient sub populations • Agreement on clinical endpoints need to be discussed with regulatory through early dialogue 	<ul style="list-style-type: none"> • EMA could decide additional real world data requirements (e.g. efficacy data) and then coordinate with local / regional registries and regional coordinators to collect the required data with the simplest method possible.
Lessons learned	<ul style="list-style-type: none"> • Conditional approval can facilitate use of some forms of MEA (improving access) but requires some flexibility by the payer around the use and availability of data to work effectively today. 	<ul style="list-style-type: none"> • In some cases, price more than data seems to be the true underlying issue. 	<ul style="list-style-type: none"> • Despite well-established registries, the implementation of MEAs remains challenging but the data are proving useful in understanding real life experience.

Conclusion

Adaptive Pathways is about managing uncertainty over time. It is based on the understanding of additional data collection post launch. We have tried to understand the implication of MAPPs for MEAs by using products with conditional approvals as a proxy. Our research finds that there are only a few cases where a product receiving conditional regulatory approval has subsequently gone through an outcomes-based MEA. Therefore, we therefore need to be cautious about drawing strong conclusions from a small subset of the products. However, there are some lessons we can draw from the product where coverage with evidence development has been used.

What is needed to ensure MEAs can support adaptive pathways?

Payers/HTA agencies request local data and more detailed product specific information especially around the relative clinical efficacy of the product, which sometimes differ from data collected for regulatory purposes. However, there are also cases where the HTA system has been able to use the information collected through the CMA (notably oncology products). It is also clear that not all products with a CMA subsequently need an outcomes-based agreement (particularly OMP based on the results of our interview programme).

Better alignment of data requirements between HTA bodies and regulators could improve the collection of more appropriate data and the compilation of evidence in the context of the MAPPs process and the subsequent use in outcomes-based MEAs. If there was the possibility to do so, many companies indicated they would be keen to explore such opportunities. It is acknowledged that some initiatives to set up a sustainable process for joint scientific advice involving regulators and HTA bodies, already address this point.

In this case, there would be value in EMA and HTA bodies also co-ordinating their additional clinical evidence requirements. This would then provide a signal for local /regional registries and regional coordinators about the types of information already being collected and encourage agreements that efficiently use this information in the simplest way possible.

1. Introduction

EFPIA has asked Charles River Associates (CRA) to undertake an interview programme to understand how managed entry agreements (MEA) have been used for products with conditional Marketing Authorisations or Market Authorisations under exceptional circumstances (which we collectively refer to as CMAs) as a proxy for Medicines Adaptive Pathways to Patients (MAPPs).

A parallel process was undertaken by National Institute of Health and Clinical Excellence (NICE) to understand the perspective of health technology assessment (HTA) agencies and payers.

1.1. Background to this report

The growing patient demand for timely access to promising therapies in areas of high medical need has led to a debate regarding the need to develop a new product approval paradigm that balances the requirements for evidence regarding value of new medicines and the need to ensure patients have rapid access to innovative medicines (the 'access versus evidence conundrum').⁷ In this context, the European Medicines Agency (EMA) introduced in 2014 the pilot project 'Medicines Adaptive Pathways to Patients' (MAPPs).⁸

ADAPT-SMART is a Coordination and Support Action (CSA) under the Innovative Medicine Initiative (IMI) intended to deliver a series of options/recommendations to ensure that Medicines Adaptive Pathways to Patients (MAPPs) becomes actionable. This report and interview programme is one of the deliverables of the ADAPT-SMART work package three (decision-making, sustainability and their implications) on the availability and applicability of suitable managed entry agreements in the context of MAPPs.

1.1.1. MAPPs definition

The EMA describes MAPPs as a scientific concept for medicine development and data generation which allows for early and progressive patient access to a medicine.⁹

The approach makes use of the existing European Union (EU) regulatory framework for medicines and is designed to speed up the approval process to improve timely access for patients to new medicines.¹⁰ This is seen as particularly applicable in areas of high medical need where it is difficult to collect data via traditional routes and where large clinical trials would unnecessarily delay access to patients who are unlikely to benefit from the medicine.

7 Eichler, H. et al (2012). Adaptive licensing: taking the next step in the evolution of medicine approval. *Clinical Pharmacology & Therapeutics*, 91(3), 426; Eichler, et al. (2015). From adaptive licensing to adaptive pathways: Delivering a flexible life-span approach to bring new medicines to patients. *Clinical Pharmacology & Therapeutics*, 97(3), 234-246.

8 European Medicines Agency website - Human regulatory: Adaptive pathways; accessible at http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp

9 Ibid.

10 Ibid.

Adaptive pathways is based on three principles¹¹:

1. Iterative development, which either means:
 - a. approval in stages, beginning with a restricted patient population then expanding to wider patient populations; or
 - b. confirming the benefit-risk balance of a product, following a conditional approval based on early data (using surrogate endpoints) considered predictive of important clinical outcomes;
2. Gathering evidence through real-life use to supplement clinical trial data;
3. Early involvement of patients and health technology assessment bodies in discussions on a medicine's development.

MAPPs refers to flexible development and access pathways within the current regulatory framework that balances early patient access, public health and societal benefits.¹² This process starts with the regulatory body providing an early authorisation of a product with a clear safety and efficacy profile focused on a well-defined and targeted population. This target population is then adjusted as new evidence is collected and greater understanding of the product profile develops.

The process of MAPPs integrates existing tools that have already been introduced but never joined up such as adaptive clinical trial design, patient centric benefit/risk assessments and continuous re-evaluation as new evidence becomes available. MAPPs therefore should ensure a smoother and more coordinated process to speed up access throughout the entire life cycle of a medicine from development, through marketing authorisation to patient access (reimbursement and healthcare delivery).

Although already discussed in many public fora and supported by patients, industry, regulators and the academic community, MAPPs is not yet clearly defined and a number of challenges still need to be addressed. One of these will be the need to define and agree on the nature of the evidence package required for early regulatory approval but also on the implications of MAPPs on HTA, pricing and reimbursement and market access (including the impact on managed entry agreements at the national or regional levels).

The aim of this work is to explore the experiences of industry with managed entry agreement for products that have been approved in recent years under exceptional circumstances or that have received a conditional marketing authorisation (defined below). As no product has been approved under a MAPPs approach, these types of products might resemble a MAPPs scenario and provide insight on managed entry agreements in the context of MAPPs.

11 Ibid.

12 EFPIA Medicines Adaptive Pathways to Patients; What are Medicines Adaptive Pathways to Patients (MAPPs)? accessible at: <http://efpiamapps.eu/>

Current regulatory procedures on the basis of preliminary data

EMA uses two different procedures to grant marketing authorisations on the basis of preliminary data, with a view to meeting “unmet medical needs of patients and in the interests of public health”.

1. Authorisation under exceptional circumstances is generally granted when the MA holder is unable to provide comprehensive data on the efficacy and safety under normal conditions.¹³ Approval may be granted subject to a requirement for the applicant to introduce specific procedures, in particular concerning the safety of the medicinal product, notification to the competent authorities of any incident relating to its use, and action to be taken;
2. Conditional marketing authorisations are granted when the risk-benefit balance is based on preliminary, not yet full, evidence. This was developed for granting European marketing authorisations to medicinal products on the basis of incomplete data with a view to allowing early access to new treatments. Conditional approval is usually granted to medicines intended to address unmet medical needs, i.e. “any seriously debilitating or life-threatening condition for which there exists no satisfactory [...] treatment authorised”.¹⁴

1.1.2. Evolution in the use of Managed Entry Agreements

There is increasing pressure on medicines to demonstrate value for money, with the result that there is more pressure on addressing the issue of clinical uncertainty, managing affordability and justifying the prices of new medicines.¹⁵

These challenges have prompted healthcare technology suppliers and payers alike to find ways to manage the introduction of new medicines and mitigate concerns about prices, affordability and uncertainty regarding value. One way to address this has been through the introduction of contractual arrangements between manufacturers and payers referred to as Managed Entry Agreements.¹⁶

13 Conditions include: 1. When the indications, for which the product in question is intended, are encountered so rarely that the Applicant cannot reasonably be expected to provide comprehensive evidence. 2. In the present state of scientific knowledge, comprehensive information cannot be provided. 3. It would be contrary to generally accepted principles of medical ethics to collect such information.

14 Banzi, R., Gerardi, C., & Garattini, S. (2015). Approvals of medicines with uncertain benefit–risk profiles in Europe. *European Journal of Internal Medicine*, 26(8), 572-584.

15 Wilsdon T., Mitchell-Heggs A. (2016) A template for using Managed Entry Agreements – Charles River Associates, a report for EFPIA.

16 A Managed Entry Agreement is an arrangement between a manufacturer and payer/provider that enables access to (coverage/reimbursement of) a health technology subject to specified conditions. These arrangements can use a variety of mechanisms to address uncertainty about the performance of technologies or to manage the adoption of technologies in order to maximize effective their use, or limit their budget impact. Carlson JJ et al. (2010) Linking payment to health outcomes: a taxonomy and examination of performance-based reimbursement schemes between healthcare payers and manufacturers. *Health Policy*, 96 :179-190.

Based on the literature, MEAs are normally segmented into two key categories: financial and outcomes-based agreements.^{17,18}

- **Financial Based Agreements:** Agreements between manufacturer and payers based on observable financial performance (which could include the number of patients, prices, overall spending or spending per patient). These include:
 - Price agreement based on manufacturer's market share
 - Price-Volume Agreements
 - Pricing by Channel (discount on certain products/channels)
 - Capitation (discounts for specific patients)
 - Free initiation, (patient/dose dependent discount)
 - Portfolio Agreement (discounts based on manufacturer's portfolio)
- **Outcomes-Based Agreements:** Agreements based on defined outcomes (generally clinical) or agreements based on the development of new evidence. These types of models often, although not always, require the use of data developed whilst using medicines in the market. These agreements can take a variety of forms including:
 - Patient Risk Sharing Agreement (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, there is a price decrease and the company pays back the difference).
 - Performance-linked reimbursement (e.g. where companies provide a refund or provide free goods if the desired clinical outcomes are not reached), this often involved individual real time patient follow-up.
 - Coverage with evidence development or conditional reimbursement (reimbursement linked to the development of additional evidence. Additional evidence on the clinical value and cost-effectiveness can be re-submitted by the manufacturer after a few years for re-evaluation. These types of scheme are often less complex as they do not involve individual real time follow up of patients. – instead companies can submit data collected from phase IV clinical trials, from patient registries (when available) or from electronic medical records.

Of particular relevance for this project is where reimbursement is linked to the development of additional evidence. The aim is to accelerate access to safe and effective therapies while additional evidence is collected (this is sometimes referred to as using real world evidence (RWE)).

The rationale for introducing MEAs vary depending on the country and the product but include improving access, addressing uncertainty related to the therapeutic value or

17 Ibid.

18 Value Based Agreements are growing in importance mainly due to the increasing competition between similar expensive products within certain therapy areas (e.g. Multiple Sclerosis, Rheumatoid Arthritis), and also give established biopharmaceutical companies a differentiating factor over biosimilar entrants.

financial impact and allowing confidential discounts that improve the cost-effectiveness without negative repercussions that would otherwise arise due to international price referencing.¹⁹

1.2. Methodology

The aim of this research was to gather the perspective of manufacturers on the use of MEAs in the context of MAPPs (as a proxy by CMA). A parallel process was used to gather the input of HTA and payers. To ensure consistency with the parallel projects, a steering group was set up with both EFPIA and NICE.

The project involved the following steps:

1. Interview guides were developed for companies and payers based on a similar set of topics. The structure of the industry questionnaire remained the same but questions were adapted to reflect the specificities of the manufacturer
2. Drawing from a list of 56 products from 38 manufacturers that have received a conditional marketing authorisation or a marketing authorisation under exceptional circumstances from EMA between 2006 and June 2016, 20 EFPIA member companies were contacted representing 37 products. In particular, we selected manufacturers that were most likely to have negotiated MEA.²⁰ We conducted interviews on a confidential basis²¹ with 11 market access experts who have direct experience and knowledge of the products involved from seven companies. The companies interviewed were responsible for 17 products with CMA. As illustrated in Table 4, this included 11 oncology treatments (six of which were orphan medicinal products (OMP)) and six treatments in other therapeutic areas (all of which were OMPs).²²
3. The interview focused on capturing each company's experience with the following topics (see I Questions for Industry in Appendix A):
 - a. The types of MEAs that were typically used by their companies.
 - b. The conditions under which MEAs are introduced and agreed between industry and payers.
 - c. The interaction between MEAs and conditional MA/MA under exceptional circumstances and the criteria for success.

19 Ferrario, A., & Kanavos, P. (2013). Managed entry agreements for pharmaceuticals: the European experience. London School of Economics and Political Science, 154.

20 This excluded vaccines and HIV product manufacturers for which MEA are not commonly used as a P&R mechanism.

21 It was agreed that we would not name individual medicines or directly attribute comments to individual companies or individuals.

22 Even though the interviews were undertaken on a confidential basis, MEAs are confidential agreements and not all terms of the agreement could be discussed or reported.

In order to understand the different pricing and reimbursement systems across Europe, interviews were conducted with respondents from various European countries.²³

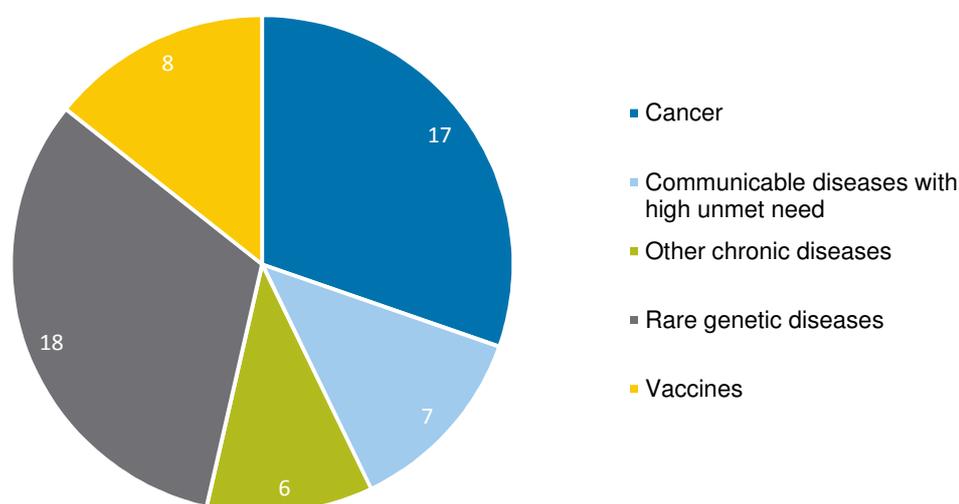
4. The results have been summarised to ensure anonymity. Both Charles River Associates and NICE collated results on an anonymous basis in terms of their experience and how this depends on the type of product (and the challenge it faced), the type of conditional approval, and whether the conditional approval affected the use, role and benefits from using MEAs.

1.2.1. Types of products with conditional marketing authorisations

As illustrated in Figure 1, out of 56 medicinal products which received conditional MA/MA under exceptional circumstances by the EMA between 2006 and June 2016 (excluding generics and biosimilars), there are:

- 18 are for rare genetic conditions
- 17 are oncology medicines
- 7 are for communicable diseases with high unmet need such HIV
- 8 are vaccines
- 6 are for other chronic conditions (e.g. Multiple Sclerosis)

Figure 1: Distribution of products that have a conditional MA/MA under exceptional circumstances by EMA between 2006 and June 2016



Source: CRA analysis using list of conditional MA/MA under exceptional circumstances from the European Medicines Agency

²³

Where possible the interviews involved experts from multiple countries but, given the size of the interview programme it was not possible to cover the experience in all the countries where MEAs were agreed.

Unsurprisingly, the sample is focused primarily on oncology products and products for rare genetic diseases (some of which have obtained an OMP status). In addition, conditional marketing authorisation is reported as more common for products which have an OMP status as many of these have no proven alternative treatment and for which there are evidential clinical uncertainty because of small patient numbers.²⁴

Amongst the seven companies who took part in the 11 interviews we conducted, two are large pharma companies, three are medium size companies and two are companies focusing on rare diseases. Looking more closely at the 17 products with conditional approval/exceptional circumstances which were discussed, our research includes 11 oncology products (six of which are OMP and five which are not) and the remaining six treatments were non-oncology OMP in other therapeutic areas. This is illustrated in Table 4.

Table 4: Types of products with conditional MA/MA under exceptional circumstances discussed during the interviews

	Oncology	Other therapeutic areas
OMP	6 (T-LBL, aRCC, CLL, BCC ²⁵)	6 (MPS, Laron Syndrome, RA, Amyloidosis, Hyper-lipoproteinemia ²⁶)
Non OMP	5 (NSCLC, mRCC, CML, aBCC ²⁷)	
Total	11	6

1.3. Structure of the report

The rest of the report is structured as follows:

- Section 2 considers the manufacturer experience with MEAs in general, before turning to the experience with products with CMAs.
- Section 3 discusses the future prospect of MEAs in the context of MAPPs and what is needed to ensure MEAs can support adaptive pathways.

²⁴ Gutierrez, L., Patris, J., Hutchings, A., & Cowell, W. (2015). Principles for consistent value assessment and sustainable funding of orphan medicines in Europe. *Orphanet Journal of Rare Diseases*, 10(1), 1.

²⁵ T-cell lymphoblastic lymphoma (T-LBL); Advanced Renal Cell Carcinoma (aRCC); Chronic lymphocytic leukaemia (CLL); basal cell carcinoma (BCC)

²⁶ Mucopolusaccharidosis (MPS), rheumatoid arthritis (RA)

²⁷ Non-small cell lung cancer (NSCLC); Metastatic renal cell carcinoma (mRCC); Chronic myeloid leukaemia (CML); Advanced Basal Cell Carcinoma (aBCC)

2. The use of MEAs in conditionally approved products

All of the interviews started with a general discussion on the use of MEAs in general regardless of the regulatory approval status but then focused on whether conditional regulatory approval (proxied by conditional MA or MA under exceptional circumstances) has an impact on the use of MEAs. We distinguished between the use of financial based agreements and outcomes-based agreements.

2.1. General experience with financial based agreements

All respondents indicated that they had little experience with outcomes-based agreements but that financial agreements were much more common, especially volume based agreements and discount schemes.

For most products, the agreements between manufacturer and payers were based on observable financial performance (which could include the number of patients, prices, overall spending or spending per patient). It was suggested that most payers favour simple MEAs (such as discounts and payback agreements) over more complicated arrangements. This is consistent with existing studies on MEA such as Ferrario & Kanavos (2013) which points out that “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%)”.²⁸

From the manufacturers perspective this suggests an unwillingness of payers to agree to more complex agreements. They reported that:

- “As of today, in many countries, payers are more interested in striking a financial based deal”.²⁹ This most frequently involves price-volume agreements or budget impact/payback agreements. Payers are trying to negotiate price levels that they can afford and also seek to deliver short term savings and financial MEAs make budget planning much simpler.³⁰
- The most important consideration for payers is to understand the potential budget impact of the medicines.³¹ One orphan medicinal product (OMP) manufacturer indicated that “while the price of some OMPs was not very high and the patient population was small, the payers’ main concern was focused on ensuring budget impact and as such, all the agreements options were largely financial”.³²
- This also applied to oncology products where manufacturers suggested that financial deals remain the dominant form of agreements even if some more sophisticated forms of MEA are starting to be considered.

28 See supra note 19

29 Interview with pharmaceutical company

30 Interview with pharmaceutical company

31 Interview with pharmaceutical company

32 Interview with OMP manufacturer

Many respondents highlighted that given the payer's concerns revolved largely around cost and budget impact, financial agreements were the most straightforward tool to address this, and the level of costs incurred in conducting financial agreements, such as simple price-volume agreements, is much lower than for more complex outcomes-based agreements. However, it was also suggested that this is highly dependent on how these agreements are integrated into the HTA, pricing and reimbursement system.

2.2. General experience with outcomes-based agreements

Most respondents indicated that outcomes-based MEAs remain attractive although they are more complex and can involve substantial administrative burden. It was noted that some MEAs could be too administratively cumbersome for reimbursement agencies and often more complex in practice than anticipated (for example, there was an MEA for a product for Multiple Sclerosis but this was stopped because of the associated administrative burden). The feasibility of an MEA depends on the duration of the MEA (e.g. if it will last for the lifetime of the product).

This is also in line with conclusions of existing studies such as Ferrario & Kanavos (2013) which indicates that outcomes-based agreements are relatively novel and less common although some countries such as the Netherlands, Sweden and Italy have started to make greater use of these options.³³

Industry pointed out three main challenges around the use of outcomes-based MEAs:

- 1) The lack of experience and timelines: outcomes-based MEAs (with individual real-time patient follow-up) are much more complex and, as many countries do not have any experience with outcomes-based MEAs, the process of negotiation can be challenging.
- 2) Complexity in collecting the data: it remains difficult to convince clinicians and hospital pharmacists to conduct additional administrative tasks to collect data as they see this as an additional burden.
- 3) The willingness of the payer: there needs to be more interest in MEAs from payers and cooperation to ensure data collection. One company indicated that "in general, it is difficult to discuss MEAs with national payers and there are still issues around obtaining alignment in expectations and data coverage between regulators and payers".³⁴

2.3. Experience of MEAs in the context of conditional MA and MA under exceptional circumstances

Turning to the products with conditional marketing authorisations. All manufacturers indicated that they were systematically asked by the medicines regulatory agency (i.e. EMA) to collect additional data as part of conditions for conditional approval through either safety studies, patient registries or retrospective studies. In Table 5 we list some of the data

33 See supra note 19

34 Interview with oncology medicine manufacturer

that was requested by the EMA as part of the conditional marketing authorisation approval for products considered in the interviews.

Table 5: Additional data requested by the European Medicines Agency on selected products with conditional MA/MA under exceptional circumstances

Name	Category	Approval status	CMA additional data requirement
Increlex (mecasermin)	Orphan	Exceptional Circumstances	A long-term study looking at the safety of the medicine, when treatment is started in young children and continued into adulthood.
Tyverb (lapatinib)	Oncology Product	Conditional Approval	A study comparing the effects of treatment containing Tyverb and treatment containing trastuzumab on the spread of cancer to the brain.
Votrient (pazopanib)	Oncology Product	Conditional Approval	Votrient was originally given 'conditional approval' because there was more evidence to come about the medicine, in particular in the treatment of renal cell carcinoma.
Atriance (nelarabine)	Oncology Product	Exceptional Circumstances	Supply of information from safety studies in children and young adults, including one study of Atriance taken in combination with other anticancer medicines.
Zykadia (ceritinib)	Oncology Product	Conditional Approval	Provision of final results from the ongoing second study used to approve licensing, as well as the results of a further study comparing Zykadia with other cancer medicines (chemotherapy) in patients with ALK-positive NSCLC previously treated with crizotinib.
Arzerra (ofatumumab)	Oncology Product	Conditional Approval	A study comparing treatment with Arzerra to treatment with other cancer medicines chosen by the doctor, in patients with CLL whose previous treatment with fludarabine has failed.
Ilaris (canakinumab)	Orphan	Exceptional Circumstances	Provision of regular long-term safety and effectiveness information of Ilaris in adults and children suffering from CAPS. This information comes from a registry.
Bosulif (bosutinib)	Oncology Product	Conditional Approval	A larger study with Bosulif in patients with Ph+ CML previously treated with one or more tyrosine-kinase inhibitors and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options with submission of results to CHMP for evaluation.

Xalkori (crizotinib)	Oncology Product	Conditional Approval	Provision of final results of a study in patients with ALK-positive NSCLC comparing the safety and effectiveness of Xalkori and chemotherapy treatments, to confirm how long patients lived overall. Additional safety data from this study will also be provided.
Vyndaqel (tafamidis)	Orphan	Exceptional Circumstances	An additional study on the effects of the medicine in a subgroup of patients with certain genetic mutations. Provision of long-term post-marketing safety data.
Erivedge (vismodegib)	Oncology Products	Conditional Approval	Provision of results from a large safety study in patients with metastatic disease.
Adcetris (brentuximab vedotin)	Oncology Products	Conditional Approval	Provision of follow-up data on patients' survival from the main studies submitted in HL and sALCL. Two further studies on the benefits of the medicine and a safety study in a larger population of HL and sALCL patients.
Glybera (alipogene tiparvovec)	Orphan	Exceptional Circumstances	Provision of further data on fat levels in the blood after meals and on the immune response to Glybera in new patients. Additional data from a registry to monitor the outcome of patients treated with Glybera, and will add a step to the manufacturing of the product to improve the safety profile.

Source: European Medicines Agency

Out of the 17 products with a CMA which were discussed in our interviews, only nine were reported to have been subject to some form of managed entry agreement.

The most common cases were:

- Five financial agreements (price volume agreements, utilisation cap, payback agreement)
- Four outcomes-based agreements. These were all for oncology products and concentrated in three different countries.

We did not come across any outcome agreements for orphan medicines with CMA as part of our research. It was reported by the OMP manufacturers that given the smaller patient population and the administration cost involved, outcomes-based schemes for OMP were not normally warranted given the cost/complexity involved in following up on individual patients.³⁵ However, we note that there are some CMA products that do have outcomes-based agreements. In a 2013 comparative study of managed entry agreements applied to OMPs between 2006-2012 across seven European countries conducted in, Morel et al

(2013) identify a small number of “performance-based risk-sharing arrangements” (23) applicable to OMPs, all located in the Netherlands, Italy and Sweden. Out of these 23 “performance-based risk-sharing arrangements”, seven applied to OMPs with a CMA.³⁶ These often involved a conditional reimbursement based on the long term performance of the product, often involving a re-evaluation of clinical and cost data re-submitted by the manufacturer after a few years. These types of scheme are often less complex as they do not involve individual real time follow-up of patients – instead companies can submit data collected from phase IV clinical trials, from patient registries (when available) or from electronic medical records.

Whilst OMP manufacturers are often required to setup a patient registry along with additional data requirements to collect post-launch regulatory data as part of conditional approval, according to our interviews, this is rarely used/leveraged by payers.³⁷ It was also suggested that “once the financial deal is done and a price has been agreed, there is little interest for payers to engage in additional data analysis to review the price”.³⁸

2.3.1. Experience with financial agreements

Although five of the products with CMA had financial MEAs, there seemed to be little interaction between the financial deal which was negotiated and the conditional nature of the approval. All five products had an OMP status (including two in oncology, as well as in other rare diseases (MPS, Laron Syndrome, and Hypolipoproteinaemia) and the agreements were primarily based on price volume agreements and overall budget caps.

The financial agreements were primarily to manage budget certainty and did not make reference to the data collected through the CMA. Indeed, there is no evidence that the CMA influenced the nature of the deal.

2.3.2. Experience with outcomes-based agreements

Out of the 17 products with conditional approval, only four products (all oncology and non-orphan) were reported to have been subject to some form of outcomes-based agreement particularly in instances of coverage with evidence development. This includes different forms of deals including:

- *Conditional coverage with evidence development* (Sweden) whereby products will be granted reimbursement for certain indications or patient subgroups or certain product lines, whilst additional evidence on the medicine’s effectiveness is collected to update the reimbursement decision and expand coverage.
- *Conditional reimbursement in the form of limited time coverage restrictions* (e.g. Poland and the Czech Republic) on the use and access of certain high-cost innovative medicines whereby reimbursement is limited in time (2-3 years) until additional evidence is considered and reimbursement restrictions are lifted.

36 Morel, T., Arickx, F., Befrits, G., Siviero, P., van der Meijden, C., Xoxi, E., & Simoens, S. (2013). Reconciling uncertainty of costs and outcomes with the need for access to orphan medicinal products: a comparative study of managed entry agreements across seven European countries. *Orphanet Journal of Rare Diseases*, 8(1), 1.

37 Interviews with OMP manufacturers

38 Interview with a pharmaceutical company

- A combination of *discounts, payment-by-result and conditional treatment continuation* to improve cost-effectiveness (Italy) whereby additional patient data for some products is used to establish automatic discounts based on the number of patients.

We note that in this sample of products, all of the CMA products with an outcomes-based MEA are oncology, but given the small sample size considered, we clearly cannot make a broad conclusion on oncology, and it is certainly not the case that all oncology products with a CMA resulted in an outcomes-based agreement. One company indicated that it obtained conditional approval for one of its advanced lung cancer therapy medicines using Phase II data. Given the lack of clinical data, it experienced some challenges in some countries such as Germany and France who had specific data requirements for payer purposes. However, despite the level of clinical uncertainty and the presence of a CMA, the use of an outcomes-based agreement was not discussed and a financial agreement was negotiated in most countries.³⁹

We note that all four of these products had the following characteristics:

- Potential high patient population leading to potential high budget impact
- Difficulty in demonstrating cost effectiveness at local level
- Manufacturers were already asked to collect additional RWE data by regulators

Looking at the types of data requested by the European Medicines Agency (EMA) it was pointed out that these studies or registries did not necessarily provide the specific data that national HTA agencies and payers required. As illustrated in

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Interview with oncology medicine manufacturer

Table 6, respondent reported important differences between the data requested by regulators and the data requested by payers for products with CMA subject to outcomes-based MEAs. One respondent indicated that “a registry was developed by physicians in the clinical setting to collect data on clinical efficacy whilst payers wanted to know about cost estimates and budget impact - therefore, although the data collected was useful, it was not useful for all steps to market access.”⁴⁰

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Interview with orphan medicines manufacturer

Table 6: Data requested by regulators vs payers for products with conditional MA/MA under exceptional circumstances subject to outcomes-based MEAs

Product	Therapy area	CMA	Data request by EMA	Type of MEA	Payer data requested
Product 1	Oncology mRCC	Conditional Approval	Review of Phase III data	Conditional reimbursement (Czech Republic)	Not specified
Product 2	Oncology NSCLC	Conditional Approval	Information on patient population for proof of epidemiology-eligible patient population. Phase IV trial was conducted.	Conditional reimbursement (Poland)	Local clinical & epidemiological data (to support the reimbursement application (e.g. drawing data from electronic medical records)).
Product 3	Oncology CML	Conditional Approval	A larger study on specific patients sub population previously treated with one or more tyrosine-kinase inhibitors.	Conditional reimbursement (Sweden)	Uncertainty in the clinical efficacy for the indicated patient population due to lack of clinical trial information
Product 4	Oncology BCC	Conditional Approval	Additional safety study in specific patients sub population	Combination of discounts & payment-by-result (Italy)	Concerns on the safety and efficacy - requested additional safety data for specific sub populations

Source: CRA analysis

Focusing on the four CMA oncology products with outcomes-based MEAs, it is possible that the data requirements on the development of the products such as developing retrospective studies or setting patient registries could have formed the basis for outcomes-based MEAs.

However, drawing on our interviews, this was not universally the case and depended on the type of MEA. It is useful to look at these cases in more detail. We found four countries where outcomes-based MEAs were concluded for products with conditional marketing authorisation. All these countries (Sweden, Italy, Poland and the Czech Republic) applied different forms of schemes requesting different types of evidence. However, the type of reimbursement setting means this type of scheme can take many different forms and make use of additional evidence in different ways.

Conditional coverage with evidence development

As pointed out by Ferrario & Kanavos (2013), 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 medicine effectiveness will

be collected and to update the reimbursement decision afterwards based on the new cost-effectiveness results.⁴¹

In Sweden, payers (county councils) have developed conditional reimbursement schemes whereby products will be granted reimbursement for certain indications or patient subgroups or certain product lines. According to our interviews, the HTA agency (TLV) makes use of additional cost-effectiveness evidence including additional data collected under conditional approval or exceptional circumstances, to further expand coverage post-launch.

The TLV has a mandate whereby in the case of uncertainty, manufacturers must submit additional information that demonstrates cost effectiveness in order to maintain the medicine's reimbursement status or receive further coverage. Whilst TLV is the initiator of the request for additional information, it is the company's responsibility to demonstrate cost-effectiveness using all information available to the company including the possibility to draw on data collected as part of the submission to the European Medicines Agency. This provides the opportunity to leverage efficacy data in the case of conditionally approved products. It was pointed out that "TLV are very flexible and have not defined the types of information required so the manufacturer is able to provide any type of reliable data to support the cost-effectiveness analysis. It is therefore the company's choice to leverage the type of additional data that it wishes to submit."⁴² This appears to be working well although one respondent indicated that "more alignment around clinical endpoints could be beneficial to enhance this process through early dialogue with payers".⁴³

It was noted that even though the scheme is flexible regarding the type of data, it is still not possible to increase the price as a result of the additional evidence showing the product performs better than expected. In order to revise the price, it would be necessary to take the product off the reimbursement list and then re-submit a new reimbursement dossier with a higher price and additional cost-effectiveness data to support this price rise. It was indicated that the TLV have engaged in discussion on "dynamic pricing" so that in the future, additional evidence collected post-launch could be considered to increase or decrease prices as new information comes in.

Conditional reimbursement with limited time coverage restrictions

A second way that payers address uncertainty is to decrease the price or to limit utilisation so that the cost-effective ratio is improved because of lower costs.⁴⁴ This is the case in countries such as Poland or the Czech Republic where payers have introduced conditional reimbursement in the form of limited time coverage restrictions on the use and access of certain high cost, innovative medicines (2-3 years). 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. Additional post-launch data is used to

41 This model is used in the Netherlands, Sweden and Portugal. See supra note 19

42 Interview with oncology medicine manufacturer

43 Interview with pharmaceutical company manufacturer

44 See supra note 19

understand real world utilisation of the product and confirm whether the product will be reimbursed beyond the initial time restriction.

However, according to our interviews, companies often find such data requirements difficult to collect and have difficulty submitting the type of data required by payers due to the lack of early dialogue with payers. The data required for these schemes differ from the clinical data required by the regulators under any conditional marketing authorisation. Some manufacturers indicated that they often follow up with additional studies or setup registries for regulatory purposes which do not necessarily provide the specific data that national HTA agencies and payers require. One reason for this is that payers are often looking for clinical and epidemiological data against an appropriate comparator to support cost-effectiveness analysis and budget impact assessment. Another issue is that whilst regulators look for European or international data, payers seek national or local data which is often difficult to collect – especially for medicines with small eligible patient populations.

Conditional reimbursement through the combination of discounts & payment-by-result

Finally, we discussed schemes that use a combination of discounts, payment-by-result and conditional treatment continuation to improve cost-effectiveness (Italy) whereby additional patient data for some products is used to establish automatic discounts based on the number of patients.⁴⁵ This was illustrated by Italy.

In Italy, registries are introduced as part of managed entry schemes and payers combine both financial agreements (to determine initial prices) and some level of coverage with evidence development. Companies must submit additional patient data for some products which is used to establish automatic discounts based on the number of patients. This additional clinical evidence is also used to manage utilisation (understand prescribing trends and use of the product in the real-world) and ensure appropriate use of medicines to control expenditure. However, this data is not used to renegotiate the price or develop value based/flexible pricing.

There is also no evidence that the data required by the regulator under conditional approval is subsequently used by the payer, as the registry development did not, in the examples discussed, collect the same data as for the EMA. For example, one manufacturer indicated that the EMA had asked for a registry to be created to collect additional safety information (specifically real world evidence on safety outcomes) which focuses more specifically on patient sub-populations (e.g. pregnant women) whilst the AIFA wanted additional efficacy data and a more clear identification of the total patient population.⁴⁶

In fact it has been argued that such schemes are largely financial agreements whereby the payback to AIFA and the monitoring of appropriate use is made possible through the data collected in the AIFA registry (discount based on volume).

2.4. Summary

There are few products that have a conditional marketing authorisation and use outcomes-based managed entry agreements. However, from the manufacturer's perspective, it was

45 Ibid.

46 Interview with oncology medicine manufacturer

suggested that outcomes-based MEAs remain attractive for some oncology products for which clinical trials data may not represent real-world patient care. The application of rigid cost effectiveness processes also poses a challenge. This also includes those with conditional regulatory approval, although it was recognised there was still limited experience with such schemes. It was pointed out that this is especially relevant for oncology products demonstrating health outcomes in stratified patient populations which are becoming more common.

3. Conclusions and policy implications

Adaptive Pathways is about managing uncertainty over time; it is based on the understanding of additional data collection. Our research finds that there were few cases where a product receiving conditional regulatory approval has subsequently used outcomes-based MEA; the few observed cases focus on oncology products. Overall, for the majority of products, payers will prefer financial-based MEA such as price discounts or price volume agreement.

Despite the low interest for outcomes-based MEAs on the payer side, there is strong interest from industry for these types of MEAs that most effectively leverage the additional evidence collected through conditional approval (e.g. registries/ retrospective studies).

Based on our research, this is most applicable for products with the following characteristics:

- Potential high patient population leading to potential high budget impact
- Difficulty in demonstrating cost effectiveness at local level
- Having clinical trials that are less representative of real-world patient care

According to our research, this was seen as less relevant today for medicines with small patient populations considering current transaction costs involved in developing an additional data collection mechanism on low numbers of patients. However, we note that other studies indicate that some products with low patient population (and indeed very low patient population, sometimes referred to as ultra-orphan medicinal products) were, in fact, subject to outcomes-based MEAs, specifically coverage with evidence development, reflecting a concern about clinical performance when clinical data is inevitably sparse.⁴⁷ There are clearly some barriers. Payers/HTA agencies want local data and more detailed product specific information, which differ from data collected for regulatory purposes. However, better alignment of data requirements between payers and regulators could feed into flexible pricing agreements, although this is not the case today. If there was the possibility to do so, many companies indicated they would be keen to explore such opportunities (as this allows price to reflect data on the value of the product). It is possible that if additional data requirements on the regulatory side were better aligned to the data evidence requirement from payers, this would encourage more outcomes-based MEAs. This appears to be a possibility for products where setting up infrastructure to measure outcome is a barrier.

In terms of policy conclusions:

- Better alignment of data requirements between HTA bodies and regulators could improve evidence development for MAPPs and help to encourage the use of MEAs including outcomes-based agreements.
- If there was the possibility to carry out flexible pricing agreements, many companies indicated they would be keen to explore such opportunities (as this allows price to reflect data on the value of the product).

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See supra note 4

- There would also be value in EMA and HTA/payers to coordinate also additional real world data requirements. This would then provide a signal for local /regional registries and regional coordinators about the types of information already being collected and encourage agreements that efficiently use this information in the simplest way possible.

Appendix A: Interview Questions for Industry



Background:

Introduction: Medicines Adaptive Pathways to Patients (MAPPs) and Adapt smart

Objectives of WP3.05-07:

- *To collect actual experience from stakeholders on managed entry agreements*
- *Insights will inform best practices recommendations for market entry agreements in the context of products approved under adaptive pathways.*

Interview structure

- *Demographics*
- *General experience with MEAs*
- *Experience with P&R agreements for product under conditional marketing authorisations and products authorised under exceptional circumstances*
- *Additional evidence development*
- *Interactions with payers*
- *Post-launch re-evaluation*
- *Prospective thinking – projecting MEA in the context of MAPPs*

NB: for the purpose of this research, products approved under conditional approval or exceptional circumstances are used as proxy for future adaptive pathways approvals.

Demographics

1. What is your role within [company X]?

How much experience do you have with Managed Entry Agreements (MEA) for products that have gone through conditional marketing authorisations?

How long have you been involved in managing access for [product Y]

General experience with Managed Entry Agreement (MEA)⁴⁸

MEAs are normally segmented into two key categories:

- **Financial Based Agreements:** Agreements between manufacturer and payers based on observable financial performance. This includes:
 - *Price agreement based on manufacturer's market share*
 - *Price-Volume Agreements*
 - *Pricing by Channel (discount on certain products/channels)*
 - *Capitation (discounts for specific patients)*
 - *Free initiation, (patient/dose dependent discount)*
 - *Portfolio Agreement (discounts based on manufacturer's portfolio)*
- **Outcome-Based Agreements:** Agreements based on defined outcomes (generally clinical) or agreements based on the development of new evidence. This includes:
 - *Patient Risk Sharing Agreement (price decided based on patient subtypes with respect to probability of benefits of treatment)*
 - *Performance-linked reimbursement (e.g. outcome guaranteed)*
 - *Conditional Coverage (reimbursement linked to the development of additional evidence)*

2. Could you indicate what types of MEAs your company has experience with (see above list):

3. Could you describe your experience with MEAs in general (both **financial-based and outcomes-based MEAs**)? With regards to **outcomes-based MEAs**,

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"A Managed Entry Agreement is an arrangement between a manufacturer and payer/provider that enables access to (coverage/reimbursement of) a health technology subject to specified conditions. These arrangements can use a variety of mechanisms to address uncertainty about the performance of technologies or to manage the adoption of technologies in order to maximize effective their use, or limit their budget impact".

what were the concerns? What were the reasons to undertake them? If possible, please take the following aspects into account:

- Feasibility of measuring outcomes data in clinical practice
- Reversibility of coverage decisions (in case of coverage with evidence development)
- Administrative burden
- Timeframes for MEA
- Ease of executing MEA in clinical practice
- Availability of adequate IT and data infrastructure
- Cooperation of all stakeholders if required (company, healthcare professionals, patients)
- Ability to control how product is used in practice
- Resource implications

Experience with price & reimbursement agreements for product under conditional marketing authorisations and products authorised under exceptional circumstances

We have observed that [Company name] has received a conditional MA for [product X, Y, Z] and/or an MA under exceptional circumstances for [product X, Y, Z]

4. Could you describe the experience of your organisation regarding the price and reimbursement procedures for products under conditional approval/ MA granted under exceptional circumstances? Probe:
 - Difference of experience across EU countries?

5. What were the specific questions/uncertainties related to this/these product(s) brought forward by payers in the in P&R or HTA process? Probe:
 - Strength of the clinical evidence
 - Efficacy profile
 - Safety profile
 - Epidemiology- size of eligible patient population
 - Cost-effectiveness ratio
 - Financial risk
 -

6. How did these questions/uncertainties affect the launch price and reimbursement conditions or even the HTA assessment?

7. What type of MEA was selected to facilitate access to [product X, Y, Z]? Outcomes-based or non-outcomes based? What element of uncertainty did they seek to address?
 - Effectiveness
 - Price
 - Use

8. What were your organisation's goals/motivations in pursuing MEA for the above compounds? Probe:
 - Address uncertainty
 - Maximise their use
 - Ensure the proposed price could be achieved
 - Manage budget impact
 - Others...

9. Could you describe your experiences with the outcomes-based agreements for these products? If possible, could you include the following details:
 - Feasibility of measuring outcomes data in clinical practice
 - Reversibility of coverage decisions (in case of coverage with evidence development)
 - Administrative burden
 - Timeframes for MEA
 - Ease of executing MEA in clinical practice
 - Availability of adequate IT and data infrastructure
 - Cooperation of all stakeholders if required (company, healthcare professionals, patients)
 - Ability to control how product is used in practice
 - Resource implications

10. Did the approval with a conditional MA make arranging an MEA easier or harder?

11. What were reasons to **not** engage in managed entry agreements for products on the list (multiple answers possible):
 - Not needed as sufficient evidence in support of reimbursement was available
 - Not needed as sufficient evidence in support of no reimbursement was available
 - Additional data collected not feasible

- Not launched
- Insufficient patients for MEA
- No infrastructure for MEA
- No perceived benefit of MEA

Additional evidence development

12. Were the data required by regulators (e.g. EMA) in conditional MA the same as data required by payers for an MEA? Did this cause a problem?
13. If additional evidence development was deemed necessary in the context of the MEA, can you describe how your organisation addressed the request? Probe:
 - Built-up on RCT / EMA post-approval commitments
 - Ad-hoc cohort
 - Real-world registry
 -
14. How were the conditions in terms of providing additional information? On what basis was this established?
 - Was there a request for country-specific data?
15. If there is experience with outcomes-based MEAs where patient-level data was collected, how was patient consent arranged?
16. Can you please comment on the specific questions/challenges faced by your organization in collecting the appropriate evidence?

Interactions with payers/HTA agencies

17. Could you describe your experiences in your interactions with payers? If possible, could you include the following items:
 - Easy or difficult to find an agreement on the terms of an MEA
 - Differences between different countries in interactions
 - Compliance with terms of MEA (if applicable)
18. Could you describe the following about organisational matters:
 - Who proposes the MEAs – is it the government, payer, company, other?
 - What are the rules and instructions for proposing an MEA?
 - Are contracts involved? If so, between what parties?

Post-launch re-evaluation

19. How did the additional data/evidence provided post-launch affect the price and reimbursement conditions agreed at time of launch? Probe

- list price
- MEA conditions /limitations
- Reimbursement scope

20. Could you indicate for the following items that have been named as advantages/opportunities of outcome-based MEAs whether or not, in your experience, these are advantages of MEAs:

	Major advantage	Minor advantage	Not an advantage
Ability to reduce uncertainty on effectiveness and/or cost-effectiveness			
Enables patient access to innovative treatments			
Offers more flexibility of coverage decision			
Different needs can be addressed by different schemes			
Better control of budget impact			
Improves cost-effectiveness			
Improved decision-making			
Streamlining of data collection post-marketing			
Enables re-negotiation of price			

21. What were the major barriers/challenges for your organisation in engaging in outcome-based MEAs for such products? Please order by importance

	Major barrier	Minor barrier	Not a barrier
Little empirical evidence available in support of perceived benefits of MEAs			
Lack of transparency			
Voluntary/non-voluntary nature of MEAs			
Difficulties in measuring outcomes data in practice			
Limited ability or willingness to delist product once introduced			
Difficult to evaluate effectiveness of MEAs in achieving aims			

Requires significant additional efforts			
Lack of motivation of stakeholders to participate in MEA			
Limited capacity to implement and assess evidence			
Additional burden to healthcare system			
Difficult to implement at national level/lack of international cooperation			

22. What would you say are typical characteristics of **successful or unsuccessful** MEAs (if any)?

What are the minimum requirements that are needed for successful MEA to be achieved?

Are MEA time critical?

Complexity of MEA?

23. What are the aims of successful MEA? Retrospectively, were the initially agreed upon aims met?

24. What are the lessons from your experience with MEAs?

What went well?

Are there types of MEAs your organisation will no longer engage in based on previous experience? If so, what types and why?

Prospective thinking – projecting MEA in the context of MAPPs

25. Based on your experience, what do you think would contribute to reducing the concerns/barriers for MEA in context of MAPPs?

26. What could be a launch price scenario at national level for products approved under MAPPs?

Probe - adaptive pricing (on list price or confidential discount level)? Other?

27. How should additional data collection ideally be organised/ resourced in the context of MAPPs?

28. What would need to happen/ be in place in the future for MAPPs to be adopted by the various stakeholders? Probe:

Acceptability of different data sources

Early dialog among stakeholders

Predictability on requests for monitoring of treatment outcomes, evidence generation plans, acceptance of data sources, eligible patients

29. What aspects of the development of MEA in context of MAPPs need to be tackled collectively?

Wider benefit of MAPPs?

Data collection?

Thank you very much for participating in this study. Please feel free to share any additional comments or other information you believe would be relevant to this study (optional)