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Performance-based managed entry agreements for new medicines in OECD countries and EU member states: How they work and possible improvements going forward

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How they work and possible improvements going forward

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Abstract

This paper presents findings of an OECD review of managed entry agreements in OECD countries and EU member states conducted in 2018 and 2019. Findings are based on discussions with the OECD Expert Group on Pharmaceuticals and Medical Devices, responses by experts from 12 OECD countries to a survey and semi-structured interviews (see Annex A), and on the literature as well as information published by national authorities responsible for coverage and pricing of medicines.

Managed entry agreements (MEAs) are arrangements between firms and healthcare payers that allow for coverage of new medicines while managing uncertainty around their financial impact or performance. Financial agreements, which can reduce prices and/or budget impact of medicines without disclosing price concessions to third parties and without linking them to product performance, are currently used or were used in the past in at least two-thirds of OECD countries and EU member states. Many of these countries also use performance-based agreements, which make coverage, payments to firms or rebates paid by firms conditional on product performance, but these MEAs are less common and their primary objectives are often also financial. Patient-level payment-by-result (PbR) and population-level coverage with evidence development (CED) are the most common agreement designs. Patient-level PbR agreements help payers manage budget impact or increase cost-effectiveness by paying firms only for treatments to which patients respond, while CED agreements are used to reduce uncertainty around comparative effectiveness or cost-effectiveness.

It is difficult to assess to what extent performance-based MEAs have so far been successful. Few countries have formally evaluated their experience. Confidentiality of agreements continues to be a barrier to independent evaluation and little evidence is public. However, information available from expert interviews and from prior studies indicates that CED agreements have so far had a poor track record of reducing uncertainty around the performance of medicines. As a result, some countries have recently reformed CED schemes and some are discontinuing CED agreements altogether in favour of alternatives. The latter include restricted or conditional coverage without a MEA, whereby coverage is initially restricted to certain indications or patient groups and only broadened if and when additional evidence becomes available. Payment-by-result agreements continue to be used quite widely, but they do not always generate evidence on product performance because data used for triggering payments are not always aggregated and analysed. The administrative burden of collecting and analysing data on the performance of the medicines can also make them costly to execute.

Despite the lack of evidence, experience with performance-based agreements so far points to a number of good practices. These span four main themes:

- Defining a strategy to guide the use of performance-based MEAs and ensuring that they are used only where the benefit of additional evidence on product performance outweighs the cost of negotiating and executing MEAs;
- Clearly identifying uncertainties in each coverage decision and designing performance-based MEAs to ensure that data sources and research designs are appropriate to address the uncertainties at hand;

- Implementing a governance framework that ensures transparency of process and allows payers to act upon the additional evidence generated as a result of MEAs in accordance with that evidence, including exit from MEAs and potential withdrawal of temporary coverage; and
- Ensuring a minimum level of transparency of content, limiting confidentiality to those parts of MEAs that may be commercially sensitive (in particular prices).

While payers could greatly benefit from international sharing of information on performance-based MEAs, little information is currently shared or published. This is true for information on the products for which MEAs are in place, on the design of MEAs and on their results. In particular, information on how performance of products is measured under MEAs and the results of MEAs are often kept confidential. This is the case despite interest across countries in accessing such information. Especially the potential non-disclosure of results of clinical studies conducted under performance-based MEAs raises ethical concerns as available information on the effectiveness of medicines could be withheld from the public. Greater sharing of information would benefit payers, for example, by reducing duplication of effort between countries, by allowing payers to learn from experience gained elsewhere to inform their negotiations with firms, and by reducing uncertainty that results from small patient samples (e.g. in the case of rare diseases). In addition, greater transparency of relevant information on the performance of products would also be useful for other stakeholders with legitimate interests and the general public.

To achieve these benefits, payers would need to change their policies in negotiations with pharmaceutical firms to ensure that information on future MEAs is not confidential. Further assessments might be necessary to determine which information is commercially sensitive and ought therefore to be protected. While existing laws may also need to be reviewed in each country to assess the current level of protection of information, changes to legislation might not be necessary in most countries to achieve greater transparency. Expert interviews conducted for this paper suggest that there is significant interest in sharing of information on the existence of MEAs, on how product performance is measured, and in decisions made as a result of MEAs. Payers could agree on which information to share, in which form and through which mechanism. Various mechanisms of information exchange are possible, including publishing information on existing websites, establishing new central repositories and using existing initiatives for sharing of information on medicines and health technologies.

Résumé

Ce document présente les résultats d'une étude de l'OCDE effectuée en 2018 et 2019 sur les contrats d'accès au marché (« conventions » en Belgique et « clauses contractuelles » en France) pour des produits de santé dans les pays de l'OCDE et les États membres de l'UE. Les conclusions de cette étude reposent sur des discussions avec le Groupe d'experts de l'OCDE sur les produits pharmaceutiques et les dispositifs médicaux, des réponses d'experts de 12 pays de l'OCDE à une enquête et à des entretiens semi-structurés (voir annexe A), et sur la littérature ainsi que les informations publiées par des payeurs, ou autorités nationales responsables de la prise en charge et de la tarification des médicaments.

Les contrats d'accès au marché (CAM) sont des contrats entre les entreprises pharmaceutiques et les payeurs qui permettent la prise en charge des nouveaux médicaments tout en gérant l'incertitude concernant leur impact financier ou leur performance. Les accords financiers, qui peuvent réduire les prix et / ou l'impact budgétaire des médicaments sans divulguer leurs prix nets à des tiers et sans les lier à la performance des produits, sont actuellement utilisés ou ont été utilisés dans le passé dans au moins les deux tiers des pays de l'OCDE et des États membres de l'UE. Beaucoup de ces pays utilisent également des contrats de performance, qui lient la prise en charge, des paiements aux entreprises ou des remises versées par les entreprises à la performance des produits, mais ces types de CAM sont moins courants et leurs objectifs principaux restent souvent également financiers. Le paiement selon le résultat évalué au niveau du patient (dit « patient-level payment-by-result » ou « patient-level PbR » en anglais) et la prise en charge au niveau de la population conditionnée sur le recueil des données probantes (dit « population-level coverage with evidence development » ou « population-level CED » en anglais) sont les modèles de contrat de performance les plus courants. Les accords PbR au niveau des patients aident les payeurs à contenir l'impact budgétaire ou à accroître le rapport coût-efficacité des produits en ne payant les entreprises que pour les traitements auxquels les patients répondent, tandis que les accords CED sont utilisés pour réduire l'incertitude quant à l'efficacité comparative ou au ratio coût-efficacité.

Il est difficile d'évaluer l'impact des contrats de performance. Peu de pays ont étudié leur expérience de manière formelle. La confidentialité des contrats continue d'être un obstacle à une évaluation indépendante et peu d'information est publique. Cependant, les informations recueillies par cette étude suggèrent que les accords CED ont jusqu'à présent peu contribué à la réduction de l'incertitude concernant les performances des médicaments. En conséquence, certains pays ont récemment réformé leurs doctrines CED et certains abandonnent complètement les contrats CED en faveur d'alternatives. Ces derniers incluent une prise en charge restreinte ou conditionnelle sans CAM, la prise en charge étant initialement limitée à certaines indications ou groupes de patients et élargie uniquement si et lorsque des données probantes supplémentaires deviennent disponibles. Les accords PbR continuent d'être utilisés de manière assez courante, mais ils ne contribuent pas toujours à la réduction de l'incertitude concernant les performances des produits car les données utilisées pour déclencher les paiements ou les remises ne sont pas toujours agrégées et analysées. La charge administrative de la collecte et de l'analyse des données peut également rendre l'utilisation de ce type de contrat coûteuse.

Malgré le manque d'information, un certain nombre de bonnes pratiques peuvent être identifiées à partir de l'expérience acquise à ce jour par rapport aux contrats de performance, selon quatre thèmes principaux:

- Élaborer une stratégie pour guider l'utilisation des contrats de performance et faire en sorte qu'ils ne soient utilisés que lorsque les avantages attendus de données supplémentaires sur la performance des produits l'emportent sur les coûts de négociation et de mise en œuvre des contrats ;
- Identifier clairement les incertitudes dans chaque décision de prise en charge et concevoir les contrats de performances d'une manière qui garantit que les sources de données et les méthodes de recherche soient appropriés pour répondre aux incertitudes identifiées ;
- Mettre en œuvre un système de gouvernance qui garantit une transparence de processus et permet aux payeurs d'agir en accord avec les données supplémentaires générées à la suite des CAM, y compris la sortie du CAM et le déremboursement potentiel du produit ou l'arrêt de la prise en charge temporaire ; et,
- Assurer un niveau minimum de transparence sur le contenu de ces contrats, en limitant la confidentialité aux éléments des CAM qui peuvent être sensibles du point de vue commercial (en particulier les prix).

Alors que les payeurs pourraient bénéficier d'un partage international d'informations sur les contrats de performance, peu d'informations sont actuellement partagées ou publiées. Cela est vrai pour les informations sur les produits pour lesquels des CAM sont en place, sur la conception des CAM et sur leurs résultats. En particulier, les informations sur la façon dont la performance des produits est évaluée dans le cadre des CAM et les résultats des CAM sont souvent confidentielles. C'est le cas malgré l'intérêt manifesté par les pays à accéder à ces informations. La non-publication potentielle des résultats d'études cliniques menées dans le cadre des contrats de performance pose des problèmes éthiques car les informations disponibles sur l'efficacité des médicaments pourraient ne pas être portées à la connaissance du public. Un plus grand partage d'informations bénéficierait aux payeurs, par exemple, en réduisant la duplication de tâches entre les pays ; en permettant aux payeurs d'apprendre de l'expérience acquise ailleurs pour mener leurs négociations avec les entreprises ; et en réduisant l'incertitude qui résulte de petits échantillons de patients (par exemple dans le cas des maladies rares). En outre, une plus grande transparence des informations sur les performances des produits serait également utile pour les autres parties prenantes ayant des intérêts légitimes et le grand public.

Pour y parvenir, les payeurs devraient modifier leurs politiques de négociation avec les entreprises pharmaceutiques afin d'éviter que les informations sur les futurs CAM soient confidentielles. Des études additionnelles pourraient être nécessaires pour déterminer quelles informations sont commercialement sensibles et devraient donc être protégées. Bien que les lois existantes puissent également devoir être revues dans chaque pays pour évaluer le niveau actuel de protection des informations, des modifications de la législation pourraient ne pas être nécessaires dans la plupart des pays pour atteindre une plus grande transparence. Les entretiens avec les experts menés pour cette étude suggèrent qu'il existe un intérêt significatif au partage d'informations sur l'existence des CAM, à la façon dont la performance des produits est évaluée et aux décisions prises à la suite des CAM. Les payeurs pourraient se mettre d'accord sur les éléments d'information à partager, sous quelle forme et par quel mécanisme. Divers mécanismes d'échange d'informations sont possibles, notamment la publication d'informations sur les sites Web existants, la création de nouveaux référentiels centraux et l'utilisation des initiatives existantes pour le partage d'informations sur les médicaments et les produits de santé.

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Part I. The track record of performance-based MEAs in OECD countries

1 Introduction

1. The use of managed entry agreements (MEAs) has increased in the past decades. The majority of OECD countries and European Union (EU) member states now use MEAs, albeit to varying extents, when adding new medicines to the basket of products covered by health coverage schemes. The design and implementation of MEAs vary widely across countries, depending on the purposes the agreements are intended to serve, payers' strategies and technical capacities. While some stakeholders claim that MEAs have been successful in achieving a number of goals of pharmaceutical policy, such as accelerating access to new treatments, reducing uncertainty around product performance or managing budget impact, critics often argue that they have reduced transparency and increased administrative workload. Part I of this paper summarises past and current practices in the use of MEAs in OECD countries and EU member states, with a focus on performance-based agreements. Sections 1. and 2. provide an overview of all types of MEAs while Section 3. discusses the experience with performance-based MEAs only.

1.2. A definition of managed entry agreements

2. A variety of terms have come to be used to describe arrangements that attach conditions to the coverage of a new health technology and which are negotiated between the firm that sells the technology and the payer or authority responsible for price regulation or coverage decisions related to it. These arrangements are known as managed entry agreements (MEAs) but have also been referred to by a number of other terms including risk-sharing agreements, special pricing arrangements or patient access schemes (Stafinski, McCabe and Menon, 2010[1]; Kanavos et al., 2017[2]). The use of different terms across countries often reflects the primary policy objectives the arrangements are intended to achieve or the nature of the agreements themselves (Ferrario et al., 2017[3]).

3. This paper uses a broad definition proposed by Klemp, Frønsdal and Facey (2011[4]) to refer to *managed entry agreements* (MEAs) as,

> *"Arrangement[s] between a manufacturer and payer/provider that enable 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 their effective use, or limit their budget impact." (p.79)*

4. The terms *manufacturer* and *payer* in this definition of MEAs should be understood in a broad sense. Manufacturers can include any firm that sells health technologies and are referred to as *firms* in the remainder of this paper. The scope of MEAs in this paper includes agreements between health care payers, government departments or national authorities responsible for coverage or pricing decisions and/or health technology assessment (HTA), on the one hand, and firms, on the other hand. For simplicity, the contractual counterparties of *firms*, whether they are payers, government departments or national authorities, are referred to as *payers*. MEAs can also exist between health care providers and firms.

1.3. MEAs are tools for achieving patient access to new medicines while managing uncertainty

5. Payers generally aim to provide patients with access to new medicines quickly after marketing authorisation while firms can maximise revenue by selling the highest possible volume of their products at the highest possible price. Firms also have an interest in earning revenue as early as possible in the life cycle for medicines because the period of market exclusivity is limited and to achieve high prices early in the process because these serve as signals for payers that make subsequent coverage decisions. While both parties therefore aim to reach an agreement quickly after marketing authorisation, the motivation for MEAs stems from a difference in views between firms and payers regarding the potential impact of a new technology on health outcomes and healthcare budgets, or in their willingness to accept that impact or uncertainty around it (Garrison et al., 2013[5]). MEAs thus allow firms to sell a technology and earn revenue even when payers are unwilling to pay the full asking price or assume the risks of unconditional coverage. MEAs are therefore also frequently referred to as risk sharing agreements.

6. MEAs reduce the consequences of making a poor coverage decision in the face of uncertain effects of a new treatment on health outcomes and/or health care budgets. Extending coverage for treatments that are later shown to be ineffective and denying coverage for treatments that are later seen to be effective or cost-effective can lead to poorer health outcomes and waste of resources, either through patients being denied access to effective treatments, or being administered ineffective treatments (Stafinski, McCabe and Menon, 2010[1]; Garrison et al., 2013[5]). In the longer term, poor decisions can compromise the credibility of the decision-making processes and engender scepticism among stakeholders and the public (Stafinski, McCabe and Menon, 2010[1]).

1.4. A taxonomy of MEAs

7. To classify the various types of MEAs, this paper proposes a three-level taxonomy based on the objectives, the level at which financial mechanisms operate and the design of the agreements. It is based on a number of previous classifications, published by Carlson et al. (2010[6]), Gerkens et al. (2017[7]) and Ferrario and Kanavos (2013[8]).

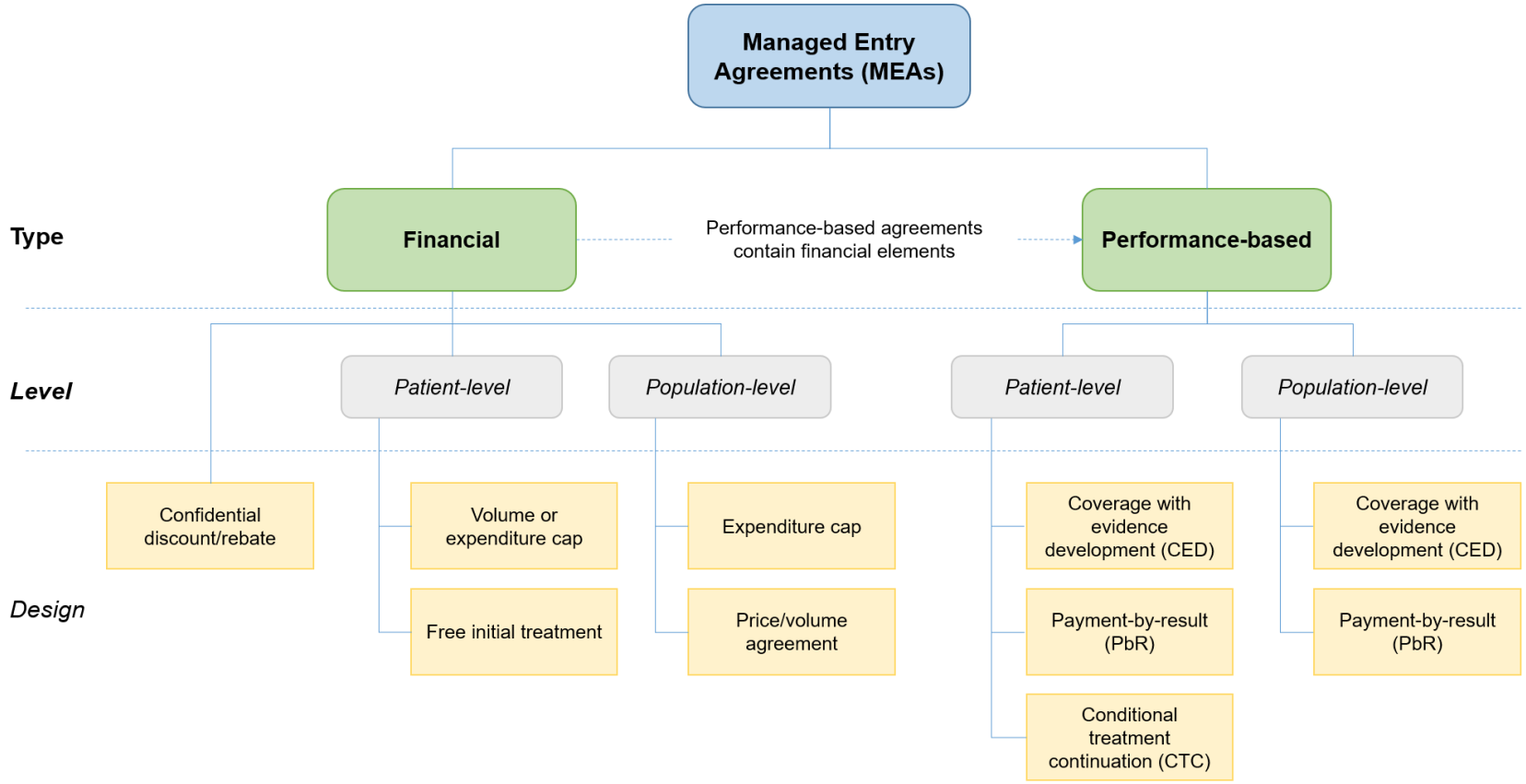
8. First, this taxonomy categorises agreements into two broad types. On the one hand, financial agreements generally only aim to manage uncertainty around the budget impact of a new technology or, in the case of simple confidential discounts or rebates, reduce the price and budget impact of the technology without disclosing price concessions to other payers. Financial agreements are not linked to the performance of treatments and do not require the analysis of data related to health outcomes. While such agreements may help manage budget impact and can, in the case of volume caps, also support appropriate use, they also reduce price transparency. On the other hand, performance-based agreements entail the analysis of data on product performance, with coverage by payers, payments to firms or rebates paid by firms contingent on the collection of data and/or on the outcomes achieved. Performance-based agreements thus also have an ultimate financial objective but make financial effects for payers and firms contingent on the performance of the technology.

9. Second, within these two main types, MEAs are broken down according to whether the mechanisms that trigger financial aspects of the agreement are defined at the patient- or population-level. In this context, *population* can refer to any group of patients, for instance all treatment-eligible patients in the country or all patients whose treatment is covered by the payer that is a party to the MEA. On the other hand, the defining criterion of *patient-level* MEAs is that the mechanisms of the agreement are defined at the level of an individual patient treated. Simple confidential discounts or rebates are exceptions within financial agreements because they do not contain mechanisms that make the discount or rebate

conditional on volume, expenditure or another parameter. However, they still make coverage conditional on the existence of a discount or rebate and are therefore included in the broad definition of MEAs above.

10. Third, they are broken down into distinct MEA designs according to how the mechanism to control budget impact or manage uncertainty around performance is specified in the agreement. Mechanisms can have similar designs but be defined at the patient- or population-level. Thus the same MEA design can exist at both levels. The taxonomy is illustrated in Figure 1.1. A description of each MEA design and a corresponding example are provided in Table 1.1.

Figure 1.1. A taxonomy of Managed Entry Agreements



Note: This taxonomy is only based on how agreements are structured. All types of agreements above can exist not only between firms and health care payers but also between firms and other types of entities that constitute a health system, including government departments or national authorities responsible for coverage or pricing decisions and/or health technology assessment (HTA), regional health authorities, health care providers, etc. Especially for products used in the hospital inpatient sector, MEAs may be in place between firms and hospitals.

Source: Authors based on Carlson (2010[6]), Ferrario and Kanavos (2013[8]) and Gerkens et al. (2017[7])

Table 1.1. Examples of types and designs of Managed Entry Agreements (MEAs)

Agreement type	Agreement level and design	Description	Example
Financial	Confidential discount or rebate	An unconditional reduction off the list price is agreed in a confidential contract, taking the form of an up-front discount or an ex-post rebate refunded by the firm.	Lenvatinib (Kisplyx®) for renal cell carcinoma (RCC) in England and Wales (since January 2018). A simple discount at the point of purchase or invoice has been agreed confidentially between the Department of Health and the firm.
	Patient-level treatment or expenditure cap	A patient-level treatment (number of products, dosage or duration) or expenditure ceiling is agreed on, and the firm provides products exceeding the cap free of charge.	Lenalidomide (Revlimid®) for treating myelodysplastic syndromes in England and Wales (since 2014). The firm is paid for treatment of up to 26 monthly cycles and provides products free of charge for patients who receive more than 26 monthly cycles.
	Patient-level free initial treatment	The firm provides initial treatment units free of charge up to an agreed level for each patient treated, after which additional units are purchased at an agreed price.	Certolizumab pegol (Cimzia®) for treating rheumatoid arthritis after inadequate response to a TNF-alpha inhibitor in England and Wales (since 2016). The first 12 weeks of treatment (10 pre-loaded syringes of 200mg each) are free of charge. Acquisition cost is GBP 6,793 in the first year of treatment and then GBP 9,295 per year.
	Population-level expenditure cap	An aggregate expenditure ceiling for all patients/ a defined number of patients treated is agreed on, and the firm provides products exceeding the cap free of charge.	Direct-acting antivirals (DAAs) for hepatitis C in Australia (since 2015). The government defined an annual budget cap above which firms provide a rebate for the full treatment costs.
	Population-level price-volume agreement	Tiered prices are agreed on, which decrease with increasing aggregate volume purchased for all patients treated.	Commonly used in France. Information on specific agreements are not public.

Performance-based	Patient-level coverage with evidence development (CED)	The treatment is covered temporarily by the payer only for patients who agree to enrol in a study that evaluates the performance of the treatment. Based on the results of the study, coverage is withdrawn or extended, or prices adjusted.	Clofarabine (Evoltra®) in Korea (2018). Patients must have been enrolled in a clinical trial to receive reimbursement of the medicine. This agreement ended in December 2018 as clinical effectiveness was confirmed and reimbursement maintained.
	Patient-level payment by results	Payment to the firm for treatment provided is contingent on the achievement of pre-specified response to treatment in each patient. Payers may withhold payment partially or entirely for each patient until the result is achieved, receive full or partial refunds for patients who do not achieve the response, or receive free additional products with which to treat subsequent patients.	Alglucosidase alpha for late-onset Pompe disease in Estonia (ongoing). The product is reimbursed only when a positive effect is confirmed by a panel of 4 specialist doctors.
	Patient-level conditional treatment continuation	Coverage of the treatment is continued only for patients who achieve a pre-specified response to treatment; firms provide products free of charge or discounted for patients who do not achieve results.	Several Alzheimers medicines in Italy (2007). The firm provides products free of charge for the first 3 months of treatment and short-term effectiveness is assessed. If treatment goals are met after 3 months, treatment is continued for a maximum of 2 years and the firm paid by the national health service (SSN).
	Population-level coverage with evidence development (CED)	The treatment is covered temporarily by the payer for all treatment-eligible patients while a study evaluates the performance of the treatment. Based on the results of the study, coverage is maintained, withdrawn or extended, or prices are adjusted.	Axicabtagene ciloleucel (Yescarta®) for B-cell lymphoma in England (ongoing). The Cancer Drugs Fund (CDF) covers the treatment under the condition that further evidence is collected to reduce uncertainty around survival estimates. Evidence includes an ongoing phase II trial and observational data from a cancer registry. At the end of the agreement, the medicine is reappraised and if there is insufficient evidence or the medicine is considered not to be clinically or cost effective, the medicine may be removed from the CDF and no longer available on the National Health Service. In this case, patients will continue to receive the drug at the pharmaceutical company's cost until the prescribing physician deems it appropriate to discontinue treatment.
	Population-level payment by results	Payment to the firm for treatments provided is contingent on the achievement of an agreed result in the population treated. Payers may withhold payment partially or entirely until the result is achieved, receive a full or partial refund if the result is not achieved, or receive free additional products.	Interferon beta and glatiramer acetate for multiple sclerosis in England and Wales (2002). Treatments were initially priced at the level demanded by the firm and, based on a 10-year cohort study estimating disability using the extended disability status scale (EDSS), prices were expected to be adjusted every 2 years to meet a cost-effectiveness threshold of GBP 36,000 / QALY gained.

Source: Authors. Examples of MEAs are drawn from Carlson et al. (2010[6]) for Italy and France, Devon CCG (2016[9]), NICE (2019[10]) and Raftery (2010[11]) for the United Kingdom, and OECD interviews with experts from Korea and Estonia.

2. While financial MEAs have proliferated, the use of performance-based MEAs remains more limited

11. This section provides an overview of the use of managed entry agreements (MEAs) in OECD countries and EU member states, based on information available from public sources and information collected by the OECD Secretariat through the survey and expert interviews described in Annex A. It provides an overview of the countries in which MEAs are used; discusses the objectives, types and designs of MEAs; and provides information on health outcome measures and data sources used for the execution of performance-based MEAs.

2.1. Two-thirds of OECD and EU countries use MEAs

12. The OECD survey conducted for this paper and public sources indicate that by 2019 MEAs were being or had been used in at least 28 of 41 countries that are members of the OECD and/or the European Union (see Table 2.1).

13. Initial implementations of MEAs were either preceded or followed by explicit policies on MEAs related to the coverage of medicines. In Belgium, for example, they were introduced after legislation allowing for MEAs entered into force in 2010 (Gerkens et al., 2017[7]). A survey by the European Medicines Information Network (EMiNet) found that in 2012 legislation governing MEAs was also in place in the Czech Republic, Lithuania, Norway, Portugal and Slovakia (Ferrario and Kanavos, 2013[8]). While there was no specific legislation, countries such as France or Italy also had in place defined processes for MEAs based on laws related to the coverage of medicines (ibid.).

14. In Germany contracts between sickness funds and pharmaceutical firms that make pricing subject to specified conditions are permissible by legislation related to the pharmaceutical market, and it is up to individual sickness funds to decide if and how to use them (Schremser et al., 2017[12]). However, because they do not affect coverage, these contracts are not considered MEAs per the definition adopted in this paper. All new medicines are covered by statutory health insurance in Germany upon marketing authorisation. Following HTA for patented medicines, prices paid by sickness funds are subsequently set based on internal reference pricing or negotiations between sickness funds and pharmaceutical firms.

15. The published literature also suggests that the use of MEAs has increased over time (Ferrario and Kanavos, 2013[8]; Carlson, Chen and Garrison, 2017[13]; Ferrario and Kanavos, 2015[14]). The pharmaceutical industry sometimes promotes MEAs as a flexible means of enhancing patient access to medicines while managing pharmaceutical expenditure.[1] Sweden (in 2003), Italy and the Netherlands (in

[1] See, for example, the EFPIA response to the Draft Opinion on Innovative payment models for high-cost innovative medicines of the European Expert Panel on effective ways of investing in health

2006) were early adopters in Europe (Ferrario and Kanavos, 2015[14]). A large number of MEAs are now found in Australia, Belgium, Italy, the United Kingdom and in a number of Central and Eastern European (CEE) countries, such as Bulgaria, Estonia, Hungary and Slovenia. Although performance-based MEAs have been used in the United States at least since the late 1990s (Stafinski, McCabe and Menon, 2010[1]), it is difficult to provide a complete picture of their use because of the high number of payers and the lack of public information on activities of payers in the private sector. Box 2.1 summarises information on the United States available from public sources.

Table 2.1. OECD countries and EU member states in which MEAs are used or were used in the past

Country	Financial	Performance-based	Notes
Australia	Yes	Yes	
Austria	Yes	No data	
Belgium	Yes	Yes	
Bulgaria	Yes	Yes	MEAs are required for all new medicines covered since 2015 and for patented medicines already covered before 2015 to maintain coverage (Ferrario et al., 2017[3]).
Canada	Yes	Yes	
Chile	No data	No data	
Croatia	Yes	Yes	
Cyprus[1]	Yes	No	A 2012 survey found 5 MEAs (Ferrario and Kanavos, 2013[8])
Czech Republic	Yes	Yes	
Denmark	Yes	No	
Estonia	Yes	Yes	
Finland	Yes	No	Since 2017, both financial and performance-based MEAs are possible by law.
France	Yes	Yes	
Germany	No	No	
Greece	No data	No data	
Hungary	Yes	Yes	
Iceland	No data	No data	
Ireland	No data	No data	
Israel[2]	No data	No data	
Italy	Yes	Yes	
Japan	No	No	
Republic of Korea	Yes	Yes	
Latvia	Yes	Yes	
Lithuania	Yes	Yes	
Luxembourg	No data	No data	
Malta	Yes	No data	A 2012 survey found 1 MEA (Ferrario and Kanavos, 2013[8])
Mexico	No data	No data	Kanavos et al. (2017[2]) note that MEAs have been adopted on a pilot-basis.
Netherlands	Yes	Yes	
New Zealand	Yes	No data	A 2012 literature review found 5 MEAs (Lu et al., 2015[15])
Norway	Yes	Yes	
Poland	Yes	Yes	Surveys found that MEAs were used but are confidential (Ferrario et al., 2017[3]; Rotar et al., 2018[16]).

(https://www.efpia.eu/media/288630/final_efpia-response-to-exph-draft-opinion-7_12_2017_wir.pdf) or EFPIA response to statements by a former European Commissioner for Health and Food Safety (https://www.efpia.eu/news-events/the-efpia-view/efpia-news/151002-efpia-welcomes-member-states-sharing-experience-on-new-models-for-patient-access/).

Country	Financial	Performance-based	Notes
Portugal	Yes	Yes	A 2012 survey found 84 MEAs (Ferrario and Kanavos, 2013[8])
Romania	Yes	Yes	
Slovak Republic	No	No	No MEA in place per February 2017 but relevant legislation under discussion (Ferrario et al., 2017[3]).
Slovenia	Yes	No data	MEAs mandatory for all new medicines covered since 2005 (Ferrario et al., 2017[3]).
Spain	No data	Yes	
Sweden	Yes	Yes	
Switzerland	No data	Yes	The review by Gerkens et al. (2017[7]) identified 46 CED agreements between 1996 and 2013.
Turkey	No data	No data	Kanavos et al. (2017[2]) note that MEAs have been adopted on a pilot-basis.
United Kingdom	Yes	Yes	
United States	Yes	Yes	
Count of countries using MEAs *% of all countries*	**28** *68%*	**23** *56%*	

Notes: 1. Note by Turkey: The information in this document with reference to "Cyprus" relates to the southern part of the Island. There is no single authority representing both Turkish and Greek Cypriot people on the Island. Turkey recognises the Turkish Republic of Northern Cyprus (TRNC). Until a lasting and equitable solution is found within the context of the United Nations, Turkey shall preserve its position concerning the "Cyprus issue". Note by all the European Union Member States of the OECD and the European Union: The Republic of Cyprus is recognised by all members of the United Nations with the exception of Turkey. The information in this document relates to the area under the effective control of the Government of the Republic of Cyprus.
2. The statistical data for Israel are supplied by and under the responsibility of the relevant Israeli authorities. The use of such data by the OECD is without prejudice to the status of the Golan Heights, East Jerusalem and Israeli settlements in the West Bank under the terms of international law.

Source: Authors based on OECD survey and public sources

16. Beyond medicines, MEAs have also been used for various types of non-pharmaceutical health technologies in the past, including medical devices and a diagnostic or surgical procedures (Carlson, Chen and Garrison, 2017[13]; Stafinski, McCabe and Menon, 2010[1]; Lu et al., 2015[15]). For instance, Stafinski, McCabe and Menon (2010[1]) identified 32 CED schemes for non-pharmaceutical technologies in Australia, Canada, France, Italy, the Netherlands, United Kingdom, United States between the 1990s and 2009, of which approximately one-third were diagnostic, one-third were non-surgical interventions, and one-third were surgical procedures. However, MEAs now appear to be relatively uncommon for non-pharmaceutical products. In their review of performance-based MEAs in Australia, Italy, the Netherlands, Sweden, the United States and the United Kingdom, Carlson, Chen and Garrison (2017[13]) found that more than 90% of agreements adopted since the late 1990s across these countries involved medicines. At the same time, a number of prior studies cited above explicitly limited their scope to pharmaceuticals so the apparent focus on medicines could also be partly an artefact of study designs.

17. Experts from 16 OECD countries[2] responded to the OECD survey that requested information on the existence of MEAs, whether currently active or closed, and their type for a sample of 57 product/indication pairs across a number of therapeutic areas. Respondents could also report information for additional product/indication pairs for which MEAs were in place. Details on the survey are in Annex A. Among the 16 countries that responded, 13 countries provided data on the existence of performance-based MEAs for the product/indication pairs in the sample. The Czech Republic reported that MEAs were used but that all information related to MEAs was confidential. Japan reported that MEAs were not used. The United States provided no information in their response on the existence of MEAs for sample of

[2] Australia, Belgium, the Czech Republic, Estonia, France, Hungary, Japan, Korea, Lithuania, the Netherlands, Norway, Portugal, Spain, Sweden, the United Kingdom (England only) and the United States.

product/indication pairs. Data from Italy was added by the Secretariat for the final sample of products/indications based on information published by AIFA (2018[17]). Data for England and Hungary were collated by the Secretariat for the final sample of products/indications based on information provided in response to the OECD survey as well as information published by NICE (2019[10]) and the National Institute of Health Insurance Fund Management of Hungary (NEAK, 2019[18]). Information on the existence of MEAs by product and indication was thus available for 14 countries.

18. Overall, information from the 14 countries related to a final sample of 104 distinct product/indication pairs, covering the 57 pairs included in the initial sample and 47 product/indication pairs added by respondents. However, not all countries provided information for all of the 104 pairs so the final sample size varies by country. Table 2.2 shows the number of product/indication pairs for which information was available from each country and the number of pairs subject to MEAs. Information on the existence of a MEA for a given product and indication is generally not confidential in these 14 countries. In Australia, however, even the existence of a MEA may be confidential in some cases. According to the response by Australia, the existence of MEAs could not be disclosed for 7 product/indication pairs in the sample due to confidentiality requirements. In Belgium and also for some MEAs in England, information on the type and/or design of MEA can be confidential.

19. There was some overlap between countries in terms of the products/indications subject to MEAs. Among the 104 product/indication pairs for which information was available from 14 countries, 67 were subject to MEAs in two or more countries (64%). Fourteen product/indication pairs (13%) were subject to MEAs in more than 7 countries and 4 (4%) in more than 10 of 14 countries (see Table 2.3). This may, however, underestimate the overlap because of non-response for some product/indication pairs.

20. It is more difficult to assess whether performance-based MEAs are in place for the same or different products/indications across countries because the information on the type and design of MEA in place for a given product/indication is confidential in some countries, including for some MEAs in Australia, Belgium and England, where performance-based MEAs are commonly used. Based on information available, eight product/indication pairs in the sample are subject to performance-based MEAs in at least two countries (Table 2.4).

Box 2.1. Performance-based MEAs in the United States

It is difficult to provide a complete picture of performance-based agreements in the United States due to the high number of payers and the opacity of the private payer sector. Agreements may be negotiated between firms and private payers or providers as well as public payers at state and federal levels. While various prior studies reviewed MEAs, it is likely that they only identified a small subset of the total number of performance-based MEAs in the United States.

The Centers for Medicare & Medicaid Services (CMS), overseeing the main publicly-funded health coverage schemes, use CED as part of coverage restrictions but not as part of agreements with firms. CED was part of 24 national coverage determinations according to the CMS website as of September 2019, mostly for technologies such as medical devices, procedures and diagnostics, and one medicine (CMS, 2018[19]). These restrictions are defined at the patient-level, as national coverage of the technology is only provided for patients who participate in a clinical study.

A review by Carlson, Chen and Garrison (2017[13]) identified 62 performance-based agreements between 1997 and 2016, of which 47% for medicines, 34% for devices, and 19% for diagnostics. Cardiology was the most common therapeutic area, followed by oncology (ibid.) According to a recent report by IQVIA (2018[20]), there were 24 performance-based MEAs for medicines in the United States between 2013 and 2017. This number is predicted to increase to 65 between the years 2018 and 2022 (ibid.). Another systematic review of performance-based agreements for medicines only found 26 agreements publically announced or initiated between 1997 and 2017, between firms and a variety of payer types, including multistate insurers, CMS, regional insurers and pharmacy benefit managers (Yu et al., 2017[21]). Factors associated with implementation of performance-based agreements included: the recent launch of a treatment with high budget impact; presence of competitors in the same class of medicine; presence of competing therapies for the same disease; lack of head-to-head trials with standard of care for approved indications; and high overall drug spending in previous years.

CED agreements were the predominant MEA design initially, whereas payment-by-result agreements, including arrangements with private payers, have subsequently become more common (Carlson, Chen and Garrison, 2017[13]; Stafinski, McCabe and Menon, 2010[1]). The review by Carlson, Chen and Garrison (2017[13]) also concluded that the use of payment-by-result agreements may become more common in the future, as a result of the willingness of CMS to experiment with such arrangements.

Source: Authors based on sources cited in the text.

Table 2.2. Number and types of MEAs by country

In 14 countries for which information is available

Country	Number of product / indication pairs in sample				Notes
	Data available for	Subject to MEAs (active[1] / total)	Subject to performance-based MEAs (active[1] / total)	Subject to performance-based MEAs by type (total)	
Australia	72	n.d.[2] / ≥43	Confidential	Confidential	Within the 72 product/indication pairs for which Australia reported data, 60 were considered for coverage. Australia confirmed that no MEA was in place for 10 pairs and reported that the existence of MEAs could not be disclosed for 7 pairs due to confidentiality.
Belgium	58	25 / 28	Confidential	Confidential	Based on expert interviews, CED agreements are common but PbR are also used.
Estonia	64	n.d.[2] / 11	n.d.[2] / 8	Patient-level PbR: 8	
France	59	n.d.[2] / 48	≤3[2] / 4	Patient-level PbR: 3 Population-level CED: 1	France reported that financial MEAs for 3 product/indication pairs and patient-level CED for 1 pair were closed but provided no agreement end dates for the remaining pairs.
Hungary	70	16 / 16	7 / 7	n.d.	Hungary only reported information on MEAs currently active but no information on MEAs that were already closed. Performance-based MEAs take the form of PbR or CTC.
Italy[3]	n.d.	25[4] / 37	16[4] / 22	n.d.	
Korea	58	≤8 / 10	0 / 1	Patient-level CED: 1	Korea reported MEA end dates prior to 31 Dec 2018 for 2 product/indication pairs MEAs; no dates were reported for the remaining pairs.
Lithuania	57	n.d.[2] / 22	n.d.[2] / 1	Patient-level CTC: 1	
Netherlands	19	10 / 13	n.d.	n.d.	13 product/indication pairs include 3 MEAs still in negotiation per March 2019. According to the expert interview, no performance-based MEAs are currently used.
Norway	67	1 / 2	0 / 0[5]	n.a.	
Portugal	66	43 / 43	3 / 3	Patient-level PbR: 3	
Spain	3	3 / 3	3 / 3	Patient-level PbR: 3	
Sweden[6]	58	22 / 26	0 / 0	n.a.	10 patient-level PbR agreements are in place for product/indication pairs not included in the initial sample of 57.
United Kingdom (England only)[7]	n.d.	n.d[7]. / 57	n.d.[8] / ≥27	Population-level CED: ≥22 Others: n.d.	All products in the current Cancer Drugs Fund (CDF) are subject to population-level CED. NICE confirmed existence of performance-based MEAs for a number of other product/indication pairs. No data are available on the total number and types of performance-based MEAs outside of the CDF.

Notes: CED…coverage with evidence development, CTC…conditional treatment continuation, PbR…payment-by-result, n.a.... not applicable; n.d…. no data, NICE… National Institute for Health and Care Excellence

1. Per end of 2018, i.e. agreements are counted as active if their end date is after 31 December 2018.
2. No data provided by respondents on agreement start and/or end dates.

3. Based on information published by AIFA and added by the authors. Numbers represent the number of product/indication pairs subject to MEAs among the 57 pairs included in the initial sample and any other product indication/pairs added by other countries that responded to the survey.
4. Per 11 November 2018, based on information published by AIFA.
5. After the data collection period ended, Norway reported that population-level CED agreements were put in place in August 2019 for 2 product/indication pairs in the sample.
6. According to the survey response, MEAs were in place for 65 additional products that were not in the initial sample but no information was provided according to the corresponding indications; these are not reflected above.
7. Based on information provided in OECD survey (7 March 2019) as well as published by NICE as of 27 February 2019. Numbers represent the number of product/indication pairs subject to MEAs among the 57 pairs included in the initial sample and any other product/indication pairs added by England and other countries that responded to the survey.
8. Data on agreement start and end dates not available for all product/indication pairs in the sample

Sources: Authors based on OECD survey, AIFA (2018[17]) for Italy, NEAK (2019[18]) for Hungary and NICE (2019[10]) for England.

Table 2.3. Product/indication pairs subject to MEAs in seven or more countries

In 14 countries for which information is available

Subject to MEAs in	Active substance (ATC code)	Brand name	Disease area, ICD 10 chapter	Indication	Subject to MEAs in[1]
≥10 / 14 countries	nivolumab (L01XC17)	Opdivo®	neoplasms	non-small cell lung cancer	Australia, Belgium, England, Italy, Korea, Lithuania, Netherlands, Portugal, Sweden
	nivolumab (L01XC17)	Opdivo®	neoplasms	melanoma	Australia, Belgium, England, Italy, Korea, Lithuania, Netherlands, Portugal, Sweden
	olaparib (L01XX46)	Lynparza®	neoplasms	ovarian, fallopian tube and peritoneal cancer	Australia, Belgium, England, Estonia, Hungary, Italy, Korea, Lithuania, Portugal
	pembrolizumab (L01XC18)	Keytruda®	neoplasms	melanoma	Australia, Belgium, England, Italy, Korea, Lithuania, Netherlands, Portugal, Sweden
8 – 9 / 14 countries	brentuximab vedotin (L01XC12)	Adcetris®	neoplasms	Hodgkin lymphoma	Australia, Belgium, England, Estonia, Italy, Lithuania, Portugal
	lenalidomide (L04AX04)	Revlimid®	neoplasms	multiple myeloma	Australia, Belgium, England, Italy, Korea, Lithuania, Portugal, Sweden
	osimertinib (L01XE35)	Tagrisso®	neoplasms	non-small cell lung cancer	Australia, Belgium, England, Hungary, Korea, Netherlands, Portugal, Sweden
	pembrolizumab (L01XC18)	Keytruda®	neoplasms	non-small cell lung cancer	Australia, Belgium, England, Italy, Korea, Netherlands, Portugal, Sweden
7 countries / 14 countries	adalimumab (L04AB04)	Humira®	diseases of the skin and subcutaneous tissue	hidradenitis suppurativa	Australia, Belgium, England, Italy, Lithuania, Portugal, Sweden
	alirocumab (C10AX14)	Praluent®	endocrine, nutritional and metabolic diseases	hypercholesterolaemia	Belgium, England, Hungary, Italy, Norway, Sweden
	nivolumab (L01XC17)	Opdivo®	neoplasms	renal cell carcinoma in adults	Australia, Belgium, England, Netherlands, Portugal, Sweden
	nivolumab (L01XC17)	Opdivo®	neoplasms	head and neck cancer	Australia, Belgium, England, Netherlands, Portugal, Sweden
	pazopanib (L01XE11)	Votrient®	neoplasms	advanced renal cell carcinoma	Australia, England, Hungary, Italy, Lithuania, Portugal
	sacubitril / valsartan (C09DX04)	Entresto®	diseases of the circulatory system	heart Failure	Australia, Belgium, Hungary, Lithuania, Portugal, Sweden

Notes: The final sample of product/indication pairs for which information was provided in the survey varies between countries. These numbers may therefore be underestimated because of non-response for individual product/indication pairs.

1. Not all countries are listed in this column because in some countries this information is not published and survey respondents reported the existence of the MEA for each product/indication pair in confidence to the OECD Secretariat.

Sources: Authors based on OECD survey, AIFA (2018[17]) for Italy, NEAK (2019[18]) for Hungary and NICE (2019[10]) for England.

Table 2.4. Product/indication pairs subject to performance-based MEAs in at least 2 countries

In 14 countries for which information is available

Active substance (ATC code)	Brand name	Disease area ICD 10 chapter	Indication	Subject to performance-based MEAs in
axicabtagene ciloleucel (L01X)	Yescarta®	neoplasms	B-cell lymphoma	England, Spain
brentuximab vedotin (L01XC12)	Adcetris®	neoplasms	Hodgkin lymphoma	Estonia, Italy (MEA type confidential in Australia, Belgium)
gefitinib (L01XE02)	Iressa®	neoplasms	non-small cell lung cancer	England, Italy (MEA type confidential in Australia)
pazopanib (L01XE11)	Votrient®	neoplasms	advanced renal cell carcinoma	England, Italy (MEA type confidential in Australia)
pasireotide (H01CB05)	Signifor®	endocrine, nutritional and metabolic diseases	Cushing's disease	Italy, Lithuania
tisagenlecleucel (L01)	Kymriah®	neoplasms	B-cell acute lymphoblastic leukaemia	England, Spain (MEA type confidential in the Netherlands)
crizotinib (L01XE16)	Xalkori®	neoplasms	non-small cell lung cancer	England, Italy (MEA type confidential in Australia)
dabrafenib (L01XE23)	Tafinlar®	neoplasms	melanoma	Estonia, Italy

Sources: Authors based on OECD survey, AIFA (2018[17]) for Italy, NEAK (2019[18]) for Hungary and NICE (2019[10]) for England.

2.2. MEAs most commonly have financial objectives

22. There is a wide range of MEAs used across countries as well as a variety of different terms used to refer to such arrangements (for example *deeds*, *special pricing arrangements* or *risk-sharing agreements* in Australia, *conventions* in Belgium or *patient access schemes* in the United Kingdom). Payers use MEAs to achieve a variety of objectives. However, financial objectives, such as managing budget impact and achieving a desired level of cost-effectiveness predominate.

2.2.1. Many countries use MEAs but agreements are predominantly financial

23. The use of MEAs is common in OECD countries. Among a total of 104 product/indication pairs for which information was available from the OECD survey and public sources, MEAs were in place for at least 20 pairs (>20% of the sample) in more than half (8 of 14) countries (Table 2.2). The existence of performance-based MEAs for more than 20 product/indications could only be established for England and Italy. The published literature also indicates that the use of MEAs has increased in Europe over time and financial MEAs are now increasingly common (Ferrario and Kanavos, 2013[8]; Ferrario and Kanavos, 2015[14]; Ferrario et al., 2017[3]; Rotar et al., 2018[16]). Prior survey-based studies of eleven CEE countries that are members of the OECD or the European Union found that the vast majority of MEAs are financial, and there is only a small number of performance-based MEAs (Ferrario et al., 2017[3]; Rotar et al., 2018[16]).

2.2.2. The number of performance-based MEAs is small in most countries

24. Among the 14 countries for which information was available, all countries reported that performance-based MEAs are currently used or were used in the past. However, the number of agreements is relatively small in most countries, with less than 10 product/indication pairs subject to performance-based MEAs in 10 of 14 countries. Sweden reported that none of the 57 product/indication pairs in the initial sample were subject to performance-based MEAs, but that performance-based agreements were used for other products. This confirms findings of prior studies from Europe, suggesting that most countries use financial and performance-based agreements, but that the number of performance-based agreements is small (Ferrario and Kanavos, 2013[8]; Ferrario and Kanavos, 2015[14]; Ferrario et al., 2017[3]; Rotar et al., 2018[16]). England and Italy are notable exceptions.[3] Based on survey responses and public information, at least 27 (26%) of 104 product/indication pairs were subject to performance-based MEAs in England and 22 (21%) in Italy, representing 44% of all product/indication pairs with MEAs in England and 59% in Italy.

25. Interviews conducted by the OECD Secretariat with experts in 12 OECD countries[4] revealed that payers are more cautious with adopting performance-based MEAs because of difficulties with measuring relevant health outcomes and the high administrative burden associated with executing performance-based agreements. Studies by Pauwels et al. (2017[22]) and Ferrario and Kanavos (2015[14]) have also ascribed the preference for financial agreements to these difficulties related to performance-based agreements.

2.2.3. Performance-based MEAs are most often used to manage budget impact or to achieve a desired level of cost-effectiveness

26. The survey and interviews conducted by the OECD indicate that the objectives of performance-based MEAs are often primarily financial; in 11 of 12 countries the objectives of performance-based MEAs are to achieve a desired level of cost-effectiveness and to manage budget impact (see Table 2.5). In seven countries, MEAs are also used to reduce uncertainty around comparative effectiveness. Patient-level payment-by-result (PbR) is the most common design of performance-based MEAs, used in eight countries (see Table 2.6). Under PbR agreements, firms receive payment only for patients who respond to treatment or achieve some other specified health outcome, or firms are required to refund upfront payments (in part or in their entirety) for treatments of patients who turn out not to respond. While these agreements can increase average cost-effectiveness of a medicine by lowering the average price per patient treated, they do not necessarily contribute to reducing uncertainty around the comparative effectiveness of the medicine. In Estonia, for example, routine data are used to determine whether a patient responds to treatment and to trigger payments but data are not aggregated and analysed to study the effectiveness of the treatment in terms of ultimate health outcomes. In seven countries, performance-based MEAs are used to reduce uncertainty around comparative effectiveness (see Table 2.5). Six of these countries use population-based CED, making this the second-most common design of performance-based MEAs (Table 2.6). Some countries also use conditional treatment continuation (CTC), although these are not always based on agreements between payers and firms; they can also be part of general coverage restrictions.

[3] Interviews conducted by the OECD Secretariat and prior studies suggest that performance-based MEAs are also common in Belgium and Australia but confidentiality requirements preclude disclosure of the MEA design for a specific product and indication so it could not be established how many product indication/pairs were subject to performance-based MEAs in these countries.

[4] Australia, Belgium, Czech Republic, Estonia, France, Hungary, Italy, Korea, Lithuania, Netherlands, Sweden, United Kingdom (England only) (see Annex A.).

Table 2.5. Objectives of performance-based MEAs

Based on interviews with experts from 12 OECD countries that use performance-based MEAs

Country	Reduce uncertainty around comparative effectiveness	Reduce uncertainty around cost-effectiveness	Manage budget impact
Australia[1]	Yes	Yes	Yes
Belgium	Yes	Yes	Yes
Czech Republic		Yes	Yes
Estonia		Yes	Yes
France	Yes	Yes	Yes
Hungary		Yes	Yes
Italy	Yes	Yes	Yes
Korea[2]			Yes
Lithuania		Yes	Yes
Netherlands[3]	Yes	Yes	
Sweden	Yes	Yes	Yes
United Kingdom (England only)[4]	Yes	Yes	Yes
Total (count)	***7***	***11***	***11***

Notes: 1. Refers to Managed Entry Scheme (or Managed Access Program) agreements only. These may be, but are not limited to, a form of population-level CED. Information on ad-hoc performance-based MEAs is confidential.
2. Refers to standard types of performance-based MEAs foreseen in Korea. Pharmaceutical companies can propose ad-hoc types of MEAs that address uncertainty in other parameters.
3. Refers to CED schemes in place between 2006 and 2012. Currently no performance-based MEAs are used.
4. Refers to Managed Access Agreements only (31 under the Cancer Drugs Fund and 4 in other disease areas) as this is publically accessible. The objectives of other Patient Access Schemes, including financial and performance-based agreements, are not available in the information published by NICE.

Source: Authors based on OECD expert interviews

27. These findings are in line with prior studies. A 2012 survey by the European Medicines Information Network (EMiNet) among 13 European Union member states and Norway found that 75% of all MEAs aimed to address budget impact, either alone (42%), in combination with addressing cost-effectiveness (16%), by managing utilisation (15%) or addressing utilisation and budget impact (2%) (Ferrario and Kanavos, 2013[8]). Similarly, the most important goal of MEAs in CEE countries is to limit budget impact, with most agreements being financial (Ferrario et al., 2017[3]; Rotar et al., 2018[16]). A survey of senior decision makers at HTA agencies and/or payers in eight OECD countries[5] found that MEAs are one response to increasing prices and budget impact of new medicines and the use of fast-track approvals, which increase uncertainty regarding the efficacy of new products for payers (Leopold, Morgan and Wagner, 2017[23]). Toumi et al. (2017[24]) argued that providing rapid patient access to novel treatments—possibly in response to pressure by the public or specific interest groups—while at the same time managing costs may be a key motivation for health care payers to adopt performance-based MEAs, in particular payment-by-result.

[5] Australia, Austria, Canada, the Netherlands, New Zealand, Sweden, the United Kingdom (Scotland) and the United States.

Table 2.6. Types of performance-based MEAs

Based on interviews with experts from 12 OECD countries that use performance-based MEAs

Country	MEA Level and Design				
	Patient-level			Population-level	
	PbR	CED	CTC	PbR	CED
Australia[1]					Yes
Belgium[2]	Yes			Yes	Yes
Czech Republic	Yes				
Estonia	Yes		Yes		
France	Yes				Yes
Hungary	Yes		Yes		
Italy	Yes				
Korea[3]		Yes	Yes		
Lithuania	Yes		Yes		
Netherlands[4]					Yes
Sweden	Yes		Yes		Yes
United Kingdom (England only)[5]					Yes
Total (count)	***8***	***1***	***5***	***1***	***6***

Notes: 1. Refers to Managed Entry Scheme (or Managed Access Program) agreements only. These may be, but are not limited to, a form of population-level CED. Information on ad-hoc performance-based MEAs is confidential.
2. Most performance-based MEAs concluded in Belgium are population-level CED. However, some concluded payment-by-results.
3. Refers to standard types of performance-based MEAs foreseen in Korea. Pharmaceutical companies can propose ad-hoc types of MEAs that address uncertainty in other parameters.
4. Refers to CED schemes in place between 2006 and 2012. Currently no performance-based MEAs are used.
5. Refers to Managed Access Agreements only (31 under the Cancer Drugs Fund and 4 in other disease areas) as this is publically accessible. The designs of other Patient Access Schemes are not available in the information published by NICE.

Source: Authors based on OECD expert interviews

2.2.4. MEAs are mainly used for therapies in oncology and rare diseases

28. Available information suggest that MEAs are common for products that treat cancer and rare diseases. In the final sample of 104 unique product/indication pairs in the OECD survey and across the 14 countries for which information was available, there was a total of 359 instances of MEAs for these product/indication pairs. Of these, 203 (57%) were for indications in the WHO International Classification of Diseases (ICD) Chapter for cancer, followed by diseases of the eye (n=33, 9%) and the skin (n=28, 8%) (Figure 2.1). Confidentiality of information on MEA types in a number of countries makes it more difficult to analyse the indications for which performance-based MEAs are in place. However, of the 76 known instances of performance-based MEAs in the final sample of products/indications across 9 countries,[6] two-thirds were related to cancer (n=51, 67%), followed by endocrine, nutritional and metabolic diseases (n=6, 8%) and diseases of the eye and adnexa (n=5, 7%).

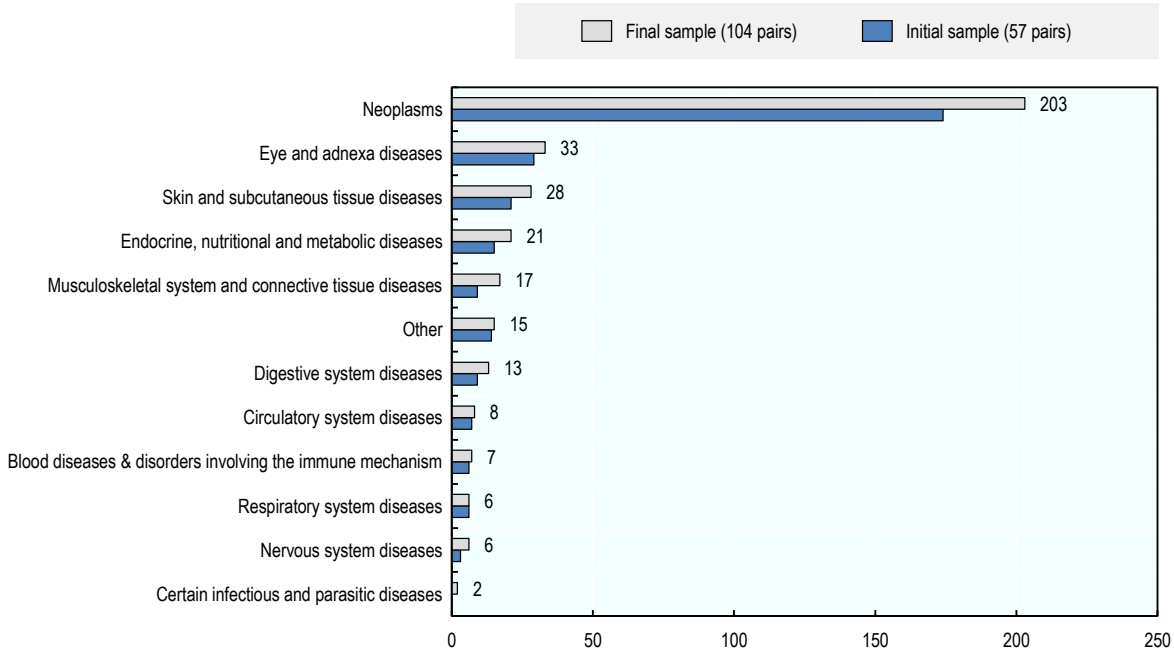
29. Studies in the published literature suggest that MEAs are common for high-cost therapies, in particular medicines to treat cancer and rare diseases, although MEAs were also found in relation to treatments for diabetes and in neurology, rheumatology and endocrinology (Kanavos et al., 2017[2]; Ferrario et al., 2017[3]; Carlson, Chen and Garrison, 2017[13]; Gerkens et al., 2017[7]; Toumi et al., 2017[24]; Lu et al., 2015[15]; Toumi et al., 2017[24]; Vitry and Roughead, 2014[25]). In the United States, when MEAs for medical devices are also taken into account, cardiology is another therapeutic area in which MEAs play

[6] Excluding Australia, Belgium and the Netherlands, where information on the type of MEA is confidential, and Norway and Sweden, where no product/indication pair in the sample was subject to performance-based MEAs.

a role (see Box 2.1). Performance-based MEAs may be more common for products with orphan indications, where marketing authorisation may allow treatments to come to market with a greater degree of uncertainty surrounding their effectiveness (Campillo-Artero, Del Llano and Poveda, 2012[26]; TLV, 2017[27]). The review by Morel et al. (2013[28]), which identified 42 MEAs for 26 orphan drugs adopted in Belgium, Italy, the Netherlands, Sweden and the United Kingdom, found that 55% of these MEAs were performance-based. Antineoplastic agents were also the therapeutic class with the highest number of MEAs.

Figure 2.1. Number of product/indication pairs MEAs by ICD-10 Chapter

In 14 countries for which information is available, in the initial sample (57 product/indication pairs) and final sample (104 pairs)



Source: Authors based on OECD Survey and WHO ICD-10 Version:2016 (WHO, 2016[29]).

2.3. Performance-based MEAs use a wide variety of outcome measures and data sources

30. Contents of performance-based MEAs are often confidential, including information on health outcome measures used to evaluate product performance (see Part II.). It is therefore not possible to provide a comprehensive overview of measures used in the MEAs identified through the OECD survey. A prior review by Toumi et al. (2017[24]) examined specifically the endpoints used to measure health outcomes in 87 performance-based MEAs for which such information was available. The review found that 33 of these used surrogate endpoints and 54 used patient-relevant endpoints[7]. A majority of payment-by-

[7] Patient-relevant endpoints were defined by Toumi et al. (2017[24]) as characteristics or variables that reflect how a patient feels or functions, or how long a patient survives. They included overall survival, mortality, morbidity, population of patients to whom a drug is prescribed (size or clinical characteristics), number of treatment discontinuations, delay in switch to a different drug, number of hospitalizations or emergency department visits, side effects, dosage, treatment

result agreements (85%) used surrogate endpoints while 92% of CED schemes used patient-relevant endpoints.

31. Expert interviews suggest that, in some countries that use payment-by-result, no data on ultimate health outcomes are collected or analysed to execute these agreements. In the Czech Republic, Italy and Sweden, for example, patient response to treatment is sometimes inferred from prescribing data. If treatment continues beyond a certain duration it is assumed that the patient responds and that the treatment is successful to trigger payment, while discontinuation is interpreted as non-response. Such data are not informative of the *true* underlying performance of the medicine in terms of health outcomes.

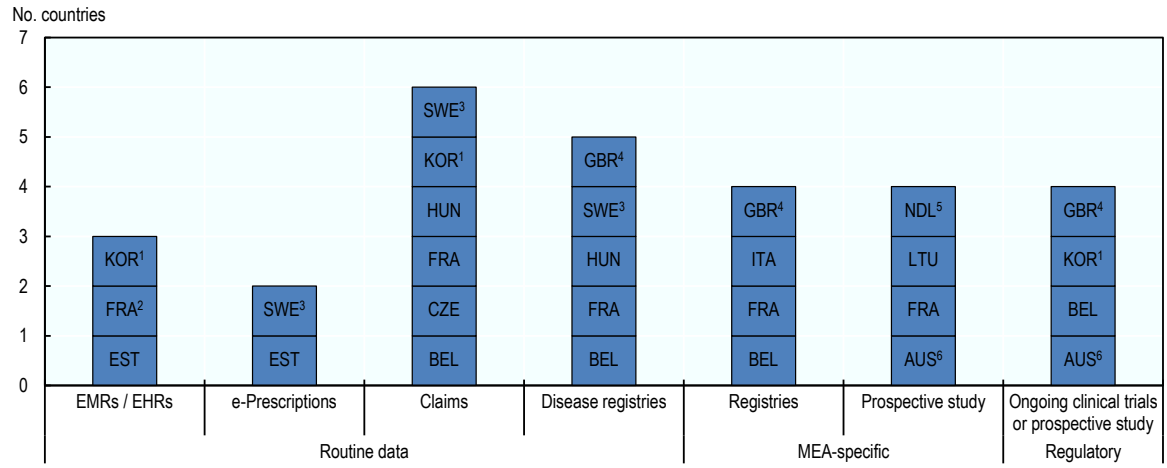
32. Various types of data sources are used for the execution of performance-based MEAs, including routinely collected data, ongoing clinical trials and data collected specifically for the execution of the agreements. Based on interviews with experts from 12 countries that use performance-based MEAs, insurance claims data are used in six countries, making it the most frequently used type of data sources, followed by data from existing disease registries, used in five countries (Figure 2.2). Registries and prospective studies established specifically for executing the MEA as well as ongoing clinical trials that primarily collect data for regulatory purposes (e.g. post-marketing requirements following initial marketing authorisation) are used in 4 of 12 countries. Data from electronic medical or health records and e-prescription data are used less frequently (3 of 12 countries).

33. Because routine data are commonly used to execute performance-based MEAs, payers or providers are commonly the custodians of the relevant datasets. This is the case in 10 of 12 countries surveyed. However, in seven of 12 countries pharmaceutical firms are also data custodians, especially in countries where prospective studies specific to the MEA or ongoing regulatory trials serve as data sources (Table 2.7).

duration, quality of life, long-term treatment outcomes, comparative compliance, weight gain or loss and other measures of comparative effectiveness (i.e. additional trials in which the strategy is compared to alternative therapeutic options).

Figure 2.2. Data sources used for the execution of performance-based MEAs

Based on interviews with experts from 12 OECD countries that use performance-based MEAs



Notes: EMRs… electronic medical records, EHRs… electronic health records, Pb MEA… performance-based managed entry agreement, CED… coverage with evidence development.

1. Refers to data sources used for standard types of Pb MEAs in Korea. Pharmaceutical companies can propose ad-hoc types of MEAs that address uncertainty in other parameters.
2. Refers to a database of hospital discharge summaries. EHRs are not used in France.
3. In Sweden, the Social Board of health and welfare has a register of all prescriptions pharmaceuticals that are dispensed at pharmacies. This data is the main data source for Pb MEAs and can include e-prescriptions and paper-prescriptions and the data is wider than insurance claims.
4. Information for England refers to Managed Access Agreements only (31 through Cancer Drugs Fund and 4 for other disease areas) as this is publically accessible. The data sources used by other Patient Access Schemes are not available in the information published by NICE.
5. Information for the Netherlands refers to CED schemes in place between 2006 and 2012. Currently no performance-based agreements are used
6. Information in Australia refers to Managed Entry Scheme (or Managed Access Program) agreements only. These may be, but not limited to, a form of population-level CED. Information on ad-hoc Pb MEAs is confidential.

Source: Authors based on OECD expert interviews

Table 2.7. Custodians of data used for the execution of performance-based MEAs

Based on interviews with experts from 12 OECD countries that use performance-based MEAs

Country	Payers / providers	Pharmaceutical firms
Australia[1]		Yes
Belgium	Yes	Yes
Czech Republic	Yes	
Estonia	Yes	
France	Yes	Yes
Hungary	Yes	
Italy	Yes	
Korea[2]	Yes	Yes
Lithuania	Yes	Yes
Netherlands[3]		Yes
Sweden	Yes	
UK (England)[4]	Yes	Yes
Total (count)	***10***	***7***

Notes: There is only one custodian per dataset. In countries where payers/providers and pharmaceutical firms are data custodians, more than one type of dataset are used, either for the same or for different agreements.
1. Refers to Managed Entry Scheme (or Managed Access Program) agreements only. These may be, but are not limited to, a form of population-level CED. Information on ad-hoc performance-based MEAs is confidential.
2. Refers to standard types of performance-based MEAs foreseen in Korea. Pharmaceutical companies can propose ad-hoc types of MEAs that address uncertainty in other parameters.
3. Refers to CED schemes in place between 2006 and 2012. Currently no performance-based MEAs are used.
4. Refers to Managed Access Agreements only (31 under the Cancer Drugs Fund and 4 in other disease areas) as this is publically accessible. The data custodians in other Patient Access Schemes, including financial and performance-based agreements, are not available in the information published by NICE.

Source: Authors based on OECD expert interviews.

3. The limited experience with performance-based MEAs is mixed

34. This section summarises country experience with performance-based MEAs. Little information is available on how successful payers have so far been in using performance-based MEAs to meet their stated objectives. This is because few countries have formally evaluated their experience with performance-based MEAs. Also, as discussed in Part II., key information on performance-based MEAs is often confidential or not readily available to third parties, including information on the health outcome measures used, details on the analyses of product performance, and the decisions made as a result of these analyses. This makes it very difficult for third parties to evaluate whether MEAs achieve their objectives. The discussion below is based on information available from public sources and expert interviews conducted by the OECD Secretariat (see Annex A.). Short case studies illustrate the experiences in Australia, England, Estonia and the Netherlands, where performance-based MEAs are common or were common in the past.

3.1. Few countries have formally evaluated performance-based MEAs and available evidence is mixed

35. Among the 12 countries interviewed, independent evaluations by third parties have been only been conducted in two countries: in Belgium, by the Belgian Health Care Knowledge Centre (KCE) (published in Gerkens et al. (2017[7])), and in Sweden, by two local universities in 2007. Experts from Australia and Lithuania reported that evaluations are done internally by the payer or government department responsible for performance-based MEAs, but results of these evaluations are not published.

3.1.1. Performance-based MEAs have so far made a small contribution to reducing uncertainty around product performance

36. The evaluation of the Belgian experience by Gerkens et al. (2017[7]) concluded that performance-based MEAs did not reduce uncertainty around the performance of the products in terms of comparative and cost-effectiveness. It also concluded that, while MEAs provided the short-term advantage of coverage of new medicines at lower confidential prices, the confidentiality of financial mechanisms in the agreements and the non-publication of results of data analyses were detrimental to sound evaluation of the effect of agreements on uncertainty around product performance and health care budgets.

37. In Sweden, the 2007 evaluation found that CED agreements that required firms to evaluate the effectiveness of medicines in clinical practice resulted in studies that were mainly of poor quality and were not able to answer the research questions.[8] This led to change in the design of performance-based MEAs, towards monitoring of the appropriateness of use and payment-by-result based on utilisation data.

[8] The Swedish Dental and Pharmaceutical Benefits Agency (TLV) commissioned researchers at the Karolinska Institute and the University of Lund to evaluate the methodological quality of 11 studies submitted to TLV as part of CED agreements. Both evaluations concluded that the majority of studies were of low methodological quality and one study concluded that 8 studies did not meet the minimum standards to inform health technology assessment (HTA).

38. Although payers in Australia and the Netherlands have not had performance-based MEAs formally evaluated, peer-reviewed articles have been published. Their findings are summarised below.

Case study: Coverage with Evidence Development in Australia

39. A comprehensive review of documents published by the Pharmaceutical Benefits Advisory Committee (PBAC) between January 2010 and January 2017 aimed to characterise the Australian CED scheme experience (Tuffaha and Scuffham, 2018[30]). It found that CED was considered for 11 medicines (of 930 submissions for approximately 350 indications reviewed). Of these, 75% were oncology medicines, with the main uncertainty being around overall survival. Manufacturers made over half of the proposals, with PBAC proposing the remaining schemes. Most proposals were considered after previous rejection or deferral of coverage. Despite high levels of uncertainty, CED schemes were not established for 8 of 11 medicines (73%). Of these 8, 6 were listed for coverage after manufacturers reduced their prices. Three CED schemes were implemented, with required data submitted within the timeframe for submission of evidence set by the PBAC. The authors noted that it was difficult to evaluate the success of the Australian CED experience. Updated evidence was provided and the financial risk to the payer reduced. However, in the absence of quantitative assessment of decision uncertainty, the authors stated that it was unclear whether the collected evidence sufficiently reduced uncertainty around outcomes (e.g. overall survival) or whether it provided better value for money over alternative funding arrangements.

40. Kim et al. (2018[31]) reviewed the effectiveness of a single CED agreement in achieving its stated objectives. The MEA aimed to address uncertainty around the magnitude of clinical benefit of ipilimumab in treating metastatic melanoma, resulting from very small patient numbers in the pivotal regulatory trials used as the basis for modelling survival curves at the end of the time horizon. Coverage of this medicine for the indication was conditional on assessment of two-year overall survival in patients who received the medicine in its first year of routine clinical practice (Kim et al., 2018[31]). Of the 910 patients who received ipilimumab, two-year overall survival rate was estimated at 34.2%, which exceeded the 23.5% observed in the key ipilimumab registration trial. While this result supported the cost-effectiveness claim by the firm, the authors nevertheless identified a number of limitations to the success of the CED scheme. In general, patients who received ipilimumab in routine practice were more severe cases than in the trial and it was difficult to assess the impact of confounders, such as changing practice patterns and availability of other therapies. Large amounts of data on outcomes was missing, with 17.5% of patients having an unconfirmed outcome at the end of the two years and 6.3% of patients lost to follow-up. While no detail on costs was provided by the authors, the setup of the scheme was resource intensive and costly. In light of these limitations, the authors deemed that such arrangements can be successful but drew no definitive conclusion on the success of the specific agreement reviewed.

Case study: Coverage with Evidence Development in the Netherlands

41. The Netherlands were an early adopter of MEAs in Europe (Ferrario and Kanavos, 2015[14]). Between 2006 and 2012, the Dutch National Healthcare Authority implemented *conditional financing* for expensive hospital medicines in the form of a four-year coverage with evidence development (CED) framework (Makady et al., 2018[32]). Medicines were chosen if they met three criteria: “a budget impact above EUR 2.5 million / year, a proven additional therapeutic value in comparison to available comparator treatments, and a well-defined proposal for outcomes research to address uncertainties regarding appropriate use and cost-effectiveness in routine practice” (Makady et al., 2018, p. 268[32]). Here, outcomes research referred to the gathering of evidence on appropriate use and cost-effectiveness in routine practice. Coverage of the medicines was reassessed after four years. Inclusion of medicines into the conditional financing scheme was discontinued in 2012 and there are currently no performance-based MEAs in the Netherlands.

42. Three studies that evaluated the conditional financing scheme were published in 2018 and 2019. They generally concluded that the scheme provided accelerated access to medicines but that additional evidence generated in the scheme poorly addressed uncertainties.

43. Makady et al. (2018[32]) concluded that conditional financing with CED provided accelerated access to medicines, but the authors identified weaknesses in the design and implementation of the scheme. The study evaluated the procedural, methodological, and decision-making aspects of the scheme. Between 2006 and 2012, 25 medicines were included in the scheme. At the time of the study by end of December 2017, only 12 medicines had undergone the full HTA reassessment, 5 were undergoing reassessments and 8 had reassessments pending. Only one reassessment had been completed within the intended four-year period. Evidence generated was insufficient to reach grounded conclusions on a third of all research questions and half of the re-assessed medicines required yet further evidence generation to address remaining uncertainties.

44. For 5 of 12 medicines that had been reassessed, additional research under the conditional financing scheme generated insufficient evidence to conclude on cost-effectiveness and/or appropriate use. Discontinuation of coverage was recommended for two of these; in both cases, conclusions on appropriate use in clinical practice could not be reached and incremental cost-effectiveness ratios (ICERs) presented were not substantiated. One of these two medicines remains in the basic healthcare package per March 2019 (Zorginstituut Nederland, 2019[33]). Continuation of coverage was advised for 3/5 medicines. Additional conditions for evidence generation to address remaining uncertainties were put in place for 2 of the 3. In both cases, the evidence submitted did not substantiate the ICERs. No conclusions were reached on appropriate use for the medicine that did not require additional evidence, pemetrexed (Altima®), but cost-effectiveness was deemed acceptable in light of nearing patent expiry. The first generic of pemetrexed was authorised by the EMA in 2015 (European Medicines Agency, 2015[34]). Per March 2019, the original brand of this medicine (Altima®) remained in the basic healthcare package, without introduction of generic products (Zorginstituut Nederland, 2019[33]).

45. For 7 of 12 medicines, evidence was sufficient to conclude on appropriate use and cost-effectiveness, resulting in a recommendation to maintain coverage. ICERs of 3 medicines were below the threshold of EUR 80 000 per quality-adjusted life year (QALY). For the 4 others, continuation of coverage was recommended despite ICERs above the threshold and further evidence generation was required for all 4 of them.

46. Pouwels et al. (2019[35]) also examined whether conditional financing successfully addressed uncertainties in practice. The study assessed whether uncertainties were systematically identified prior to engaging in evidence collection and whether the research design addressed these uncertainties. Authors investigated the uncertainties identified in the initial HTA assessment; how these uncertainties were integrated into the assessments; whether research plans aimed to address the uncertainties; and issues and solutions around managing uncertainty in CED research. Three CED agreements were analysed and 16 stakeholders interviewed. Only 40% of uncertainties identified during initial assessments were included in the CED research plans. Stakeholders concluded that the research did not address the identified uncertainties.

47. Makady et al (2019[36]) published a systematic evaluation of 30 public and private stakeholder perspectives on implementation of the conditional financing scheme. Stakeholders were asked about the perceived aims, functioning, impacts, conclusions, and future perspectives of the conditional financing scheme. Stakeholder perspectives varied with regard to the aims of the scheme, with 55% indicating that the scheme aimed to balance early access with evidence generation. Stakeholders highlighted weaknesses such as the 4-year time frame, the methodological quality of the studies, and external political influence on advice at the reassessment stage. Perceived positive aspects of the scheme included stakeholder and public awareness of high drug prices and its contribution to the sustainability of the health care system. Half of the stakeholders believed that the scheme had not achieved its aims, with the other

half believing it had partially achieved them. Most stakeholders indicated that the scheme should be replaced or be improved and reintroduced. Options for replacement included adaptive pathways, adaptive pricing or the use of electronic health record for data generation. Suggestions for improvement centred on the aforementioned short comings. A small percentage of stakeholders (7%) stated that CEDs should be discontinued as they do not work in practice.

3.1.2. Experts also report varying experiences

48. In the absence of formal evaluations in many countries, experts interviewed have mixed views as to whether such agreements are effective means of achieving their stated objectives. In general, performance-based MEAs are considered successful in accelerating coverage decisions, and therefore patient access to new medicines, in the face of uncertainty. Specifically, payment-by-result (PbR) agreements are considered an effective means of managing budget impact by limiting payment to patients who respond to treatment. While coverage with evidence development (CED) schemes also allow for faster coverage decisions despite uncertainty around comparative effectiveness or cost-effectiveness, experts question their ability to reduce such uncertainty.

49. The main concern raised during interviews was that performance-based MEAs have so far not been a very effective means of reducing uncertainty around product performance. There are difficulties with interpreting data and making appropriate coverage decisions as a result of data analyses. This is the result of a lack of data on appropriate health outcomes or other relevant parameters of product performance, poor data quality or methodological issues in the studies conducted.

50. The administrative burden of executing performance-based MEAs was another concern raised frequently during the interviews. This may be a particular issue for PbR agreements, which frequently use routine data sources to track patient response and to trigger payments (or refunds) (see Section 2.2). The burden can be even higher where registries are specifically set up for the purpose of executing the MEAs, such as in Italy. Such arrangements may require health professionals to collect additional data and payers or providers to devote significant resources to data analyses.

51. Experts also pointed out that the purpose of PbR to manage budget impact could also be achieved through simple price reductions or financial MEAs, such as budget caps, which would remove the administrative burden of tracking patient response. In the case of CED agreements, it is more common for pharmaceutical firms to take on the task of data collection and analyses for resubmission of dossiers to payers or HTA agencies to support their claims of product effectiveness or cost-effectiveness, limiting the administrative burden for payers.

52. The high level of confidentiality was another concern raised in the interviews. Most experts agree that information related to product performance should not be confidential and that only commercial information, and in particular prices, should be protected from disclosure as necessary. Not only does confidentiality preclude the sharing of information with third parties but it can also make coverage decisions for payers more difficult: for instance, when estimates of effectiveness or cost-effectiveness or prices of a comparator or complementing therapy cannot be disclosed in the evaluation process to determine coverage of a given product. At the same time, however, some experts raised concerns that increasing transparency of future MEAs might make negotiations with firms more difficult and be counterproductive to payers' primary goal of providing access to new medicines. Confidentiality is discussed further in Part II.

53. Three experts interviewed by the OECD Secretariat suggested that performance-based MEAs were a response to pressure by the public and the industry to cover new and high-priced medicines. Rather than implementing these agreements as a result of a strategic choice, payers had little choice but to accept agreements offered by firms in order to make high-priced products affordable while firms use such agreements to make unjustified prices acceptable.

54. Finally, a concern was raised that PbR could lead to risk selection in the patient population treated. If firms are only paid for treatments that result in a positive outcome, there is a financial incentive, and therefore a risk, that firms could encourage providers to only use the product in selected patient sub-groups in which treatment success is more likely. However, this risk was discussed hypothetically and experts interviewed did not point out actual instance of where such patient selection occurred in the past.

3.1.3. Findings of recent studies and OECD expert interviews are consistent with the prior literature

55. Findings of recent evaluations of performance-based MEAs in Australia, Belgium and the Netherlands are largely consistent with survey-based studies and literature reviews published since 2010. Confidentiality of information, not only related to prices and commercial clauses, but also related to the existence of agreements and their content in terms of product performance was identified as a barrier to objective evaluation by a number of prior studies (see, among other studies, (Ferrario et al., 2017[3]; Gerkens et al., 2017[7]; Kanavos et al., 2017[2]; Pauwels et al., 2017[22]; Rotar et al., 2018[16])). Studies have been largely based on reviews of the published literature, reports published by governments or government agencies, and expert opinion elicited through surveys. Most of them acknowledge that their findings are therefore necessarily incomplete.

56. Prior studies also identified the following general weaknesses of MEAs and related challenges (Gerkens et al., 2017[7]; Kanavos et al., 2017[2]; Toumi et al., 2017[24]; Pauwels et al., 2017[22]; Klemp, Frønsdal and Facey, 2011[4]; Stafinski, McCabe and Menon, 2010[1]):

- Significant administrative burden and costs for providers, firms or payers involved in executing the agreement and collecting and/or analysing data.
- Difficulties for payers in reducing prices, recouping payments already made to firms or de-listing treatments from coverage if the data analysed under MEAs show that the treatment is less effective than expected.
- Difficulties in obtaining data that are informative about relevant health outcomes and, particularly for oncology treatments, identifying easily-measured and validated surrogate endpoints or biomarkers.
- Uncertainty for firms as to the financial returns from the additional research, and the potential impact that the new evidence could have on future prices or revenues, can create disincentives for additional data collection once an agreement has been put in place or when conditional coverage has been granted.

57. Previous criticisms of the use of performance-based MEAs have frequently related to the costs of establishing and maintaining data infrastructure (Garrison et al., 2013[5]; Klemp, Frønsdal and Facey, 2011[4]; Gonçalves et al., 2018[37]; Gonçalves et al., 2018[37]). For example, Italy has longstanding experience with performance-based MEAs that rely on registries specifically established for data collection, which represents a significant administrative burden. However, data in these registries cannot be accessed by third parties to assess effectiveness of medicines in routine practice (Toumi et al., 2017[24]). A recent systematic literature review of the challenges related to CED agreements for medical devices, many of which are equally relevant for medicines, is available in Reckers-Droog (forthcoming[38]).

58. Some performance-based MEAs may also require that mature HTA systems and reliable IT infrastructure are in place for recording health outcomes in routine and analysing data on the performance of products (Rotar et al., 2018[16]; Leopold, Morgan and Wagner, 2017[23]) – this is not yet the case in all countries.

3.2. Some countries have changed their policies on performance-based MEAs following initial experience

59. Some countries that were early adopters of performance-based MEAs have recently changed their policies on such agreements while other countries maintained their practices. In particular countries that faced difficulties in executing CED agreements, such as the Netherlands and Sweden, have either discontinued such agreements altogether or moved gradually towards other alternatives. Payment-by-result (PbR) agreements, on the other hand, continue to be used relatively widely.

3.2.1. Coverage with Evidence Development schemes have evolved or been discontinued

60. In the Netherlands, the *conditional financing* CED scheme was not considered successful at reducing uncertainty around product performance to inform coverage decisions and was discontinued. At the time of writing of this report, the government was considering the introduction of a policy of *conditional approval* of coverage, which, however, does not take the form of a MEA because it is not based on a contract between a payer and the firm. Instead, if this scheme is adopted, products subject to such conditional approval would stay outside the basic package of covered products for a period of 4-7 years while the Ministry of Health funds additional research and treatment for patients enrolled in the studies. Studies would be based on a research protocol put forward by a scientific assessment body and approved by all stakeholders. The process and research results would be fully public, while only prices would be permitted to stay confidential. Similar to prior CED schemes, an HTA reassessment would be conducted after the period of conditional approval, which can recommend exclusion from coverage if evidence is insufficient or the product is shown not to be cost-effective.

61. Similarly, the Swedish Dental and Pharmaceutical Benefits Agency (TLV) has gradually moved towards a policy of recommending temporary coverage and away from CED agreements that did not prove informative. In this approach, products are typically covered for a period of 2 years conditional on the firms' providing of additional evidence to reduce uncertainties. The product is then re-evaluated, which can lead to making coverage permanent, removal of coverage or price adjustments. Financial MEAs may be in place during this period but these are unrelated to the generation of additional evidence. So far, temporary coverage has never led to removal of coverage but only to price adjustments.

62. Temporary or conditional restrictions to coverage that are not part of an agreement between payers and firms are also used in the Czech Republic and France.

63. In England, performance-based MEAs among the *Patient Access Schemes (PAS)* published by NICE have become less common over time. In parallel, a new CED scheme has been introduced in 2016 under the reformed Cancer Drugs Fund (CDF). Further details are provided below.

Case study: Coverage with Evidence development under the new Cancer Drugs Fund in England

A case study, based on document review, of a small sample of MEAs in England was undertaken to evaluate whether they can achieve or have achieved their stated objectives. England was chosen as a country example as some information on MEAs is publically accessible. The document review aimed to

- Summarise key information on marketing authorisation by the European Medicines Agency (EMA), including the evidence base and the main remaining uncertainties;
- Describe the nature of performance-based MEAs concluded between the marketing authorisation holder and NHS England; and

- Compare the evidence base and uncertainties at the time of marketing authorisation with uncertainties underlying the performance-based MEA and evidence to be generated under the MEA.

Background to performance-based agreements and the Cancer Drugs Fund

64. MEAs take two main forms in England, which are locally referred to as *Patient Access Schemes (PAS)* and *Managed Access Agreements (MAA)*. The vast majority of PAS are financial, but some *complex* PAS take the form of payment-by-result (PbR). MAAs, on the other hand, are a form of population-level CED.

- A list of all technologies recommended for use in the NHS with a PAS and other commercial arrangements is published by NICE (2019[10]). As of 1 September 2019, approximately 190 products had one of these agreements (including ongoing and closed agreements, but excluding MAAs). The fact that a simple PAS (financial) is in place is published for the relevant product/indications, although the level of discount is not published. Information on the type of complex PAS is also public (e.g. cap, rebate at a point in time if no response, etc.). Commercial arrangements are similar to complex PAS but have a higher level of confidentiality. In general, information related to performance measures (such as outcome measures, data sources used, and follow-up time) are confidential in PAS, as well as raw data collected. Information on the results of the analyses and decisions based on the results are in the public domain. There may be some instances where the type of performance-based agreement is also confidential.
- Managed Access Agreements comprise two separate documents: Data Collection Arrangements, which describe planned data collection and analyses to address the uncertainties identified in the initial HTA by NICE; and Commercial Access Agreements, which define prices and commercial conditions under which the NHS purchases the medicine during the term of the MAA. While the former are public, the latter are confidential. As of 1 September 2019, there were 35 product/indication pairs with MAAs, 31 of which were for oncology medicines funded through the Cancer Drugs Fund (CDF) described below and four in other disease areas.

65. Most MAAs are used under the reformed CDF, a ring-fenced source of funding for cancer medicines that aims to provide patient access to promising new treatments while further evidence is collected to address residual uncertainty regarding clinical effectiveness (NHS England Cancer Drugs Fund Team, 2016[39]). It was initially established in 2011 to fund cancer medicines not recommended by NICE for use in the NHS, but, following significant budget overruns, was reformed into a CED scheme in 2016. A product/indication pair is referred to the CDF by NICE and a MAA is signed with the firm if the clinical effectiveness and cost effectiveness of a medicine for an indication is plausible but uncertain, and NICE can therefore not recommend it for routine use within the NHS based on the evidence available, and if it is feasible to collect data to address these clinical uncertainties. Among the 57 product/indication pairs in the initial sample of the OECD Expert Survey (see Annex A.), 12 had MAAs with temporary coverage under the CDF.

66. At the end of the agreement, NICE reappraises the medicine for clinical and cost-effectiveness. If sufficient evidence has been generated to consider the medicine clinically and cost-effective for the indication, NICE may make a positive recommendation and the medicine exits the CDF to be made available for routine use in the NHS for the relevant indication. If there is insufficient evidence or the medicine is considered not to be clinically and cost effective in this indication, NICE may make a negative recommendation. In this case, the medicine may be removed from the CDF and no longer be available in the NHS. The firm is, however, required to continue providing the medicine at its own cost until the prescribing physician deems it appropriate to discontinue treatment. Per March 2019, only two product/indication pairs have been removed from (i.e. exited) the CDF, both of which received positive recommendations by NICE. After an agreement has been completed and a resulting coverage decision has been made, the MAA is no longer publically available; only information reflected in the NICE Technology Appraisal Guidance remains public.

Analysis of 25 product/indication pairs in the Cancer Drugs Fund in England

67. At the time of analysis (March 2019), there were 25 product/indication pairs with active or past agreements through the CDF after it was reformed in 2016. Analysis was therefore performed on those 25 product/indication pairs with MAAs across 16 different active substances, which included the 12 pairs from the initial OECD survey sample as well as 13 additional pairs in the CDF with MAAs published prior to 31 March 2019. Fourteen of the pairs were for solid tumour indications, with 11 for the treatment of haematological malignancies. A short summary from the analysis is presented below. Box 3.1 provides further details on brentuximab vedotin (Adcetris®) for CD30+ Hodgkin Lymphoma, a medicine that recently exited the CDF in England and is subject to a payment-by-result agreement in Estonia.

68. The marketing authorisations for the 25 product/indication pairs were mainly based on single pivotal trials (with more than half being single-arm phase II trials with no comparators) using surrogate or intermediate endpoints alone as primary outcomes and final clinical endpoints reserved as secondary outcomes. In contrast, MAAs largely used a combination of ongoing clinical trials (often the same used to fulfil post-marketing requirements by EMA) and routine data as data sources, focusing on final clinical endpoints. For the MAAs using ongoing trials, over half were based on RCTs alone, 32% on single-arm studies, and 14% using a combination of both. All of the RCTs were phase III studies with an active or placebo comparator, while all but two single-arm studies were phase II. Routine data for MAAs included data from Public Health England population-wide cancer datasets (such as the Systemic Anti-cancer Therapy database and NHS England's Blueteq database).[9] The uncertainties at marketing authorisation, post-marketing evidence requirements, and uncertainties addressed by the agreements were compared across all product/indication pairs. The magnitude of long-term clinical benefit, such as overall survival, was the most common uncertainty identified in all instances. Other uncertainties highlighted at marketing authorisation were similar to those addressed in the agreements: comparative effectiveness, generalisability to target population, and the relationship between biomarker expression and final clinical endpoints. In addition, the agreements aimed to address concerns around duration of therapy and subsequent treatment and thus requested collection of data in routine clinical practice.

69. Annex B presents detailed information from the analysis, including a summary of the marketing authorisation, HTA results, and MAAs in the sample, as well as further details on individual product/indication pairs with CDF agreements.

Preliminary conclusion on CED within the Cancer Drugs Fund

70. With only two agreements completed at the time of this review, it was not possible to assess the extent to which CED agreements may be considered successful in meeting their stated objectives within specified agreement timeframes. However, the English CDF has the characteristics of a solid CED framework. There are clear criteria for entry, a clearly limited period of temporary coverage linked to requirements for evidence generation, transparency of the non-commercial parts of the agreements, it is embedded within the HTA process, and there is a clearly defined exit process. It only includes product/indication pairs that are plausibly cost-effective and for which it is feasible to address clinical uncertainties through further data collection; reassessment occurs within a maximum of two years; the process is embedded within NICE appraisal process; there are mechanisms for removing coverage for products not recommended by NIC upon re-appraissal (Aggarwal et al., 2017[40]; NICE, n.d.[41]).

[9] The Systemic Anti-Cancer Therapy database is a national registry that includes mandatory collection of systemic anti-cancer activity from all NHS England chemotherapy providers (see http://www.ncin.org.uk/collecting_and_using_data/data_collection/chemotherapy). NHS England's Blueteq database is the standard electronic contractual prior approval system, which covers a range of high cost drugs (see http://www.blueteq.com/).

3.2.2. Payment-by-result agreements continue to be used more widely but do not always generate evidence of product performance

71. In contrast to many early examples of coverage with evidence development (CED) schemes, payment-by-result (PbR) agreements continue to be used in many countries, notably in Estonia, Italy and Sweden but also in Belgium, France, Hungary and Portugal. However, interviews with experts from Estonia, Italy and Sweden indicate that data analyses for the execution of these agreements do not necessarily generate evidence on product performance.

72. Estonia and Italy continue to use patient-level payment-by-result agreements whereby firms are only paid for medicines administered to patients who respond to the treatment. Firms may be paid upfront and make partial or complete refunds for non-responders or only receive payment for responders after response has been established. The primary purpose of these agreements in both, Italy and Estonia, is financial – to manage budget impact and reduce the average price by not paying for non-response, rather than to reduce uncertainty around product performance. While specific outcome measures used in the agreements are confidential, expert interviews suggest that data on health outcomes are not always collected or analysed. Patient response may be inferred from treatment duration, i.e. response is assumed if a patient still receives treatment X after Y weeks. Where data on health outcomes are collected, they are not always aggregated or analysed beyond patient-level tracking for payment to study product performance. Further details on Estonia and Italy are provided below.

Case study: Payment-by-result in Estonia and Italy

73. Italy has long-standing experience with managed entry agreements, with the first performance-based MEA adopted in 2006 and national monitoring registries in place since 2005 (Garattini and Casadei, 2011[42]; Montilla et al., 2015[43]). The focus is on high-cost medicines with uncertainty as to safety, appropriateness of use in routine practice, effectiveness, cost-effectiveness and/or budget impact (Montilla et al., 2015[43]). Performance-based agreements are widely used in Italy in the form of payment-by-results, many of which rely on registries specifically for collecting data to execute the MEA. The registries are web-based and are set up by the Italian Medicines Agency (AIFA) to share clinical data between clinicians and pharmacists and the regulatory agency. They capture information on the use of new products in routine practice, their appropriateness in treatment and patient response. Data generated in the process support payment to (or refunds by firms) based on patient response and AIFA re-evaluation (usually after a period of two years) of guidelines for the use of the product in therapy. However registry data are not public or accessible for third parties. While AIFA monitoring registries and related MEAs have been credited for informing AIFA and other stakeholders about the performance of new products, they have also been criticised for creating a significant data collection burden for health professionals and provider organisations (Garattini, Curto and van de Vooren, 2015[44]; Garattini and Casadei, 2011[42]).

74. As of October 2019, AIFA reported 71 active MEAs for 48 active ingredients in 45 distinct therapeutic areas (AIFA, 2019[45]). Of the 71 agreements, 46 were performance-based and 25 were financial (AIFA, 2019[45]). Data for executing these MEAs are collected in web-based registries established by AIFA for that purpose. Another 108 registries related to the appropriateness of prescribing were also active, of which 2 were combined with financial agreements (AIFA, 2019[45]).

75. In Estonia, there were 9 patient-level payment-by-result agreements per May 2019. The aims of these agreements are to improve cost-effectiveness and to avoid spending on ineffective therapies. Information on the existence of these agreements and their design is publically available, but not specific information on outcome measures used and payment modalities. The main sources of data are patient health records and prescription data. Firms are paid when a positive treatment effect or patient response is observed. Response is determined by observing health outcomes, or in some cases, by observing whether a patient continues to receive treatment beyond a time period specified in the agreement. In the latter case, patient response is assumed if the patient continues to receive treatment beyond the defined time period.

Box 3.1. England and Estonia: country comparison of performance-based agreement for brentuximab vedotin (Adcetris®) for CD30-positive Hodgkin Lymphoma

England, Cancer Drugs Fund

In England, brentuximab vedotin was the first product to exit the reformed CDF into routine coverage by the National Health Service (NHS). The conditional marketing authorisation by the European Commission, for treatment of adults with relapsed or refractory CD30-positive Hodgkin Lymphoma, following autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT or multi-agent chemotherapy are not a treatment option, was based on a single-arm phase II trial using an intermediate endpoint as its primary outcome (CHMP, 2012[46]). The European Medicines Agency (EMA) requested post-marketing follow up of this trial due to uncertainty around survival estimates, as well as other studies. In contrast, the managed access agreement (MAA) required observational data from routine clinical practice in England on subsequent stem cell transplant rates (Edwards et al., 2018[47]; NICE, 2018[48]; NICE, 2018[49]; NICE, 2018[50]). The EMA and NICE both identified clinical uncertainty in the sub-population who were not eligible for stem cell transplant or multi-agent chemotherapy due to immature data and a lack of comparator evidence. Due to practicality issues, the MAA did not address uncertainty around estimates of overall and progression-free survival. However, it did address the issue of comparison to single-agent chemotherapy. Retrospective data analysis per the MAA confirmed that post-treatment stem cell transplant (SCT) rates were lower than presented in the initial NICE appraisal (25% vs. 58%, respectively) and for single-agent chemotherapy used as comparator (5.3% vs 14.3%, respectively). Consequently, the most plausible ICER estimate dropped from between GBP 28,000 and 54,000 per QALY gained to between GBP 16,000 and 18,000, and NICE recommended a move from the CDF to routine coverage within the NHS (Edwards et al., 2018[47]; NICE, 2018[48]; NICE, 2018[49]; NICE, 2018[50]).

Estonia

In Estonia, brentuximab vedotin for the treatment of Hodgkin lymphoma is subject to a patient-level payment-by-result agreement. The aim of this agreement is to improve cost-effectiveness of the product in the Estonian population and to avoid spending on patients in which the therapy is ineffective. National insurance pays for the medicine for each patient who responds to treatment after a trial period, with response measured as defined in Cheson et al (2007[51]). Response is verified using patient health records.

Comparison of performance-based MEAs in England and Estonia

	Objective	Design	Outcome Measures	Data Sources	Patient Population	Results
England	Reduce uncertainty around SCT rates versus single-agent chemotherapy	Population-level CED	Post-treatment SCT rate	SCT rate from observational data from routine sources; consensus of clinical expert opinion	Adults with relapsed or refractory CD30 positive Hodgkin Lymphoma not eligible for stem cell transplant or multi-agent chemotherapy	Exit from CDF and recommendation for routine use in NHS
Estonia	Improve cost effectiveness; reduce budget impact	Patient-level PbR	Patient response as defined in Cheson et al (2007[51]) and determined by treating clinicians	Patient health records	Patients with Hodgkin Lymphoma	Agreement ongoing

Note: SCT…stem cell transplant, CED…coverage with evidence development, CDF…Cancer Drugs Fund, NHS…National Health Service, PbR…payment-by-result
Source: Authors based on citations in text and OECD expert interview for Estonia.

4. Conclusion

76. Managed entry agreements (MEAs) are tools for achieving patient access to new medicines and health technologies through quicker coverage decisions, while managing uncertainty related to the performance and/or budget impact of such products. MEAs can be classified across two main types: financial and performance-based. Financial agreements have proliferated in the last two decades, and available information suggests that they are currently or were used in the past in at least two-thirds of OECD countries and EU member states. Many countries also use performance-based agreements but their number remains much lower.

77. The most common objective of performance-based MEAs is also financial – to manage budget impact and/or to increase cost-effectiveness by reducing prices. However, payers also use these agreements to reduce uncertainty around product performance, for instance in terms of comparative and cost-effectiveness. Performance-based MEAs can further be classified according to their design and according to whether mechanisms that trigger financial aspects of the agreement are defined at the patient- or population-level.

78. Based on the OECD survey conducted for this paper, patient-level payment-by-result (PbR) and population-level coverage with evidence development (CED) agreements are the most common agreement designs. Some countries also use conditional treatment continuation (CTC), either as part of a MEA or through coverage restrictions. Patient-level PbR agreements help payers manage budget impact by paying firms only for treatments to which patients respond. CED agreements are mainly used to reduce uncertainty around the comparative effectiveness or cost-effectiveness of products.

79. It is difficult to assess with certainty to what extent performance-based MEAs have so far been successful at achieving their stated goals. Few countries have formally evaluated their experience. Confidentiality of the content of MEAs and their results continues to be a barrier to independent evaluation, including by the OECD, and little evidence is publicly available. However, interviews with experts from 12 OECD countries conducted for this paper and the available studies indicate that CED agreements have so far had a poor track record of reducing uncertainty around product performance. Some countries have recently changed their approaches to CED and some are discontinuing CED agreements altogether in favour of alternatives, such as restricted or conditional coverage without a MEA. The post-2016 Cancer Drugs Fund in England is a recent example of a well-designed CED scheme embedded in the national HTA process, with clear criteria for entry, a limited period of temporary coverage linked to requirements for evidence generation, transparency of the non-commercial parts of the agreements, and a clearly defined exit process. However, it is too early to assess its success in meeting its objectives. Payment-by-result agreements continue to be used quite widely, but they do not always generate additional evidence on product performance because data used for triggering payment is not always aggregated and analysed for the purpose of assessing product performance. The administrative burden of collecting and analysing data can also make them costly to execute.

80. Part II of this paper further discusses what factors payers could consider in deciding whether to use performance-based MEAs and how these can be designed to increases the likelihood that they achieve their objectives. It also outlines how payers could benefit from greater international sharing of information.

Part II. Towards more effective use of performance-based MEAs through sharing of information

5. Experience points to a number of good practices in the design and execution of performance-based MEAs

81. While it remains difficult to assess with certainty to what extent performance-based managed entry agreements (MEAs) have so far been successful, what is known about experience in OECD and EU countries points to a number of good practices that can make it more likely that such agreements achieve their objectives. These are largely in line with principles, guidelines and recommendations for MEAs in general, and performance-based MEAs in particular, published previously by various institutions, including payers or government departments and agencies responsible for negotiating MEAs, academics and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR). This section puts forward good practices for the use of performance-based MEAs in three sub-sections, related to the following main questions:

- When are performance-based MEAs appropriate and when are they not?
- What factors should be considered in their design?
- What considerations are necessary in terms of transparency of process and governance?
- What level of transparency of content is appropriate and necessary?

5.1. Using performance-based MEAs strategically

82. Payers should use performance-based MEAs strategically. They are a resource-intensive means of coverage of health technologies and, by making financial mechanisms more complex and dependent on performance measures, can divert attention from price negotiations and the ultimate financial impact of health technologies. Thus, the formulation of an overall strategy or policy and clear guidelines for determining when a performance-based MEA should be used is helpful for payers. Such a strategy can situate the role of MEAs in the overall process to make coverage decisions and can define a governance framework and transparency requirements (also see Section 5.3). It also makes sense to consider results of horizon scans in deciding if and when to adopt performance-based MEAs. This is because commitments under such agreements, and possibly attendant confidentiality of prices and data collected, can make it more difficult for products that enter the market subsequently to compete and gain market share. When horizon scans suggest that competition from upcoming products is imminent, this may need to be taken into account in deciding whether a MEA is appropriate and, if yes, how it should be designed so that commitments under the MEA do not to inhibit competition by follow-on products.

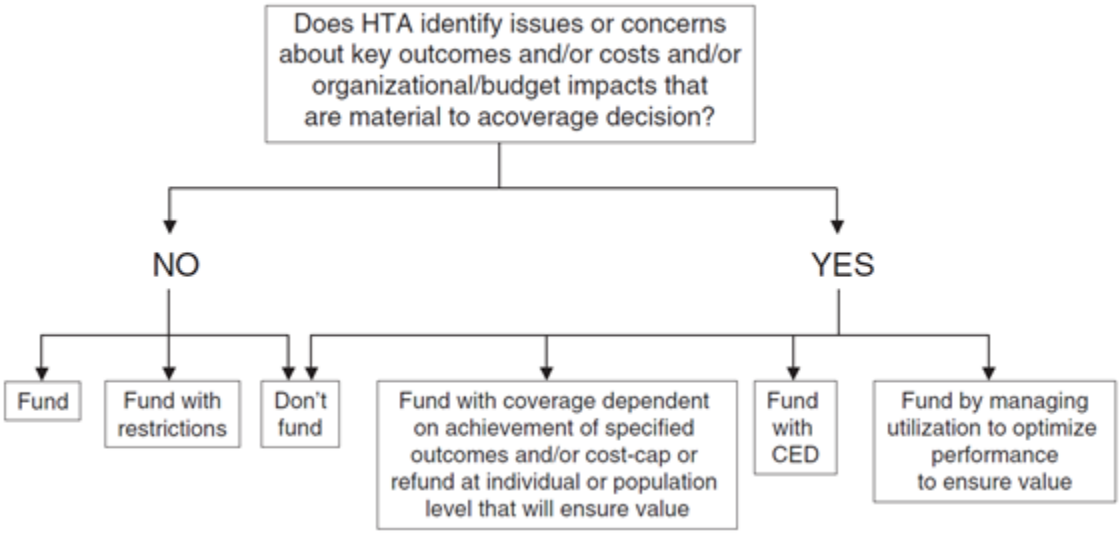
83. A *value of information framework* is one approach payers can use to guide their decisions on whether to adopt a performance-based MEA or not. Such a framework compares the value of the incremental information on product performance generated under the MEA with the incremental cost of negotiating and executing the agreement. The value of additional information derived from data collection and analysis under the MEA depends on its ability to improve resource allocation decisions, and therefore

on the direct cost of the technology and the opportunity costs of possible *wrong* or delayed decisions without this additional information. This can be compared to the direct costs of negotiating and executing the MEA. A possible framework has been suggested, for example, by the Decision Support Unit (DSU) of the National Institute for Health and Care Excellence (NICE) in England (Grimm et al., 2017[52]; Grimm et al., 2015[53]). Earlier work by Hutton, Trueman and Henshall (2007[54]) and Garrison et al. (2013[5]) also suggested approaches to determining when performance-based MEAs are suitable.

84. To assess the value of the potential adoption of a performance-based MEA, it is necessary to understand the uncertainties that could cause a *usual* coverage decision in the absence of a MEA to be wrong or delayed and whether a MEA is able reduce such uncertainty. It is therefore sensible to embed the decision of whether or not to use a MEA in the health technology assessment (HTA) process. Making the adoption of MEAs contingent on an initial HTA also has the advantage that the uncertainties around parameters of product performance that are relevant to the coverage decision, such as comparative effectiveness, cost-effectiveness and budget impact, are clearly identified. Klemp, Frønsdal and Facey (2011[4]) suggested that MEAs only be used when HTA identifies issues that are material to coverage decisions, and usual coverage decisions are therefore inappropriate. They provide examples of circumstances in which this may occur, such as in case of unmet medical need, a lack of therapeutic alternatives, the *disruptive* impact of the technology, limited data on effectiveness or cost-effectiveness, or particular urgency to provide access to an unproven technology. They proposed an HTA-based decision tree outlined in Figure 5.1. Similarly, Stafinski, McCabe and Menon (2010[1]) concluded from their review of coverage with evidence development (CED) schemes that these are suitable for technologies for severe conditions and high unmet needs and with significant budget impact (because of either a high unit cost or high volume). They suggest that CED agreements be used only when they have the potential to change a coverage decision and when they can be implemented with minimal administrative burden.

85. However, not all countries may have a formal and robust HTA process in place. Payers in some countries may therefore not always be in a position or have the capacity to identify and assess uncertainty. This may warrant caution with performance-based MEAs.

Figure 5.1. MEA decision tree based on HTA



Source: Klemp, Frønsdal and Facey (2011, p. 82[4]), reproduced with permission.

86. A number of OECD countries have formulated guidelines for when performance-based MEAs should be used. In France, for example, the use of performance-based MEAs has been subject to criteria set out in framework agreements concluded with the industry since 2009. As of 2016, the use of such agreements is recommended where their adoption (CEPS, 2019, p. 40[55]):

- Addresses an unmet medical need;
- Is straightforward and provides a sound performance guarantee; and,
- Does not increase risk for national health insurance.

87. In another example, a medicine can only be funded through the new English Cancer Drugs Fund (CDF) with a corresponding coverage with evidence (CED) agreement if it fulfils three conditions (NICE, 2018[56]):

1. There are uncertainties in the evidence of its clinical effectiveness;
2. It has the plausible potential to be cost-effective with further evidence; and
3. It is feasible to collect and analyse data to address these clinical uncertainties.

88. As a corollary, guidelines should also identify the alternatives to performance-based MEAs and help payers determine when such alternatives are more appropriate. As shown in Figure 5.1, for example, coverage with restrictions can be an alternative. Coverage can be temporary or limited to sub-groups of patients for which evidence of the effectiveness and/or cost-effectiveness of the product is most compelling. As discussed in Part I., several countries, including the Netherlands and Sweden, have moved away from CED agreements towards temporary coverage during which additional research can be conducted to address uncertainties.

5.2. Designing performance-based MEAs to address uncertainty at hand

89. For scenarios where performance-based MEAs are an appropriate means of coverage, the right MEA design needs to be chosen to address the uncertainties at hand. As discussed in Part I., population-level CED agreements are so far used more frequently to address uncertainty in comparative effectiveness and cost-effectiveness while patient-level PbR agreements are mainly used to manage budget impact. This does not necessarily mean, however, that these agreement designs can only be used for these purposes. Various agreement types and designs can be structured in different ways to address different uncertainties. It is therefore important to clearly lay out the uncertainties at hand and structure MEAs accordingly. Considering the following factors can help make these decisions and define the data collection and analyses process in a way that makes it more likely that the uncertainties will be addressed.

- Are the research questions defined so as to reduce the uncertainty in the parameters of product performance that give rise to the MEA? This requires that uncertainties have been identified upfront.
- Are sources available that provide the data on health outcomes necessary to assess product performance in the population of interest and is the suggested study design able to estimate relevant parameters of product performance with sufficient accuracy?
- What is the appropriate time frame to collect and analyse data and are the agreement term and patient follow-up time in the study defined accordingly?

90. Many of the factors above are rather technical and need to be considered in the local context for specific products. They cannot be discussed with sufficient detail in general. More specific recommendations for CED agreements based on the Dutch experience are available in Makady et al. (2019[36]). Garrison et al. (2013[5]), Gerkens et al. (2017[7]) Hutton, Trueman and Henshall (2007[54]) and Stafinski, McCabe and Menon (2010[1]) also provide guidance.

91. Where firms are required to collect additional data and submit evidence, their financial incentives to do so also need to be considered when designing performance-based MEAs. Performance-based MEAs, including CED and PbR agreements, have in the past often provided for upfront payments to firms and subsequent discontinuation of coverage, refunds or price reductions, putting financial risk on payers. This provides little incentive for firms to collect reliable data and produce additional evidence, if such evidence might show that performance of the product falls short of expectations. It may therefore be helpful to distinguish MEA designs that penalise under-performance from those that reward performance (Launois et al., 2014[57]) and structure agreements in a way that incentivises the generation of evidence. Australia has taken the latter approach in its CED MEAs, by providing coverage at a price justified by existing evidence, pending submission by firms of more conclusive evidence of cost-effectiveness to support higher prices (Vitry and Roughead, 2014[25]).

5.3. A governance framework should ensure transparency of process and that results of MEAs can be acted upon

92. In maximising the utility of performance-based MEAs it is helpful to have a sound governance framework in place and to consider which information related to MEAs should be transparent. A distinction between transparency of process and transparency of the content of MEAs is helpful here (Garrison et al., 2013[5]). Governance requires that certain information related to the process of using MEAs always be transparent.

93. The process to enter into performance-based MEAs, collect and analyse data, make decisions based on data analysed and to exit from MEAs should be transparent to ensure that stakeholders are accountable. In addition, governance processes should address independence, data ownership, audit, transparency, and appeal (Klemp, Frønsdal and Facey, 2011[4]; MacLeod and Mitton, 2010[58]). It has been suggested that these should ensure "independence of the scheme from any parties with a vested interest in its outcomes", in particular independence of investigators and decision makers from influence by clinicians, patients and firms but also independence of investigators from payers (MacLeod and Mitton, 2010, p. 106[58]). While it may not be possible to achieve independence of investigators in practice because both payers and firms usually have an interest in the outcomes of MEAs and may also be involved in data collection and analysis, processes should minimise conflicts of interest and allow for independent scrutiny.

94. The governance framework must also ensure that there is a clear and sound process for acting upon the evidence generated under performance-based MEAs and exiting from the agreements. This includes mechanisms for re-evaluation of products after the term of the MEA and mechanisms for removing coverage or adjusting prices. As discussed in Part I., the delisting of products from coverage and the reduction of prices if performance-based MEAs find product performance to fall short of expectations has often presented difficulties for payers. Clauses that trigger review or lead to the termination of the agreement have also been pointed out as an important element of governance in order to respond appropriately to breaches of contract (Stafinski, McCabe and Menon, 2010[1]).

5.4. Ensuring an appropriate level of transparency of content

95. Finally, some information related to the content of MEAs should also be made transparent. As a minimum, the evidence generated on product performance itself should be readily available to all stakeholders with legitimate interests. This allows payers and regulators across jurisdictions to use all available evidence and avoid the duplication of effort and other pitfalls of confidentiality (see Section 6.3). On the other hand, it can be necessary that some elements of MEAs remain confidential, in particular prices and related commercial clauses, but the general approach should be to put as much information as possible in the public domain (Klemp, Frønsdal and Facey, 2011[4]). Section 6. elaborates on confidentiality of information and options to increase transparency.

6. Countries could benefit from sharing information but confidentiality is one reason this does not occur

96. Performance-based MEAs generally have the objective to help make coverage decisions in the face of uncertainty, by managing budgets despite uncertainty and/or requiring additional evidence generation to reduce such uncertainty. By definition, they entail the analysis of data on product performance for that purpose although, in practice, performance is sometimes inferred by analysing data on utilisation only. This Section shows that payers, and other stakeholders with legitimate interests, could benefit from greater international cooperation and sharing of information on performance-based MEAs. However, little information sharing currently occurs. Aside from other missed opportunities, in particular confidentiality of results of clinical studies that may be conducted under MEAs raise ethical concerns. To benefit from information generated in other jurisdictions, payers could agree on which type of information should be shared in which way and change their policies when entering into future MEAs.

6.1. Sharing of information has a range of potential benefits if countries use similar criteria for coverage decisions

97. Sharing of information on product performance between jurisdictions can help payers achieve a number of objectives. The extent to which payers can benefit from sharing information depends on the degree of similarity between their jurisdictions in terms of the criteria that underlie coverage decisions and are subject to uncertainty. Realising the potential benefits of information sharing might therefore require an upfront effort to align decision criteria and product performance measures used. International standardisation of health outcome measures could support such an effort of convergence.

98. Payers could benefit significantly from sharing information if their decisions are based on comparative effectiveness of new products and if estimates of these parameters are uncertain. The benefit can be even greater if uncertainty is a result of small patient samples, as is often the case for rare diseases, and if the pooling of data or study results can therefore significantly increase the precision of estimates. However, this requires that populations are sufficiently similar between jurisdictions for evidence to be generalised and that payers agree on health outcome measures that are relevant for measuring product effectiveness. It also requires similar existing standards of care and therefore the same comparators.

99. Information sharing may be less helpful when payers struggle with generalising existing evidence to their population or face uncertainty around budget impact, for instance because they cannot estimate the number of patients in their jurisdiction that will receive a new treatment. Estimates of cost-effectiveness might also be difficult to transfer across countries when input costs vary or other input parameters for the analysis are dissimilar. Sharing of information on cost-effectiveness might only be helpful if not only study results but also raw data or model input parameters are shared, so that the latter can be adjusted to local circumstances.

100. To inform their own negotiations, payers could also benefit from knowing about ongoing negotiations in other countries and, for example, the health outcome measures and studies that will be used in an upcoming MEA elsewhere. This could help align outcome measures across countries and make sharing of information on product performance easier further downstream.

101. While this paper only discusses *horizontal* cooperation between payers or other authorities responsible for coverage and pricing, *vertical* cooperation between regulators and payers could also help these institutions achieve their objectives. In addition, greater transparency of information would also be useful for other stakeholders with legitimate interests and the general public. In particular, the potential non-disclosure of results of clinical studies conducted under performance-based MEAs raises ethical concerns as available information on the safety and effectiveness of medicines could be withheld from the public.[10] If relevant information on the performance of products that is generated from performance-based MEAs were publicly available, they could be used for a wide range of secondary purposes. These may include but are not limited to:

- Monitoring of product safety/efficacy and post-marketing requirements by regulatory agencies;
- Research by the scientific community to advance knowledge on various parameters of performance, such as comparative effectiveness and cost-effectiveness;
- Formulation of treatment guidelines by stakeholders that are not party to the MEA (e.g. professional associations); and,
- Comparison and extrapolation of performance to other patient populations, including to other countries, to inform, for example, design of further studies, and HTA by entities that are not party to the MEA.

102. Such secondary uses of data, which can make valuable contributions to the health benefits gained from medicines, require that data are made available to stakeholders that are not party to the MEA in a timely manner.

6.2. There is currently little international sharing of information between payers

103. Interviews conducted with experts in countries that use performance-based MEAs indicate that limited sharing of information currently occurs. This may be the case for various reasons. Fundamentally, the main goal of payers is to ensure timely and affordable access to new medicines. While this requires, to varying extents, information on the performance of new medicines, reducing uncertainty around product performance is not their primary goal. This results in various payer strategies that may or may not, in aggregate, contribute to advancing general knowledge about the performance of products.

104. For example, if a payer in a given country believes that a confidential MEA with a firm accelerates the reaching of an agreement on prices with the firm and there is no statutory requirement to make information publicly available, the payer may accept broad confidentiality clauses in a contract offered by the firm. Such confidentiality clauses may have the effect that all information related to the MEA remains confidential, including information on health outcomes used to asses product performance and the results of analyses. This can benefit the payer in ensuring access to the individual product in question but can have negative effects on patient access to effective medicines in general.

[10] According to the Ethical Principles for Medical Research Involving Human Subjects published by the World Medical Association (WMA), researchers, authors, sponsors, editors and publishers have an ethical obligation to publish and disseminate the results of research. See https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/.

105. Beyond creating a barrier to independent evaluation and therefore issues in terms of governance accountability, confidentiality is problematic for a number of reasons. For example:

- The non-disclosure of the results of performance-based MEAs related to a technology of interest implies that general uncertainty around the performance of the product is not reduced and may lead to duplication of efforts, unethical studies because effects of treatments have already been shown elsewhere with sufficient certainty, and a reduced level of information available to other payers who are considering MEAs as a policy option;
- Comparative assessment of treatment alternatives may be inaccurate because the omission of existing data, both in terms of health outcomes and economic variables; and,
- Price opacity makes international price benchmarking, or external reference pricing, increasingly inaccurate[11] or create problems for countries in regulating the prices of generics, if such regulation is based on prices of originators;

106. There are also examples of OECD countries where performance-based MEAs do not lead to the generation of evidence on product performance. A number of countries, including the Czech Republic, Estonia, Italy and Sweden, use payment-by-result (PbR) agreements (see Part I.). However, data are not necessarily aggregated and analysed in these countries to evaluate product performance because the objective of payers is to reduce budget impact by not paying for treatments of patients that do not respond. If such analyses are performed, they are not necessarily published.

107. Interviews suggest that in many countries that use performance-based MEAs, information related to these agreements is either confidential or, even if it not confidential by virtue of contractual clauses or statutory requirements, not published and not readily available to third parties. Information on the products and indications for which MEAs exist, as well as the type (and sometimes design) of MEAs, is public or available to third parties upon request among most of the 12 OECD countries that use performance-based MEAs and from which experts responded to OECD interviews (Figure 6.1). A number of countries, including Belgium, England, Estonia, Hungary, Italy and Sweden, regularly publish a list of the products for which MEAs are in place.

108. However, details on the content of MEAs related to product performance, in particular how product performance is measured, and information on their results are often confidential. Where publicly available, information on the results of analyses of data conducted under MEAs and decisions made on the bases of such studies is often rather limited, and available only to the extent that results of HTA reassessments and final decisions on pricing and coverage are published by the relevant authorities. For cancer medicines that are covered through the new Cancer Drugs Fund (CDF) in England, for example, NICE publishes a re-appraisal after the end of temporary funding in which the product is either recommended or not recommended for coverage by the National Health Service (NHS). These re-appraisals are based on data collected and/or secondary analysis of existing data under the MEA.

109. There is some variation of confidentiality within countries, which is partly related to the fact that contractual clauses are often the source of confidentiality requirements. Therefore, confidentiality requirements can be specific to each individual MEA. There are, however, also countries where confidentiality requirements are based on statutory law. In Belgium, for example, MEAs are constituted of a contract that is public and an annex to the contract that is confidential. Statutory law stipulates that the financial mechanisms defined in the MEA are always confidential for all types of MEAs; they are defined in the annex. For performance-based MEAs, also product performance measures are confidential because they are linked to the financial mechanisms. In addition, contractual parties can agree to further

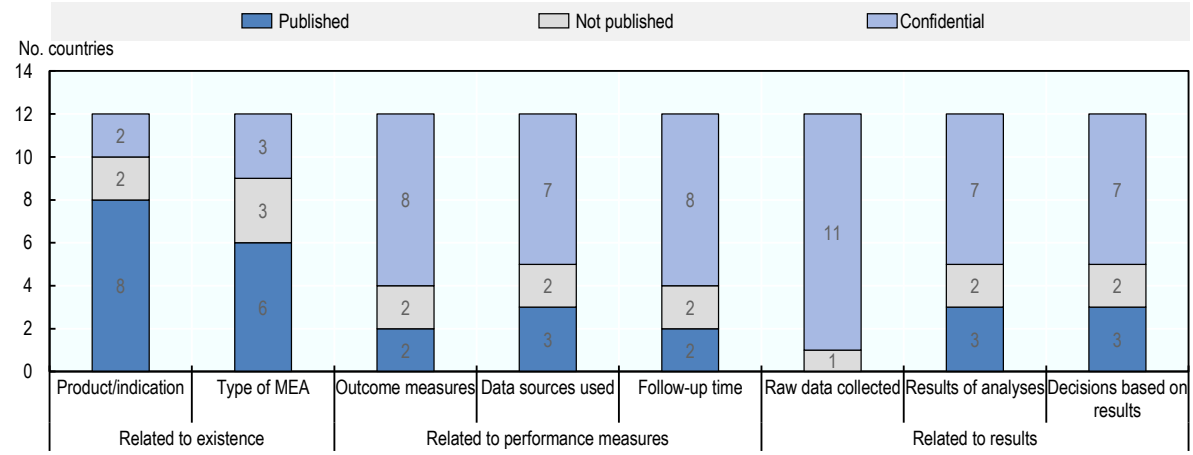
[11] Indeed, confidential prices may have been a reaction by the pharmaceutical industry to increased international price benchmarking, to maintain their ability to price discriminate between countries.

confidentiality clauses. In France, all content of MEAs is considered confidential by virtue of the protection of trade secrets.

110. In some countries, such as Australia and England, the level of confidentiality also depends on the type of MEA or the scheme under which the MEA is concluded. In Australia, agreements in the *Managed Entry Scheme (or Managed Access Program*) may be, but are not limited to, a form of population-level CED and are more transparent than other ad-hoc performance-based MEAs. Guidelines around disclosure of information related to *Managed Entry Schemes* are set out in the *Managed Access Program* framework. However, confidentiality of information is ultimately determined by contractual clauses in the agreements themselves. Information related to ad-hoc agreements, including their existence, is often confidential. In England, CED agreements locally referred to as *Managed Access Agreements (MAA)* are more transparent than other performance-based MEAs referred to as *complex Patient Access Schemes (PAS)* (see Section 3.2.1).

Figure 6.1. Availability of information related to performance-based MEAs

Number of countries in which information is published, not published and confidential based on interviews with experts from 12 OECD countries that use performance-based MEAs



Notes: MEA… managed entry agreement
Published: information is readily available in the public domain (e.g. on the internet).
Not published: information is not available in the public domain, but may be shared with 3rd parties upon request:
Confidential: information is not available in the public domain and cannot be shared with 3rd parties even upon request.
Information for Australia refers to ad-hoc agreements only. Information for England refers to Managed Access Agreements only (31 agreements under the Cancer Drugs Fund and 4 for other disease areas reviewed by the OECD), which are publically available; not to other Patient Access Schemes.
Source: Authors based on OECD expert interviews.

6.3. Information on product performance that results from MEAs could be shared

111. Payers could benefit from mutual sharing of information, both on the existence of MEAs and on product performance. This would require that information is made more readily available for third parties. Agreement among payers and clearly defined guidelines on which information to share, in which form and through which channel would facilitate such exchange. This is because, currently, even in countries where information is published, it is often published in local language, using local terminology and definitions, and is not always straightforward to access and navigate. It would also help payers define a clear policy for negotiations of future MEAs, which guides confidentiality clauses and ensures that information that is

related to product performance and is not commercially sensitive would no longer be contractually confidential.

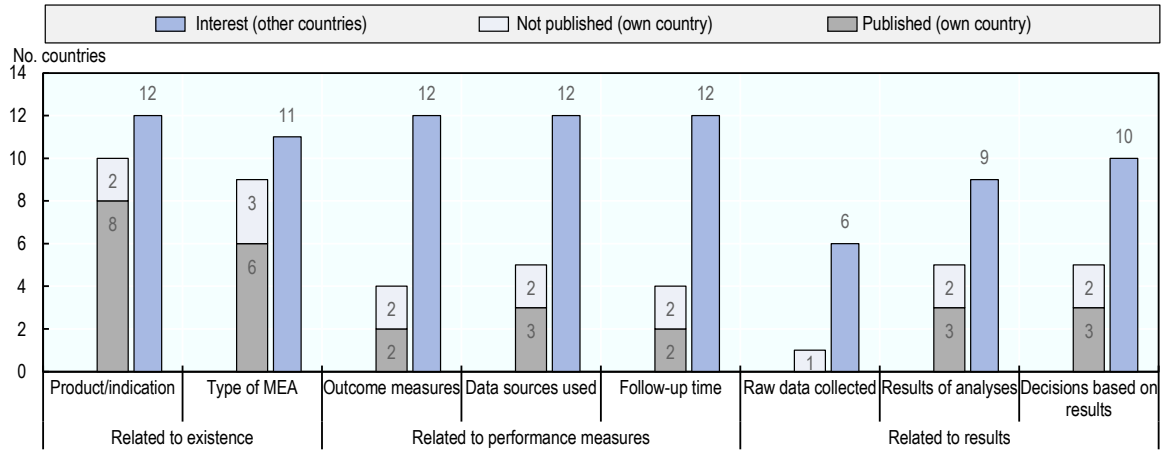
6.3.1. There is much interest in sharing of information but some policy changes would be necessary to achieve this

112. Interviews with experts in 12 countries indicate that there is interest in information on the existence of MEAs and on information related to how product performance is measured in all countries (Figure 6.2). A majority of interview respondents also stated that there would be interest in the results of MEAs, in particular the results of studies conducted under the agreements and the final decisions made on the bases of studies. There is less interest in sharing of data collected under MEAs. Interest in information on the existence of MEAs is not limited to MEAs that are already in place. Respondents also stated that it could be helpful for payers to know about MEAs in negotiation in other countries to inform their own negotiations related to the same product.

113. Interviews also indicate that the number of countries in which there is interest in accessing information on performance-based MEAs from other countries significantly exceeds the number of countries in which such information is not confidential (i.e. is either published already or is not published but can be made available to third parties upon request) (Figure 6.2). While information on the existence of MEAs is not confidential in the majority of countries, payers would need to change their policies on confidentiality to engage in sharing of other types of information.

Figure 6.2. Confidentiality of information on performance-based MEAs versus interest in such information

Number of countries in which information is not confidential and in which there is interest in such information from other countries, based on interviews with experts from 12 OECD countries that use performance-based MEAs



Notes: MEA… managed entry agreement
Published: information is readily available in the public domain (e.g. on the internet).
Not published: information is not available in the public domain, but is not confidential and may be shared with 3rd parties upon request.
Information for Australia refers to ad-hoc agreements only. Information for England refers to Managed Access Agreements only (31 agreements under the Cancer Drugs Fund and 4 for other disease areas reviewed by the OECD), which are publically available; not to other Patient Access Schemes.
Source: Authors based on OECD expert interviews.

114. Because confidentiality is predominantly based on contractual clauses, sharing of information would require that payers in most countries change their stance in negotiations with firms and no longer

accept clauses that make information related to product performance confidential. Sharing of information that is protected by existing contracts may not be possible. Further assessments might be necessary to determine which information is commercially sensitive and ought therefore to be protected. While existing laws may also need to be reviewed in each country to assess the current level of protection of information, changes to legislation might not be necessary in most countries to achieve greater transparency. This could help payers define a policy that lays out clearly which information should no longer be confidential in future MEAs. It could also help policy makers assess whether any legislative changes could be necessary.

115. As is already done in some countries, payers could separate commercial information from information that is related to product performance into separate documents. The new English Cancer Drugs Fund (CDF) provides an example of how this can be done. Each CED agreements under the CDF comprises two parts: a *Data Collection Arrangement*, which is published on a website and describes planned data collection and analyses to address the uncertainties identified by the initial HTA, and a *Commercial Access Agreement*, which define prices and commercial conditions (see Section 3.2.1 for further information on the CDF). In addition to, or instead of, publishing agreement documents, another option could be to publish information related to product performance in a standardised format in a repository created for that purpose.

6.3.2. Various mechanisms of information sharing are possible

116. Payers could agree on the mechanisms and channels through which information on performance-based MEAs could be shared.

117. For information on the existence of MEAs and MEAs under negotiation, one option is for payers to simply post information on a website. Such information could include details on how product performance is measured under each MEA, including health outcomes and data sources used. This could be relatively straightforward for the payer publishing information but might make it time consuming for third parties to navigate and access needed information.

118. Another option could be to publish information in a central repository and using a standardised format and terminology. That would have the advantage of making information easier to access and analyse by third parties. Such a repository could hold information on products for which MEA negotiations are still underway and agreements have not been signed yet; information on health outcome measures and other study details under agreements that are signed and for which data collection is ongoing; and information on results of data analyses and decisions related to closed agreements. Currently, some countries that participate in the EURIPID Collaboration already share limited information on the existence of MEAs. EURIPID is a voluntary cooperation between mostly European countries providing a members-only database with information on national prices and pricing regulations of medicinal products in a standardised format.[12] For some participating countries, the existence of a MEA for a given product is reported in the database but no further information (e.g. on the type or design of MEA) is made available.

119. For information related to the results of MEAs, and in particular results of studies and data analyses conducted under the MEA that are informative about product performance, however, it might be more appropriate to integrate information into existing frameworks and infrastructure for information sharing. This is because information generated under performance-based MEAs only represents a small share of all evidence on product performance that may be relevant to stakeholders. Much evidence is generated in clinical trials before marketing authorisation or in post-market studies, including studies of routine clinical practices, which are not related to MEAs. Also, only a subset of newly introduced medicines are subject to MEAs and performance-based agreements only represent a small share of all MEAs. Existing data sharing

[12] See https://www.euripid.eu/aboutus.

frameworks could be augmented with information from MEAs. Various initiatives are already ongoing in Europe and beyond to enhance the sharing of data on the performance of medicines. For example:

- The European Medicines Agency (EMA) is currently overseeing an initiative to create a **European Union-wide framework on patient registries** to facilitate collaboration between organisations that establish registries and collect data and potential users of registry data, such as regulatory agencies and pharmaceutical firms. A task force has been established in this initiative with the aims to increase the use of existing patient registries for regulatory purposes and, where no suitable registries exist, to facilitate the creation of new registries that adhere to a standardised set of methodological criteria (EMA, 2017[59]). The latter aims to improve the usability of registry data downstream of marketing authorisation. The definition of shared methodological standards and core outcome sets are a particularly important prerequisite for sharing of information between different entities, including regulatory and HTA agencies, and across countries.
- EMA also coordinates the **European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP®)**, which maintains a database of research organisations, networks and data sources related to medicines, including patient registries.[13]
- EMA is cooperating since 2010 with the **European network for Health Technology Assessment (EUnetHTA)** to formulate post-marketing data generation plans that are aligned between regulatory and HTA purposes (EUnetHTA, 2019[60]; EMA, 2017[61]). EUnetHTA maintains the EVIDENT database to reduce redundancy and sharing of information on coverage and assessment status of technologies, and requests or recommendations for additional studies arising from HTA (EUnetHTA, 2019[62]). However, the database is not yet publicly accessible.
- In the domain of rare diseases, there is a wealth of experience with sharing data and establishing international registries because patient populations are often too small for studies to be conducted in a single country. **RD-Connect**, for example, was established in 2012 as a worldwide platform to connect databases, patient registries, biobanks and clinical bioinformatics data for rare disease research.[14] RD-Connect currently indexes more than 60 international patient registries related to rare diseases.

[13] http://www.encepp.eu/encepp/resourcesDatabase.jsp

[14] https://rd-connect.eu/

7. Conclusion

120. Despite the lack of evidence, experience with performance-based MEAs in OECD countries and EU member states so far points to a number of good practices that could make them more likely to achieve their objectives. These span four main themes: using performance-based MEAs strategically and only where the benefit of additional evidence on product performance in terms of improved resource allocation outweighs the cost of negotiating and executing MEAs; designing performance-based MEAs appropriately to address the uncertainties at hand; adopting a governance framework that ensures transparency of process and that results of MEAs can be acted upon; and ensuring a minimum level of transparency of content, so that only commercially sensitive information is confidential (in particular prices). Performance-based MEAs should not be used when more appropriate means of providing coverage to new health technologies are possible.

121. When payers decide to use performance-based MEAs, they, and other stakeholder with legitimate interests as well as the general public, could greatly benefit from international sharing of information on performance-based MEAs. However, little information is currently shared. While information on the existence of performance-based MEAs is often published or can be accessed by third parties upon request, information on how performance of products is measured under MEAs and on the results of MEAs is often confidential. This is the case despite interest across countries in accessing such information from other countries.

122. Payers would need to change their policies in negotiations with firms to ensure that information on product performance that results from future MEAs can be shared. In most countries, contractual clauses are the main source of current confidentiality requirements. While legal assessments might be necessary to determine which information has to be considered commercially sensitive and is therefore protected, changes to legislation might not be necessary in most countries to achieve greater transparency.

123. Payers could agree on which information to share, in which form and through which channel. Various mechanisms of information exchange are possible, including publishing information on existing websites, establishing new central repositories and using existing initiatives for sharing of information on medicines and health technologies.

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Annex A. OECD data collection

124. The content of this paper is based on information available from public sources, including the peer-reviewed literature, grey literature and documents published by payers and government agencies, and data collected by the OECD Secretariat through:

1. A survey with members of the OECD Expert Group on Pharmaceuticals and Medical Devices to establish whether performance-based managed entry agreements (MEAs) exist in their country for a sample of products and indications and, if yes, what types of performance-based MEAs exist and whether or not information on their performance-related content is confidential.
2. Semi-structured interviews with members of the Expert Group or other respondents nominated by the Expert Group to explore experiences with performance-based MEAs and interest in future information sharing among countries.

125. Interviews were conducted only with Experts in countries where, based on the OECD survey, performance-based agreements were used. More details on to each part of the data collection are described below.

126. A detailed document review was performed of performance-based MEAs under the Cancer Drugs Fund (CDF) in England, which is currently the only MEA scheme in which all information in the agreements related to product performance is published. Examples of a small number of individual agreements, or a description of their design, was also provided by members of the OECD Expert Group from Belgium, Estonia and Sweden in accordance with local confidentiality requirements. These were also reviewed by the OECD Secretariat.

127. Data collection and all work by the Secretariat presented below classifies MEAs according to the taxonomy of MEAs agreed upon at the first meeting of the Expert Group in March 2018 (see Figure 1.1). An overview of respondents to the survey and interviews are in Table A A.4.

Literature review

128. The Secretariat first performed a search of the literature to collect information on MEAs from prior studies and, in particular, their effectiveness in achieving their stated objectives. This was done through searches of academic databases and review of reference lists of studies identified. Members of the OECD Expert Group on Pharmaceuticals and Medical Devices provided additional sources. Literature searches were challenging due to the current lack of a common terminology across countries for describing MEAs and because some information is published in the grey literature. As a result, the content of this paper is based on a limited number of recent studies and national reports and does not constitute a systematic review of the literature. Because information on MEAs in many countries is confidential, information presented in this paper is incomplete and may in some cases be out of date. This paper should be read with this limitation in mind and information should not be considered exhaustive or definitive.

Expert Survey

129. A convenience sample of 24 products and corresponding indications, for which at least one performance-based MEA is or was in place in England or Italy, was selected from the lists of MEAs published by Italian Medicines Agency (AIFA) and the UK National Institute for Health and Care Excellence (NICE). England and Italy are two countries that publish regularly a complete list of products and indications for which MEAs are in place. The sample was selected to include only products for which it could be ruled out that MEAs in both, England and Italy, were financial; with the aim of covering oncology and non-oncology medicines (for oncology medicines, the sample was selected to include medicines in the Cancer Drugs fund in England); and to include recent MEAs that are still ongoing as well as older ones that were likely to have been closed already. Indications were defined broadly, for example only in terms of the disease and the age group of patients (e.g. children and adults), but not specifying other restrictions to treatment eligibility, such as prior treatments received or whether a medicine was indicated for first, second or subsequent lines of treatment.

130. The OECD Secretariat launched a survey, inviting members of the Expert Group to respond to the following main questions for each product/indication pair:

1. Has the product has been considered for coverage?
2. Is/was the product subject to a MEA for the indication?
3. Is/was the MEA performance-based and, if yes, what type of performance based agreement (per the OECD taxonomy in DELSA/HEA/PHMD(2018)3) does it correspond to?
4. Start and end dates of the agreement.
5. Is the agreement in the public domain or can the Secretariat get access to performance-related parts of the agreement?

131. In addition, the data collection sheet allowed respondents to add one indication for each of the 24 products and to add product/indication pairs not in the original sample. Therefore, the final sample of product/indication pairs for each country includes products/indications in the initial sample of 57 but also additional products and indications added by respondents. Table A A.1 shows the number of indications by ICD 10 chapter in the initial sample used for the OECD survey (57 product/indication pairs), as well as the final sample (104 pairs). Neoplasms accounted for over half of the indications in both samples. Table A A.2 provides a full list of product/indication pairs in the initial sample of 57 and Table A A.3 the addition 47 product/indication pairs added by respondents.

132. Table A A.4 below shows the countries from which Experts responded to the survey.

Table A A.1. Number of indications by ICD 10 chapter in sample used for the OECD expert survey

Final sample of 104 product/indication pairs and initial sample of 57 pairs

ICD 10 Chapter	In final sample	In initial sample
Neoplasms	53	31
Endocrine, nutritional and metabolic diseases	9	4
Diseases of the eye and adnexa	8	6
Diseases of the musculoskeletal system and connective tissue	8	3
Diseases of the skin and subcutaneous tissue	7	4
Diseases of the digestive system	4	2
Diseases of the nervous system	4	1
Diseases of the circulatory system	2	1
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	2	1
Certain infectious and parasitic diseases	2	0
Diseases of the respiratory system	1	1
Other	4	3
Total	***104***	***57***

Source: Authors based on OECD expert survey.

Table A A.2. Product/indication sample for the expert survey

57 product/indication pairs included in the initial sample

Active substance	ATC code	Brand name	Indication[1]
Adalimumab	L04AB04	Humira	Hidradenitis suppurativa
Adalimumab	L04AB04	Humira	Axial spondyloarthritis
Adalimumab	L04AB04	Humira	Ulcerative colitis
Alirocumab	C10AX14	Praluent	Hypercholesterolaemia
Alirocumab	C10AX14	Praluent	Mixed dyslipidaemia
Axicabtagene ciloleucel	L01X	Yescarta	B-cell lymphoma
Axicabtagene ciloleucel	L01X	Yescarta	Transformed follicular lymphoma
Bevacizumab	L01XC07	Avastin	Breast cancer
Bevacizumab	L01XC07	Avastin	Cervical cancer
Bevacizumab	L01XC07	Avastin	Metastatic colorectal cancer
Bevacizumab	L01XC07	Avastin	Neovascular exudative macular degeneration
Bevacizumab	L01XC07	Avastin	Non-small cell lung cancer
Bevacizumab	L01XC07	Avastin	Ovarian cancer
Bevacizumab	L01XC07	Avastin	Renal cell carcinoma
Brentuximab vedotin	L01XC12	Adcetris	Hodgkins lymphoma
Brentuximab vedotin	L01XC12	Adcetris	Anaplastic large cell lymphoma
Certolizumab pegol	L04AB05	Cimzia	Active psoriatic arthritis
Certolizumab pegol	L04AB05	Cimzia	Rheumatoid arthritis
Certolizumab pegol	L04AB05	Cimzia	Axial spondyloarthritis
Cetuximab	L01XC06	Erbitux	Metastatic colorectal cancer
Cetuximab	L01XC06	Erbitux	Head and neck cancer
Collagene	M09AB02	Xiapex	Dupuytren's contracture
Delta-9-tetrahydrocannibinol / cannabidiol	N02BG10	Sativex	Multiple sclerosis
Eltrombopag	B02BX05	Revolade	Chronic immune (idiopathic) thrombocytopenic purpura
Gefitinib	L01XE02	Iressa	Non small cell lung cancer
Golimumab	L04AB06	Simponi	Rheumatoid arthritis
Golimumab	L04AB06	Simponi	Ulcerative colitis
Golimumab	L04AB06	Simponi	Axial spondyloarthritis

Active substance	ATC code	Brand name	Indication[1]
Golimumab	L04AB06	Simponi	Psoriatic arthritis
Lenalidomide	L04AX04	Revlimid	Multiple myeloma
Lenalidomide	L04AX04	Revlimid	Myelodysplastic syndromes
Lenalidomide	L04AX04	Revlimid	Amyloidosis
Lenalidomide	L04AX04	Revlimid	Large B-cell lymphomas
Lenalidomide	L04AX04	Revlimid	Mantle cell lymphomas
Nivolumab	L01XC17	Opdivo	Non-small-cell lung cancer
Nivolumab	L01XC17	Opdivo	Renal cell carcinoma in adults
Nivolumab	L01XC17	Opdivo	Head and neck cancer
Nivolumab	L01XC17	Opdivo	Hodgkin lymphoma
Nivolumab	L01XC17	Opdivo	Melanoma
Olaparib	L01XX46	Lynparza	Ovarian, fallopian tube and peritoneal cancer
Omalizumab	R03DX05	Xolair	Chronic spontaneous urticaria
Omalizumab	R03DX05	Xolair	Asthma
Osimertinib	L01XE35	Tagrisso	Non-small-cell lung cancer
Pazopanib	L01XE11	Votrient	Advanced renal cell carcinoma
Pembrolizumab	L01XC18	Keytruda	Melanoma
Pembrolizumab	L01XC18	Keytruda	Urothelial carcinoma
Pembrolizumab	L01XC18	Keytruda	Non-small-cell lung cancer
Pembrolizumab	L01XC18	Keytruda	Hodgkins lymphoma
Ranibizumab	S01LA04	Lucentis	Choroidal neovascularisation secondary to pathologic myopia
Ranibizumab	S01LA04	Lucentis	Diabetic macular oedema
Ranibizumab	S01LA04	Lucentis	Macular degeneration (Acute wet AMD)
Ranibizumab	S01LA04	Lucentis	Macular oedema secondary to retinal vein occlusion
Ranibizumab	S01LA04	Lucentis	Neovascular exudative macular degeneration
Pasireotide	H01CB05	Signifor	Cushing's disease
Sacubitril / valsartan	C09DX04	Entresto	Heart Failure
Tisagenlecleucel	L01	Kymriah	B-cell acute lymphoblastic leukaemia
Trabectedin	L01CX01	Yondelis	Soft tissue sarcoma

Note: 1. Indications were defined broadly, for example only in terms of the disease and the age group of patients (e.g. children and adults), but not specifying other restrictions to treatment eligibility, such as prior treatments received or whether a medicine was indicated for first, second or subsequent lines of treatment.
Source: Authors based on OECD expert survey.

Table A A.3. Additional products and indications added by respondents to the expert survey

47 additional product/indication pairs included in the final sample

Active substance	ATC Code	Brand name	Indication[1]
Adalimumab	L04AB04	Humira	Crohn's disease
Adalimumab	L04AB04	Humira	Fistulising Crohn's disease
Adalimumab	L04AB04	Humira	Juvenile idiopathic arthritis
Adalimumab	L04AB04	Humira	Rheumatoid arthritis
Adalimumab	L04AB04	Humira	Psoriasis
Adalimumab	L04AB04	Humira	Psoriatic arthritis
Adalimumab	L04AB04	Humira	Uveitis
Adalimumab	L04AB04	Humira	Ankylosing spondylitis
Alglucosidase alpha	A16AB07	Myozyme	Adult onset Pompe disease
Alirocumab	C10AX14	Praluent	Atherosclerosis
Asfotase alfa	A16AB13	Strensiq	Hypophosphatasia
Ataluren	M09AX03	Translarna	Nonsense mutation Duchenne muscular dystrophy

Active substance	ATC Code	Brand name	Indication[1]
Atezolizumab	L01XC32	Tecentriq	Metastatic urothelial cancer
Avelumab	L01XC31	Bavencio	Metastatic Merkel cell carcinoma
Belimumab	L04AA26	Benlysta	Systemic lupus erythematosus
Bricaracetam	N03AX23	Briviact	Epilepsy
Canacinumab	L04AC08	Ilaris	Cryopyrin-associated periodic syndromes
Clofarabiine	L01XC13	Perjeta	Acute lymphoblastic leukaemia
Crizotinib	L01XE16	Xalkori	Non-small-cell lung cancer
Dabrafenib	L01XE23	Tafinlar	Melanoma
Daratumumab	L01XC24	Darzalex	Multiple myeloma
Dolutegravir	J05AX12	Tivicay	HIV
Dolutegravir/abacavir/lamivudine	J05AR13	Triumeq	HIV
Dupilumab	D11AH05	Dupixent	Atopic dermatitis
Elosulfase alfa	A16AB12	Vimizim	Mucopolysaccharidosis type IVa
Erenumab	N02CX07	Aimovig	Chronic migraine
Etelcalcetide	H05BX04	Parsabiv	Secondary hyperparathyroidism
Golimumab	L04AB06	Simponi	Ankylosing spondylitis
Ibrutinib	L01XE27	Imbruvica	Waldenstrom's macroglobulinemia
Icatibant	B06AC02	Firazyr	Hereditary angioedema
Idebenone	N06BX13	Raxone	Leber's hereditary optic neuropathy
Ixazomib (with lenalidomide and dexamethasone)	L01XX50	Ninlaro	Relapsed or refractory multiple myeloma
Mifamurtide	L03AX15	Mepact	Osteosarcoma
Niraparib	L01XX54	Zejula	Ovarian cancer
Obinutuzumab	L01XC15	Gazya	Follicular non-Hodgkin's lymphoma
Olaratumab	L01XC27	Lartuvo	Soft tissue sarcoma
Pasireotide	H01CB05	Signifor	Acromegaly
Pazopanib	L01XE11	Votrient	Soft tissue sarcoma
Pembrolizumab	L01XC18	Keytruda	Head or neck cancer
Pertuzumab	L01XC13	Perjeta	Metastatic breast cancer
Pixantrone dimaleate	L01DB11	Pixuvri	Non-hodgkin lymphoma
Tisagenlecleucel	L01	Kymriah	Diffuse large B-cell lymphoma
Trametinib	L01XE25	Mekinist	Melanoma
Trifluridine/tipiracil	L01BC59	Lonsurf	Colorectal cancer
Triptoreline	L02AE04	Diphereline	Prostate cancer
Vemurafenib	L01XE15	Zelboraf	Melanoma
Venetoclax	L01XX52	Venclexta	Chronic lymphocytic leukaemia

Note: 1. Indications were defined broadly, for example only in terms of the disease and the age group of patients (e.g. children and adults), but not specifying other restrictions to treatment eligibility, such as prior treatments received or whether a medicine was indicated for first, second or subsequent lines of treatment.
Source: Authors based on OECD expert survey.

Expert Interviews

As part of the OECD expert survey described above, experts were also asked to nominate respondents for semi-structured interviews discuss experiences with performance-based MEAs and interest in future information sharing among countries. The interviews covered the following themes:

- Governance framework for MEAs
- Main objectives of MEAs
- MEA designs
- Data sources used for analysis product performance to execute MEAs

- Confidentiality requirements and information published
- Interest in cross-country information sharing

Interviews were conducted only with Experts and nominated respondents in countries from which a response to the OECD expert survey was received and where these responses indicated that performance-based MEAs were used. This resulted in interviews with respondents from 12 countries. Table A A.4 below shows the countries from which respondents were interviewed.

Overview of responses

Table A A.4. Responses to OECD expert survey and interviews by country

Country	Responded to survey	Responded to survey question on existence of MEAs for product/ indication sample	Participated in interview	Survey or interview indicated that performance-based MEAs were used
Australia	Yes	Yes	Yes	Yes
Belgium	Yes	Yes	Yes	Yes
Czech Republic	Yes	No[1]	Yes	Yes
Estonia	Yes	Yes	Yes	Yes
France	Yes	Yes	Yes	Yes
Hungary[2]	Yes	Yes	Yes	Yes
Italy[3]	No	No	Yes	Yes
Japan[4]	Yes	No	No	No
Korea	Yes	Yes	Yes	Yes
Lithuania	Yes	Yes	Yes	Yes
Netherlands	Yes	Yes	Yes	Yes
Norway	Yes	Yes	No[5]	Yes
Portugal	Yes	Yes	No[6]	Yes
Spain	Yes	Yes	No[6]	Yes
Sweden	Yes	Yes	Yes	Yes
England[7]	Yes	Yes	Yes	Yes
United States[8]	Yes	No	No	No
Count of countries	**16**	**13**	**12**	**15**

1. The Czech Republic reported that MEAs were used but that all information related to MEAs was confidential.
2. Data were collated by the Secretariat for the final sample of products/indications based on information provided by the OECD survey as well as information published by the National Health Insurance Fund of Hungary (NEAK, 2019[18]).
3. Data from Italy was added by the Secretariat for the final sample of products/indications based on information published by AIFA (2018[17]).
4. Japan reported that MEAs were not used.
5. After the data collection period ended, Norway reported that population-level CED agreements were put in place in August 2019 for 2 product/indication pairs in the sample. Experts from Norway were therefore not contacted for an interview.
6. Experts from Portugal and Spain did not nominate interview respondents and did not respond to requests for interviews.
7. Data for England were collated by the Secretariat for the final sample of products/indications based on information provided in the OECD survey as well as information published by NICE (2019[10]).
8. The United States provided no information in their response on the existence of MEAs for sample of product/indication pairs.

Source: Authors based on OECD survey.

Annex B. CDF England case study

133. A sample of oncology product/indication pairs with performance-based MEAs in England was identified for analysis. Medicines that are funded by the current Cancer Drugs Fund (CDF) in England have Managed Access Agreements (MAAs), which are a form of population-level CED. The sample included product/indication pairs for which a publicly accessible MAA was established as part of the CDF between 29 July 2016, after the reform of the CDF, and 31 March 2019. After an agreement has been completed and a resulting coverage decision has been made, the MAA is no longer publicly available; drugs that are no longer funded by the CDF are known to have exited the CDF. The National Health Service (NHS) and National Institute for Health and Care Excellence (NICE) were contacted to determine those product/indication pairs that had entered and subsequently exited the CDF during the specified time period.

134. Publicly accessible documents for each product/indication pair were retrospectively accessed from the following sources:

1. Marketing authorisation documentation from the European Medicines Agency (EMA) webpage (including the European Public Assessment Report [EPAR] or Variation Report)
2. Health Technology Assessment documentation in NICE Technology Appraisal Guidance published on the NICE webpage (including recommendations and committee discussion)
3. Performance-based MEA (Managed Access Agreement) documentation from the NICE Technology Guidance available on the NICE webpage

135. The following steps were completed:

1. A summary of key information on marketing authorisation by the regulator, including the evidence base and remaining uncertainties;
2. A description of the nature of MAAs concluded between the marketing authorisation holder (MAH) and the payer; and
3. A comparison of the evidence base and uncertainties at the time of marketing authorisation with uncertainties underlying the MAA and evidence to be generated under the MAA.

136. The marketing authorisation, HTA, and MAA documentation were matched using the specific product indication. A reporting template was designed to collect data on the characteristics of marketing authorisation, HTA appraisal, and agreements. The elements extracted included generic and brand names of the medicines and therapeutic area as well as summary data on: marketing authorisation (MAH, approval date, approval pathway, pivotal evidence study designs and outcome measures, comparators, approval uncertainties, and approval post-marketing requirements); on corresponding HTA (most plausible incremental cost effectiveness ratio [ICER] estimate); and on MAAs (start and end dates, status, objective, data sources used, study designs and outcome measures, comparators, and results of agreements if available). Individual information on uncertainties identified during the HTA process was not collected; an assumption was made that the key uncertainties would inform the objectives of the agreements, as the agreement process is embedded within the HTA process in England.

137. There were 25 product/indication pairs with MAAs across 16 different active substances, which included 12 pairs in the initial sample of the OECD expert survey (described in Annex A.) as well as 13 additional pairs with MAAs through the CDF published prior to 31 March 2019.

Table A B.1. Characteristics of marketing authorisation of 25 oncology product/indication pairs subject to MAAs in England

Marketing Authorisation Characteristics	N = 25	%
Application Pathway		
New active substance	12	48
Centralised Procedure	9	36
Accelerated Assessment	3	12
Post-authorisation extension of indication	13	52
Type II Variation	13	52
Extension "line extension"	0	0
Approval Type		
Standard MA	18	72
Conditional MA	7	28
MA granted under exceptional circumstances	0	0
Orphan Designation		
Yes	11	44
No	14	56
Pivot Trial Study Designs		
RCT(s) only	12	48
Single-arm trial(s) only	13	52
RCT(s) + single-arm trial(s)	0	0
Pivotal Trial Outcome Measures		
Primary		
Surrogate and intermediate endpoint(s)[1] only	19	76
Final clinical endpoint(s)[2] only	4	16
Surrogate and intermediate[1] + final clinical endpoint(s)[2]	2	8
Secondary		
Surrogate and intermediate endpoint(s)[1] only	4	16
Final clinical endpoint(s)[2] only	0	0
Surrogate and intermediate[1] + final clinical endpoint(s)[2]	21	84
Comparator(s)		
Active only	9	36
Placebo only	3	12
Active + placebo	0	0
None	13	52

Note: MAA… managed access agreement, MA…marketing authorisation, RCT…randomised controlled trial.
1. Surrogate and intermediate endpoints included objective or observed response rate (including complete or partial response), response rate, duration of response, progression-free survival, time to treatment failure or response, disease-free survival, recurrence-free survival, tumour shrinkage, disease control rate, distant metastasis-free survival, remission rate, relapse-free survival
2. Final clinical endpoints included overall survival, quality of life.
Source: Analysis based on information extracted from marketing authorisation documentation available on EMA webpage.

138. Table A B.2 presents a summary of the corresponding HTA appraisal and subsequent MAAs to the marketing authorisation information presented in Table A B.1. Information on the HTA appraisal included the most plausible ICER estimate; information on agreements included number of pairs by duration, status, data sources used, study designs of clinical trials, outcome measures, and comparators. Table A B.3.and Table A B.4 respectively provide further details on marketing authorisation and MAAs for each individual product/indication pair in the sample of 25.

Table A B.2. Characteristics of HTA appraisal and MAAs of 25 oncology product/indication pairs in England

Characteristics of HTA and MAAs	N = 25	%
Health Technology Assessment		
Upper limit of most plausible ICER estimate (£/QALY gained)		
=30,000	1	4
30,000 - 50,000	5	20
=50,000	17	68
Confidential	1	4
No estimate (highly uncertain)	1	4
MAA		
Duration (months)		
Average	29.44	N/A
Range	5-58	N/A
Status		
Ongoing	23	92
Completed	2	8
Data Sources		
Ongoing clinical trial(s) only	2	8
Routinely data only	3	12
Ongoing clinical trial(s) + routine data	20	80
Study Designs of Clinical Trials		
RCT(s) only	12	48
Single-arm trial(s) only	7	28
RCT(s) + single-arm trial(s)	3	12
Not applicable (no trials used)	3	12
Performance Outcome Measures		
Surrogate and intermediate endpoint(s)[1] only	1	4
Final clinical endpoint(s)[2] only	13	52
Surrogate and intermediate[1] + final clinical endpoint(s)[2]	11	44
Comparator(s)		
Active only	9	36
Placebo only	5	20
None	8	32
Not applicable (no trials used)	3	12

Note: MAA…managed access agreement, RCT…randomised controlled trial, QALY…quality-adjusted life year, HTA…health technology assessment, ICER…incremental cost effectiveness ratio, N/A…not applicable

1. Surrogate and intermediate endpoints included objective or observed response rate (including complete or partial response), response rate, duration of response, progression-free survival, time to treatment failure or response, disease-free survival, recurrence-free survival, tumour shrinkage, disease control rate, distant metastasis-free survival, remission rate, relapse-free survival

2. Final clinical endpoints included overall survival, quality of life.

Source: Analysis based on information extracted from HTA appraisal and Pb MEA documentation available on NICE webpage.

Table A B.3. Summary of characteristics of individual marketing authorisation for sample of 25 product/indication pairs subject to MAAs in England's reformed CDF

ID	Active Substance (Brand name)	Indication	MAH	Date of Approval	Orphan (Y/N)	Type of MA	Main Evidence[1]	Pivotal Trial Outcome Measures	Uncertainties about Favourable Effects	Approval Post-marketing Requirements[1]
1	Atezolizumab (Tecentriq®)	Monotherapy for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma after prior platinum-containing chemotherapy or who are cisplatin ineligible	Roche	21-09-2017	N	Standard MA for new active substance	Single-arm phase II trial (IMvigor210 or GO29293)	Primary: ORR; Secondary: ORR, DOR, PFS, OS and 1-year OS	Non-randomised trial design; associated uncertainties with comparisons of time-related endpoints and prognostic characteristics of study populations	Final OS results of single-arm phase II trial (IMvigor210); final results of phase III RCT (Imvigor130) comparing atezolizumab as monotherapy and chemotherapy with or without atezolizumab
2	Avelumab (Bavencio®)	Monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma	Merck Europe	18-09-2017	Y	Conditional MA for new active substance	Single-arm phase II trial (EMR100070-003 or JAVELIN Merkel 200)	Primary: ORR; Secondary: DOR, PFS, AE, OS, response status at 6 months and 12 months after study treatment; serum titers of anti-avelumab bodies, population PK profile of avelumab	No comparator arm to determine true effect size in terms of ORR, DOR and PFS; magnitude of effect of treatment in terms of PFS and OS	Final results from single-arm phase II trial (EMR100070-003 part B)
3	Axicabtagene ciloleucel (Yescarta®)	Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma, after two or more lines of systemic therapy	Kite Pharma	23-08-2018	Y	Standard MA for new active substance	Single-arm phase II trial (ZUMA-1 phase 2); pooled analysis from 2 phase III RCTs and 2 observational databases as historical control	Primary: ORR (partial or complete), RR; Secondary: DOR, PFS, OS, safety, CR	None about favourable effects; uncertainty about AE (safety database in terms of size and duration)	Post authorisation safety study (long term safety) based on a registry

ID	Active Substance (Brand name)	Indication	MAH	Date of Approval	Orphan (Y/N)	Type of MA	Main Evidence[1]	Pivotal Trial Outcome Measures	Uncertainties about Favourable Effects	Approval Post-marketing Requirements[1]
							(SCHOLAR-1)			
4	Brentuximab vedotin (Adcetris®)	Treatment of adult patients with relapsed or refractory CD30+ Hodgkin Lymphoma following ASCT or following at least 2 prior therapies when ASCT or multi-agent chemotherapy are not a treatment option	Takeda	25-10-2012	Y	Conditional MA for new active substance	Single-arm phase II trial (SG035-003)	Primary: ORR; Secondary: PFS, OS (also other parameters)	Difficult to interpret claimed effects of PFS and OS with lack of comparator to regimens in the proposed indications; median OS not yet reached; limited efficacy data in patient population with relapsed or refractory HL after at least 2 prior therapies not eligible for ASCT or multi-agent chemotherapy; optimal DOT	Final OS results of phase II single-arm trial (SG035-003); post authorisation safety study; new single-arm study in HL population not eligible for ASCT investigating RR, PFS, OS and proportion of patients proceeding to transplant and safety
5	Crizotinib (Xalkori®)	Treatment of adults with ROS1- positive advanced NSCLC	Pfizer	25-08-2016	N	Type II Variation to the terms of the MA to include extension of indication (original standard MA)	Single-arm phase I safety, pharmacokinetic and pharmacodynamic trial (A8081001 or PROFILE 1001)	ORR, DCR, DOR, TTR, PFS, TTP, OS[2]	Limited data on previously untreated ROS-1 NSCLC patients but pre-clinical and ancillary data show efficacy both in ROS1 and ALK mutated patients in the first line setting; data on prognostic value of ROS-1 positivity are sparse and difficult to interpret	None

ID	Active Substance (Brand name)	Indication	MAH	Date of Approval	Orphan (Y/N)	Type of MA	Main Evidence[1]	Pivotal Trial Outcome Measures	Uncertainties about Favourable Effects	Approval Post-marketing Requirements[1]
6	Daratumumab (Darzalex®)	Treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy	Janssen	28-04-2017	Y	Conditional MA for new active substance	Single-arm phase II trial (MMY2002) and single-arm phase I/2 safety study (GEN501)	Primary: overall RR; Secondary: DOR, OS, clinical benefit rate, TTR, PFS, TTP, time to best response, reduction in serum/urine M-protein, change in bone marrow % plasma cells	Design of study with no comparative arm is of concern as ORR, PFS, and OS data cannot be directly compared to other treatment results	Final results for phase III RCT (MMY3003) comparing lenalidomide and dexamethasone with or without daratumumab; Final results of phase III RCT (MMY3004) comparing bortezomib and dexamethasone with or without daratumumab
7	Ibrutinib (Imbruvica®)	Treatment of adult patients with Waldenstrom's macroglobulinaemia who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemotherapy	Janssen	03-07-2015	Y	Type II Variation to the terms of the MA to include extension of indication (original standard MA)	Single-arm phase II trial (PCYC-1118E)	Primary: ORR; Secondary: major RR, DOR, TTR, PFS, OS, haemoglobin improvement	Generalisability of the results to broader setting e.g. first line	None
8	Ixazomib (Ninlaro®)	In combination with lenalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy	Takeda	21-11-2016	Y	Conditional MA for new active substance	Phase III RCT (TOURMALINE MM-1 or C16010) comparing lenalidomide and dexamethasone with or without ixazomib	Primary: PFS Secondary: OS, overall RR, CR, DOR, TTP, pain RR, comparison of change in global health status, OS and PFS in high risk population carrying del(17), association between response or resistance and genes/mutations, plasma concentration-time	Uncertainty on magnitude of treatment effect; efficacy data in the overall ITT population from the first and second interim analyses do not provide the statistically compelling evidence expected for an application based on a single pivotal trial; median	Final OS results from phase III RCT (C16010) comparing lenalidomide and dexamethasone with or without ixazomib in adult patients with relapsed or refractory MM; final PFS results from phase III RCT (C16014) comparing lenalidomide and dexamethasone with or without ixazomib in adult patients with newly diagnosed MM; final

ID	Active Substance (Brand name)	Indication	MAH	Date of Approval	Orphan (Y/N)	Type of MA	Main Evidence[1]	Pivotal Trial Outcome Measures	Uncertainties about Favourable Effects	Approval Post-marketing Requirements[1]
								data	OS data immature; uncertainty associated with interpretation of post hoc subgroup analyses	PFS results from phase III RCT (C16019) investigating oral ixazomib maintenance therapy following ASCT; descriptive data on non-interventional observational study (NSMM-5001)
9	Niraparib (Zejula®)	Monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum based chemotherapy	Tesaro	16-11-2016	Y	Standard MA for new active substance	Phase III RCT (ENGOT-OV16/NOVA) compared with placebo	Primary: PFS Secondary: time to first subsequent treatment, chemotherapy-free interval, OS, patient reported outcome	Uncertainty around precise size of PFS effect; median OS not reached	None
10	Nivolumab (Opdivo®)	Treatment of locally advanced or metastatic squamous NSCLC after prior chemotherapy in adults	Bristol Myers-Squibb	28-10-2015	N	Type II Variation to the terms of the MA to include extension of indication (original standard MA)	Phase III RCT (CA209017) compared with chemotherapy	Primary: OS Secondary: ORR, PFS, DOR,TTR, OS/ORR/PFS based on pre-study PD-L1 expression	Benefit in age group =75 years seems smaller than overall population; role of biomarker expression as potential predictive or prognostic biomarkers remain undetermined	Final OS results of phase III RCT (CA209017) compared to chemotherapy
11	Nivolumab (Opdivo®)	Treatment as monotherapy of locally advanced or metastatic non-squamous NSCLC after prior chemotherapy	Bristol Myers-Squibb	04-04-2016	N	Type II Variation to the terms of the MA to include extension of	Phase III RCT (CA209057) compared with chemotherapy	Primary: OS Secondary: ORR, PFS, DOR,TTR, OS & ORR based on PD-L1 expression	Survival curve lower than that for docetaxel in the first 6 months; effect of biomarker expression on	Assessment of predictive value of biomarkers in multiple studies

ID	Active Substance (Brand name)	Indication	MAH	Date of Approval	Orphan (Y/N)	Type of MA	Main Evidence[1]	Pivotal Trial Outcome Measures	Uncertainties about Favourable Effects	Approval Post-marketing Requirements[1]
						indication (original standard MA)			endpoints (need confirmation and estimation of cut-off point for PD-L1 expression)	
12	Nivolumab (Opdivo®)	Treatment of squamous cell cancer of the head and neck in adults progressing on or after paltinum-based therapy for nivolumab as monotherapy	Bristol Myers-Squibb	28-04-2017	N	Type II Variation to the terms of the MA to include extension of indication (original standard MA)	Phase III RCT (CA209141) compared with investigator's choice (cetuximab, methotrexate or docetaxel)	Primary: OS Secondary: PFS, observed RR	Benefit over docetaxel; lack of positive results in PFS; relationship between PD-L1 expression and clinical outcomes	Further investigation in phase III RCT (CA209141) on association between improved clinical outcomes and the presence of higher mutational load/ PD-L1 tumour associated immune cell expression/ PD-L2 expression / high inflamed phenotype
13	Nivolumab (Opdivo®)	Adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection	Bristol Myers-Squibb	30-07-2018	N	Type II Variation to the terms of the MA to include extension of indication (original standard MA)	Phase III RCT (CA209238) compared with ipilimumab	Primary: RFS Secondary: AE, RFS by PD-L1 expression, HRQoL	Data too immature to see if increase in RFS and DMFS translates into positive impact of OS (i.e. long term benefit in terms of OS); efficacy in sub-populations with PD-L1 expression <1%	Final OS results of phase III RCT (CA209238) compared with ipilimumab ; assessment of predictive value of biomarkers in multiple studies
14	Obinutuzumab (Gazyvaro®)	In combination with bendamustine for treatment of follicular lymphoma refractory to rituximab	Roche	13-06-2016	Y	Type II Variation to the terms of the MA to include extension of indication (original	Phase III RCT (GAO4753g or GADOLIN) comparing bendamustine with or without obinutuzumab	Primary: PFS; Secondary: PFS assessed by investigator, best overall response, CR and overall RR, OS, DFS, DOR,	At the time of analysis, median OS could not be estimated due to small numbers and a relatively short follow up	Final OS results from phase III RCT (GAO4753g or GADOLIN) comparing bendamustine with or without obinutuzumab

ID	Active Substance (Brand name)	Indication	MAH	Date of Approval	Orphan (Y/N)	Type of MA	Main Evidence[1]	Pivotal Trial Outcome Measures	Uncertainties about Favourable Effects	Approval Post-marketing Requirements[1]
						standard MA)		event-free survival, medical resources utilisation, change in health-related patient-reported outcomes, health index scale		
15	Olaratumab (Lartruvo®)[3]	In combination with doxorubicin for the treatment of adult patients with advanced soft tissue sarcoma who are not amenable to curative treatment with surgery or radiotherapy and who have not been previously treated with doxorubicin	Eli Lily	09-11-2016	Y	Conditional MA for new active substance	Phase 1b/2 RCT (JGDG) comparing doxorubicin with or without olaratumab	Primary: PFS; Secondary: OS, 3-month PFS, ORR, change in tumour size from baseline to best overall response, PK and immunogenicity	Uncertainties around the early nature of clinical research supporting the trial and the lack of correlation between the biological basis of the disease and the clinical benefit derived from treatment	Second interim safety analysis and final results of phase III RCT (JGDJ) comparing doxorubicin with or without olaratumab, including exploratory biomarkers
16	Osimertinib (Tagrisso®)	Treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who have progressed on or after EGFR tyrosine kinase inhibitor therapy	AstraZeneca	01-02-2016	N	Conditional MA for new active substance	Single-arm phase II studies (AURA Extension and AURA2)	Primary: ORR Secondary: DOR, DCR, tumour shrinkage, PFS, OS	Lack of control group making it difficult to draw conclusions on added benefit of osimertinib; magnitude of clinical benefit in terms of OS and PFS (data immature); duration of response; subgroup analyses reveal differences in subgroups; benefit in absence	Final results of phase III RCT (AURA3) comparing osimertinib to platinum-based doublet chemotherapy

ID	Active Substance (Brand name)	Indication	MAH	Date of Approval	Orphan (Y/N)	Type of MA	Main Evidence[1]	Pivotal Trial Outcome Measures	Uncertainties about Favourable Effects	Approval Post-marketing Requirements[1]
									of previous exposure to tyrosine kinase inhibitors	
17	Pembrolizumab (Keytruda®)	As monotherapy, adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection	Merck Sharpe & Dohme	12-12-2018	N	Type II Variation to the terms of the MA to include extension of indication (original standard MA)	Phase III RCT (KEYNOTE-054) compared with placebo	Primary: RFS (including those with PD-L1 positive tumours) Secondary: DMFS (including those with PD-L1 positive tumours), PFS	Uncertainty around RFS, DMFS, OS, effect of biomarker expression	Final RFS/DMFS/OS results of phase III RCT (KEYNOTE-054) compared with placebo; assessment of predictive value of biomarkers in multiple studies
18	Pembrolizumab (Keytruda®)	Treatment as monotherapy of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy	Merck Sharpe & Dohme	24-08-2017	N	Type II Variation to the terms of the MA to include extension of indication (original standard MA)	Phase III RCT (KEYNOTE-045) compared with chemotherapy	Primary: PFS, OS Secondary: ORR, DOR, PFS	Patient's characteristics influencing a higher risk of early death during treatment	Final results of one single-arm phase II trial (KEYNOTE-052) and two phase III RCTs (KEYNOTE-045 - compared to chemotherapy, KEYNOTE-361 - comparing pembrolizumab with or without chemotherapy vs chemotherapy); assessment of predictive value of biomarkers in multiple studies
19	Pembrolizumab (Keytruda®)	Treatment as monotherapy of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing	Merck Sharpe & Dohme	24-08-2017	N	Type II Variation to the terms of the MA to include extension of	Single-arm phase II trial (KEYNOTE-052)	Primary: ORR Secondary: DOR, PFS, OS	Data from uncontrolled trial; observed ORR not that compelling compared to historical data; data	Final results of one single-arm phase II trial (KEYNOTE-052) and two phase III RCTs (KEYNOTE-045 - compared to

ID	Active Substance (Brand name)	Indication	MAH	Date of Approval	Orphan (Y/N)	Type of MA	Main Evidence[1]	Pivotal Trial Outcome Measures	Uncertainties about Favourable Effects	Approval Post-marketing Requirements[1]
		chemotherapy				indication (original standard MA)			on DOR / PFS / OS / duration of follow up insufficient	chemotherapy, KEYNOTE-361 - comparing pembrolizumab with or without chemotherapy vs chemotherapy); assessment of predictive value of biomarkers in multiple studies
20	Pembrolizumab (Keytruda®)	First line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations, in combination with pemetrexed and platinum chemotherapy	Merck Sharpe & Dohme	04-09-2018	N	Type II Variation to the terms of the MA to include extension of indication (original standard MA)	Phase III RCT (KEYNOTE-189) comparing platinum plus pemetrexed chemotherapy with or without pembrolizumab	Primary: OS, PFS Secondary: RR, DOR	Immaturity of OS; estimates in patients = 75years; lack of comparison with control arm of pembrolizumab monotherapy	Final OS results of phase III RCT (KEYNOTE-189) comparing platinum plus pemetrexed chemotherapy with or without pembrolizumab
21	Pembrolizumab (Keytruda®)	Monotherapy treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed ASCT and BV, or who are transplant-ineligible and have failed BV	Merck Sharpe & Dohme	02-05-2017	N	Type II Variation to the terms of the MA to include extension of indication (original standard MA)	Single-arm phase II trial (KEYNOTE-087)	Primary: ORR Secondary: DOR, PFS, OS	Long term benefit (immature PFS and OS data); activity in elderly subpopulation	Final results of phase Ib trial (KEYNOTE-013); single-arm phase II trial (KEYNOTE-087); phase III RCT (KEYNOTE-204) compared to BV
22	Pembrolizumab (Keytruda®)	First-line treatment of metastatic NSCLC in adults whose tumours express PD-L1 with a =50% tumour proportion score with no EGFR or	Merck Sharpe & Dohme	27-01-2017	N	Type II Variation to the terms of the MA to include extension of	Phase III RCT (KEYNOTE-024) compared with platinum-based chemotherapy	Primary: PFS; Secondary: OS, ORR	No additional remaining uncertainties and limitations that have an impact on	None

ID	Active Substance (Brand name)	Indication	MAH	Date of Approval	Orphan (Y/N)	Type of MA	Main Evidence[1]	Pivotal Trial Outcome Measures	Uncertainties about Favourable Effects	Approval Post-marketing Requirements[1]
		ALK positive tumour mutation				indication (original standard MA)			benefit risk balance	
23	Tisagenlecleucel (Kymriah®)	Treatment of paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia	Novartis	22-08-2018	Y	Standard MA for new active substance	Single-arm phase II trial (B2202 or ELIANA)	Primary: overall remission rate (including CR, CR with incomplete blood count recovery) Secondary: percentage of patients who receive best overall response, duration of remission, relapse-free survival, PFS, OS	Efficacy and safety in patients <3years	Post authorisation safety study (long term safety); post authorisation efficacy study (new study based on data from a disease registry in all patients including less than 3 years)
24	Tisagenlecleucel (Kymriah®)	Treatment of adult patients with relapsed or refractory diffuse large B cell lymphoma after two or more lines of systemic therapy	Novartis	22-08-2018	Y	Standard MA for new active substance	Single-arm phase II trial (C2201) compared with three historical datasets	Primary: ORR Secondary: TTR, DOR, EFS, PFS, OS, safety	Longer than anticipated manufacturing resulted in significant amount of patients withdrawing from the study so efficacy results may be underestimated	Post authorisation safety study (long term safety); final results with 5 year follow up from single-arm phase II trial (C2201); new observational study based on data from a registry; final results from phase III RCT (CCTL019H2301) compared to standard care
25	Venetoclax (Venclyxto®)	Monotherapy for the treatment of chronic lymphocytic leukaemia in: the presence of 17p	AbbVie	04-12-2016	N	Conditional MA for new active substance	Single-arm phase II trial (M13-982)	Primary: ORR Secondary: DOR, complete remission rate, partial	Data on patient outcome after failure on B-cell receptor signalling	Post authorisation safety study; results of phase III RCT (MURANO) comparing venetoclax

ID	Active Substance (Brand name)	Indication	MAH	Date of Approval	Orphan (Y/N)	Type of MA	Main Evidence[1]	Pivotal Trial Outcome Measures	Uncertainties about Favourable Effects	Approval Post-marketing Requirements[1]
		deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor; and absence of 17p deletion or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor						remission rate, PFS, EFS, TTP, time to 50% reduction in absolute lymphocyte count, OS, percent of subjects who move on to stem cell transplant	pathway inhibitor is limited; very few patients have been treated > 2years; PFS and OS data still immature	plus rituximab to bendamustine plus rituximab; final results from single-arm phase II trial (M14-032) investigating venetoclax after treatment with B-cell receptor signalling pathway inhibitors

Note: ID…identifier, MAA…managed access agreement , MAH…marketing authorisation holder, Y…yes, N…no, MA…marketing authorisation, RCT…randomised controlled trial, ORR…objective response rate, DOR…duration of response, PFS…progression-free survival, OS…overall survival, AE…adverse effects, PK…pharmacokinetic, RR…response rate, CR…complete response, ASCT…autologous stem cell transplant, HL…Hodgkin lymphoma, DOT…duration of therapy, ROS1…ROS proto-oncogene 1, NSCLC…non-small cell lung cancer, DCR…disease control rate, TTR…time to response, TTP…time to progression, ALK…anaplastic lymphoma kinase, ITT…intention to treat, MM…multiple myeloma, PD-L1…programmed death-ligand 1, PD-L2…programmed death-ligand 2, RFS…recurrence-free survival, HRQoL…health related quality of life, DMFS…distant metastasis-free survival, DFS…disease-free survival, EGFR…epidermal growth factor receptor, BV…brentuximab vedotin, EFS…event-free survival, EMA…European Medicines Agency

1. Clinical trial identifiers written in brackets immediately after phase and study type.
2. Source did not specify primary or secondary.
3. European Union marketing authorisation has since been withdrawn.

Source: Information extracted from marketing authorisation documentation on EMA webpage. See individual data sources for product/indication pairs below.

Data sources for marketing authorisation documentation seen in Table A B.3. Numbers correspond to ID of the product/indication pair seen in Table A B.3.

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Table A B.4. Summary of characteristics of individual HTA appraisal and MAAs from the 25 product/indication pairs subject to MAAs in England's reformed CDF

ID	Active Substance (Brand name)	Indication	NICE most plausible ICER estimates prior to MAA	MAA start date	MAA end date	MAA Status	MAA Objective	MAA Main Evidence[1]	MAA Outcome Measures
1	Atezolizumab (Tecentriq®)	Untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable	More than £95,211 / QALY based on the company's list price	01-11-2017	12-12-2020	Ongoing	Areas of clinical uncertainty: magnitude of OS and PFS benefit of atezolizumab compared to UK standard of care for metastatic urothelial carcinoma patients who are cisplatin ineligible (e.g. hazard ratio, duration of effect); HRQoL for patients with stable disease and progressive disease, receiving either standard of care or atezolizumab (e.g. EQ5D); DOT	Primary: Ongoing phase III RCT (IMvigor130) compared with placebo (OR UK standard of care, gemcitabine and carboplatin); Secondary: PH England routine population-wide cancer datasets (SACT) and NHS England Blueteq CDF system	Comparative efficacy in OS, PFS, HRQoL, DOT
2	Avelumab (Bavencio®)	Treatment of metastatic Merkel cell carcinoma	Between £58,315 and £72,033 / QALY	01-04-2018	01-02-2020	Ongoing	Areas of clinical uncertainty: absence of randomised comparator arm in the JAVELIN trial; naïve comparison with observational data; small numbers of patients with short follow-up in the JAVELIN trial (specifically immaturity of PFS and OS estimates)	Primary: Ongoing single-arm phase II trial (JAVELIN 200 Part B cohort - chemotherapy naive); Secondary: PH England routine population-wide cancer datasets (SACT) and NHS England Blueteq CDF system	OS, DOT
3	Axicabtagene ciloleucel (Yescarta®)	Treatment of diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies	Between <£50,000 and >£50,000 / QALY based on commercial agreement	01-01-2019	01-02-2022	Ongoing	Areas of clinical uncertainty: OS estimates; convergence of PFS and OS curves; assessment of intravenous immunoglobulin use post treatment	Primary: Ongoing single-arm phase II trial (5 year follow up of ZUMA-1); Secondary: PH England routine population-wide cancer datasets (SACT) and NHS England Blueteq CDF system	OS, PFS, AE (immunoglobulin usage)
4	Brentuximab	Treatment of CD30	Between £28,332 and	July 17	Nov 17	Complete	Areas of clinical uncertainty:	Retrospective collection of	Post treatment SCT

ID	Active Substance (Brand name)	Indication	NICE most plausible ICER estimates prior to MAA	MAA start date	MAA end date	MAA Status	MAA Objective	MAA Main Evidence[1]	MAA Outcome Measures
	vedotin (Adcetris®)[2]	positive Hodgkin Lymphoma	£53,998 / QALY				SCT rate following real-world treatment with BV; SCT rate following treatment with single-agent chemotherapy	post treatment SCT rate for all patients who had BV through CDF between April 2013 and March 2014; Consensus of clinical expert opinion from the NCRI Hodgkin lymphoma subgroup	rate
5	Crizotinib (Xalkori®)	Treatment of ROS1-positive advanced NSCLC	Crizotinib compared with pemetrexed plus platinum-based chemotherapy in untreated disease: =£50,000 / QALY; crizotinib compared with docetaxel in previously treated disease: =£50,000 / QALY	31-05-2018	30-04-2023	Ongoing	Areas of clinical uncertainty: lack of data comparing crizotinib with standard care in ROS1-positive disease (making assessment of relative effectiveness challenging); uncertainty as to whether the documented similarities between ALK-positive and ROS1-positive advanced NSCLC will hold true as more patients with ROS1-positive advanced NSCLC are identified; post-progression survival estimates, and OS estimates, due to high rates of cross over from chemotherapy to crizotinib in the PROFILE 1007 and PROFILE 1014 trials	Primary: PH England routine population-wide cancer datasets (SACT) and NHS England Blueteq CDF system; Secondary: Ongoing single-arm phase I (PROFILE 1001) trial and single-arm phase II trial (Ox-Onc)	Reason for treatment cessation, DOT, OS, previous treatments, ORR, PFS, OS, TTR, DOR, DCR, TTP, time to treatment failure, safety outcomes, quality of life
6	Daratumumab (Darzalex®)	Monotherapy for treatment of relapsed and refractory multiple myeloma	No estimate (highly uncertain)	17-01-2018	17-11-2020	Ongoing	Areas of clinical uncertainty: OS (generalisability of trial OS to UK clinical practice - further evidence needed in English clinical setting); subsequent treatment following daratumumab (many of treatments received after daratumumab in trials were	Primary: PH England routine population-wide cancer datasets (SACT) and NHS England Blueteq CDF system	Patient baseline characteristics, DOT, subsequent treatment, survival status, no. death events and time to death (used to validate OS observed in the daratumumab trials GEN501 and

ID	Active Substance (Brand name)	Indication	NICE most plausible ICER estimates prior to MAA	MAA start date	MAA end date	MAA Status	MAA Objective	MAA Main Evidence[1]	MAA Outcome Measures
							not available in the NHS or not available at this point in the treatment pathway, and some of these treatments were likely to prolong life when used after daratumumab - further evidence required to eliminate the confounding effect of subsequent treatment options not available to English patients and reduce uncertainty around generalisability of outcomes from MMY2002/GEN501 to English clinical setting)		MMY2002)
7	Ibrutinib (Imbruvica®)	Treatment of Waldenstrom's macroglobulinaemia in adults who have had at least one prior therapy	At least £54,100 / QALY (with patient access scheme)	28-09-2017	28-12-2020	Ongoing	Areas of clinical uncertainty: pre-progression mortality in the English setting; DOT	Primary: Systemic Anti-Cancer Therapy (SACT) database and NHS England Blueteq CDF system; Supportive: as part of the guidance review, supportive data from single-arm phase II trial (1118E) and phase III RCT (1127 iNNOVATE arm C) comparing rituximab with or without ibrutinib trial, and data from disease-specific registry	Pre-progression mortality (number of death events and time to death while on ibrutinib, patient baseline characteristics, treatment start and stop date, survival status (from both SACT, study 118E and study 1127)
8	Ixazomib (Ninlaro®)	In combination with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma	£31,691 / QALY (with commercial access agreement)	19-12-2017	19-12-2019	Ongoing	Areas of clinical uncertainty: magnitude of clinical benefit in terms of OS and DOT due to immaturity of registration trial data; HRQoL	Primary: Ongoing phase III RCT (TOURMALINE MM-1 or C16010) comparing lenalidomide and dexamethasone with or without ixazomib;	OS, DOT, EQ5D utility data, line of therapy

ID	Active Substance (Brand name)	Indication	NICE most plausible ICER estimates prior to MAA	MAA start date	MAA end date	MAA Status	MAA Objective	MAA Main Evidence[1]	MAA Outcome Measures
								Secondary: PH England routine population-wide cancer datasets (SACT) and NHS England Blueteq CDF system	
9	Niraparib (Zejula®)	Maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer after second response to chemotherapy	Germline mutation-negative-2L+ group: between £23,795 and £81,674 / QALY; Germline mutation-positive-2L group: between £20,694 and £54,632 / QALY (with patient access scheme)	01-06-2018	01-06-2020	Ongoing	Areas of clinical uncertainty: immaturity of OS data	Primary: Ongoing phase III RCT (ENGOT-OV16/NOVA) compared with placebo; Secondary: PH England routine population-wide cancer datasets (SACT) and NHS England Blueteq CDF system	OS, DOT, time to first subsequent treatment
10	Nivolumab (Opdivo®)	Treatment of previously treated squamous cell NSCLC	£50,014 / QALY (with commercial access agreement)	01-09-2017	01-06-2019	Ongoing	Areas of clinical uncertainty: different levels of clinical effectiveness according to PD-L1 expression; long term OS; DOT	Primary: Ongoing phase III RCT (CA209017) compared with chemotherapy (5 year follow up); Secondary: Systemic Anti-Cancer Therapy (SACT) database and NHS England Blueteq CDF system	OS, DOT, subgroup analysis of OS by PD-L1 expression
11	Nivolumab (Opdivo®)	Treatment of locally advanced or metastatic non-squamous NSCLC that was previously treated	£49,160 / QALY (with commercial access agreement)	01-09-2017	01-06-2019	Ongoing	Areas of clinical uncertainty: different levels of clinical effectiveness according to PD-L1 expression; long term OS; DOT	Primary: Ongoing single-arm phase III trial (5 year follow up of CA209057 - originally RCT compared with chemotherapy but switching occurred at 2 years for all patients); Secondary: Systemic Anti-Cancer Therapy (SACT) database and NHS England Blueteq CDF system	OS, DOT, subgroup analysis of OS by PD-L1 expression
12	Nivolumab	Treatment of	Between £45,000 and	01-11-	01-09-	Ongoing	Areas of clinical uncertainty:	Primary: Ongoing phase	OS, DOT, subgroup

ID	Active Substance (Brand name)	Indication	NICE most plausible ICER estimates prior to MAA	MAA start date	MAA end date	MAA Status	MAA Objective	MAA Main Evidence[1]	MAA Outcome Measures
	(Opdivo®)	recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum based therapy	73,600 / QALY (with patient access scheme); Full trial population using the commercial access agreement with 2-year stopping rule: between £30,377 and £49,408 / QALY (with commercial access agreement)	2017	2019		different levels of clinical effectiveness according to PD-L1 expression; long term OS; utility values	III RCT (CA209141) compared with investigator's choice (cetuximab, methotrexate, docetaxel); Secondary: PH England routine population-wide datasets (SACT) and NHS England Blueteq CDF system	analysis of OS by PD-L1 expression
13	Nivolumab (Opdivo®)	Adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease	Between £18,423 and £80,401 / QALY (excluding confidential discounts for subsequent treatments other than nivolumab and ipilimumab)	01-01-2019	01-12-2020	Ongoing	Areas of clinical uncertainty: long-term benefit OS; subsequent treatment use in patients relapsing post adjuvant treatment with nivolumab; efficacy and safety outcomes for patients re-treated with anti-PD-1 agents for metastatic disease following relapse	Primary: Ongoing phase III RCT (CA209238) compared with ipilimumab; Secondary: PH England routine population-wide datasets (SACT) and NHS England Blueteq CDF system	RFS, OS, data on subsequent treatment and outcomes
14	Obinutuzumab (Gazyvaro®)	In combination with bendamustine for treating follicular lymphoma refractory to rituximab	Confidential, but above the level that could be accepted as a cost effective use of NHS resources	26-07-2017	26-12-2020	Ongoing	Areas of clinical uncertainty: magnitude of OS benefit of obinutuzumab with bendamustine followed by obinutuzumab compared to bendamustine alone (e.g. hazard ratio, duration of effect)	Primary: Ongoing phase III RCT (GADOLIN) comparing bendamustine with or without obinutuzumab; Supportive: Systemic Anti-Cancer Therapy (SACT) database and NHS England Blueteq CDF system	OS ,PFS, next anti-lymphoma treatment, anti-lymphoma treatments received prior to treatment with obinituzumab, length of treatment
15	Olaratumab (Lartruvo®)[3]	In combination with doxorubicin for treating advanced soft tissue sarcoma	Between £46,000 and £60,000 / QALY	15-07-2017	15-12-2020	Ongoing	Areas of clinical uncertainty: difference in magnitude of improvement in median OS with olaratumab plus doxorubicin vs doxorubicin alone was greater than that	Primary: Ongoing phase III RCT (JGDJ) comparing doxorubicin with or without olaratumab; Secondary: Systemic Anti-Cancer Therapy (SACT)	OS, PFS, HRQoL, time of treatment and survival (DOT in UK setting)

ID	Active Substance (Brand name)	Indication	NICE most plausible ICER estimates prior to MAA	MAA start date	MAA end date	MAA Status	MAA Objective	MAA Main Evidence[1]	MAA Outcome Measures
							observed with PFS; need to extrapolate OS beyond trial period; heterogeneity of SCT; small numbers of patients; no HRQoL data; treatment duration due to generalisability of trial to UK clinical practice	database	
16	Osimertinib (Tagrisso®)	Treatment of locally advanced or metastatic EGFR T790M mutation-positive NSCLC	Between £60,663 and £70,776 / QALY	01-10-2016	01-03-2019	Ongoing	Areas of clinical uncertainty: extrapolating OS; generalisability to UK clinical practice	Primary: Ongoing phase III RCT (AURA3) compared with chemotherapy, ongoing single-arm phase II trial (AURA2); Secondary: Systemic Anti-Cancer Therapy (SACT) database	PFS, OS, DOT
17	Pembrolizumab (Keytruda®)	Adjuvant treatment of resected melanoma with high risk of recurrence	Less than £10,000 / QALY (with commercial arrangement)	01-12-2018	01-12-2021	Ongoing	Areas of clinical uncertainty: DMFS and OS compared to routine surveillance; use of subsequent treatments in the metastatic setting and the role of re-challenge	Primary: Ongoing phase III RCT (KEYNOTE-054) compared with placebo; Secondary: PH England routine population-wide datasets (SACT) and NHS England Blueteq CDF system	DMFS, OS, time to next treatment, performance status, subsequent therapies given, proportion of patients in each stage who receive pembrolizumab through CDF
18	Pembrolizumab (Keytruda®)	Treatment of untreated PD-L1 locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy	Between £44,504 and £46,447 / QALY (with commercial access agreement)	01-04-2018	01-12-2018	Ongoing	Areas of clinical uncertainty: long-term benefit OS compared to standard care in UK (docetaxel and paclitaxel)	Primary: Ongoing phase III RCT (KEYNOTE-045) compared with chemotherapy; Secondary: PH England routine population-wide datasets (SACT) and NHS England Blueteq CDF system	OS (including long term survival of those that have stopped treatment with pembrolizumab), DOT
19	Pembrolizumab (Keytruda®)	Treatment of untreated locally	Between £43,702 and £65,642 / QALY (with	01-07-2018	01-11-2019	Ongoing	Areas of clinical uncertainty: magnitude of OS and PFS	Primary: Ongoing phase III RCT (KEYNOTE-361)	OS, PFS, DOT, subgroup analyses

ID	Active Substance (Brand name)	Indication	NICE most plausible ICER estimates prior to MAA	MAA start date	MAA end date	MAA Status	MAA Objective	MAA Main Evidence[1]	MAA Outcome Measures
		advanced or metastatic urothelial cancer when cisplatin is unsuitable	commercial access agreement)				benefit compared to the UK standard of care	comparing pembrolizumab with or without chemotherapy versus chemotherapy; Secondary: PH England routine population-wide datasets (SACT) and NHS England Blueteq CDF system; Supportive: ongoing single-arm phase II trial (KEYNOTE-052)	
20	Pembrolizumab (Keytruda®)	First line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations, in combination with pemetrexed and platinum containing chemotherapy	Pembrolizumab combination compared with pemetrexed plus carboplatin or cisplatin or compared with chemotherapy plus carboplatin or cisplatin: cannot conclude with any certainty that the most plausible ICER is below £50,000/QALY gained without further evidence) (with commercial arrangement); Pembrolizumab combination compared with pembrolizumab monotherapy: cannot conclude with any certainty that the most plausible ICER is below £30,000/QALY gained without further evidence (with commercial arrangement)	01-01-2019	01-06-2019	Ongoing	Areas of clinical uncertainty: extent of OS benefit when comparing pembrolizumab in combination with pemetrexed and platinum-based chemotherapy with standard of care	Primary: Ongoing phase III RCT (KEYNOTE-189) comparing platinum plus pemetrexed chemotherapy with or without pembrolizumab	OS
21	Pembrolizumab (Keytruda®)	Monotherapy treatment of adult	Between £37,000 and £62,500 / QALY (with	01-09-2018	01-07-2022	Ongoing	Areas of clinical uncertainty: original trial used for approval	Primary: Public Health England routine	OS, DOT, proportion of patients who

ID	Active Substance (Brand name)	Indication	NICE most plausible ICER estimates prior to MAA	MAA start date	MAA end date	MAA Status	MAA Objective	MAA Main Evidence[1]	MAA Outcome Measures
		patients with relapsed or refractory Hodgkin Lymphoma who have failed ASCT and BV, or who are transplant-ineligible and have failed BV	commercial access agreement)				not designed as a bridge to transplant study so uncertainty around time at which allogenic stem cell transplant occurs and proportion of patients who receive an allogenic stem cell transplant; estimated OS	population-wide cancer data sets, including SACT and Hospital Episode Statistics, and NHS England Blueteq CDF System; Secondary: Ongoing single-arm phase II trial (KEYNOTE-087); Bone Marrow (Stem Cell) Transplant Register	receive a SCT, time from commencing treatment to transplant and intention to transplant
22	Pembrolizumab (Keytruda®)[2]	First-line treatment of metastatic NSCLC in adults whose tumours express PD-L1 with a =50% tumour proportion score with no EGFR or ALK positive tumour mutation	Between £46,083 and 61,577 / QALY	June 2017	Dec 17	Complete	No data	Ongoing phase III RCT (KEYNOTE-024) compared with standard of care (platinum-based chemotherapy)	PFS, OS, DOT
23	Tisagenlecleucel (Kymriah®)	Treatment of paediatric or young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia	Tisagenlecleucel compared with both blinatumomab and salvage chemotherapy: above £30,000/QALY (with patient access scheme); Compared with salvage chemotherapy: above £45,000/QALY (with patient access scheme)	01-11-2018	01-06-2023	Ongoing	Areas of clinical uncertainty: immaturity of data that does not fully support curative nature of the drug; rate of subsequent SCT	Primary: Ongoing single-arm phase II trials (ELIANA, ENSIGN, B2101J); Secondary: Bone Marrow (Stem Cell) Transplant Register and NHS England Blueteq CDF System	OS, rate of subsequent SCT
24	Tisagenlecleucel (Kymriah®)	Treatment of adult patients with relapsed or refractory diffuse large B cell lymphoma after two or more lines of systemic therapy	Between £42,991 and £55,403 / QALY (with the discount agreed in the commercial arrangement)	01-03-2019	01-02-2023	Ongoing	Areas of clinical uncertainty: immaturity of data to support curative nature of tisagenlecleucel, specifically OS; proportion of people who would need treatment for B-cell aplasia with intravenous	Primary: Ongoing single-arm phase II trial (JULIET or C2201); ongoing case-study series (Schuster); Secondary: PH England routine population-wide data sets (SACT) and NHS England Blueteq	OS, PFS, percentage of patients receiving tisagenlecleucel that require intravenous immunoglobulin use

ID	Active Substance (Brand name)	Indication	NICE most plausible ICER estimates prior to MAA	MAA start date	MAA end date	MAA Status	MAA Objective	MAA Main Evidence[1]	MAA Outcome Measures
							immunoglobulin; DOT	CDF System, potential to use Medical Data Solutions and Services	
25	Venetoclax (Venclyxto®)	Monotherapy for treatment of adult patients with chronic lymphocytic leukaemia	Around £50,000 and around £60,000 / QALY but ICERs are very uncertain	05-10-2017	05-12-2020	Ongoing	Areas of clinical uncertainty: uncertainty around OS as patients for whom venetoclax would be an option in clinical practice in England have more advanced disease than those in clinical trials; venetoclax trials are single-arm, and there is no comparative data in a matched population	Primary: Systemic Anti-Cancer Therapy (SACT) database	Prospective OS and DOT for venetoclax; retrospective OS and DOT for best supportive care (following failure to ibrutinib and idelalisib in combination with rituximab)

Note: ID identifier, NICE National Institute for Health and Care Excellence, ICER incremental cost effectiveness ratio, MAA Managed Access Agreement, MEA managed entry agreement, CDF Cancer Drugs Fund, PbMEA performance-based managed entry agreement, PD-L1 programmed death-ligand 1, QALY quality adjusted life year, CED coverage with evidence development, OS overall survival, PFS progression-free survival, UK United Kingdom, HRQoL health-related quality of life, DOT duration of therapy, PH Public Health, SACT Systemic Anti-cancer Therapy database, NHS National Health Service, AE adverse effects, SCT stem cell transplant, ROS1 ROS proto-oncogene 1, NSCLC non-small cell lung cancer, ALK anaplastic lymphoma kinase, NCRI National Cancer Research Institute, ORR objective response rate, TTR time to response, DOR duration of response, DCR disease control rate, TTP time to progression, RFS recurrence-free survival, EGFR epidermal growth factor receptor, DMFS distant metastasis-free survival, ASCT autologous stem cell transplant, BV brentuximab vedotin, HTA health technology assessment

1. Clinical trial identifiers written in brackets immediately after phase and study type.

2. As these MEAs were concluded, the original agreement document was not available for analysis; information was extracted from the NICE Technology Appraisal Guidance documents. Consequently, information on MEAs may be incomplete or contain some inaccuracies.

3.European Union marketing authorisation has since been withdrawn.

Source: Information extracted from HTA appraisal documentation and Managed Access Agreements on the NICE webpage. See individual data sources for product/indication pairs below.

Data sources for health technology assessment most plausible incremental cost effectiveness ratio estimate seen in Table A B.4. Numbers correspond to ID of the product/indication pair seen in Table A B.4

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Data sources for MAA documentation seen in Table A B.4. Numbers correspond to ID of the product/indication pair seen in Table A B.4.

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