Received: 4 November 2019 | Revised: 30 April 2020 | Accepted: 4 May 2020

DOI: 10.1002/hec.4112

SPECIAL ISSUE PAPER

WILEY Health Economics

The impact of managed entry agreements on pharmaceutical prices

Simona Gamba[1] | **Paolo Pertile**[2] | **Sabine Vogler**[3]

[1]Department of Economics and Finance, Università Cattolica del Sacro Cuore, Milan, Italy

[2]Department of Economics, University of Verona, Verona, Italy

[3]Pharmacoeconomics Department, Gesundheit Österreich GmbH, Austrian National Public Health Institute, Vienna, Austria

Correspondence
Paolo Pertile, Department of Economics, University of Verona, Italy.
Email: paolo.pertile@univr.it

Abstract

Managed entry agreements (MEAs) have been used for several years, with the aim of curbing the growth of pharmaceutical expenditure and enhancing patient access to innovation. Yet, much remains to be understood about their economic implications. This paper studies the impact of MEAs on list prices, that is, prices before the deduction of any discount. Using a theoretical model, we show that, under most price setting regimes, the introduction of an MEA leads to a higher list price. This is confirmed by our empirical analysis of a sample of 156 medicines in six countries, providing a conservative estimate of the increase in price due to the MEA of 5.9%. A relevant policy implication is that payers may overestimate the financial gains that can be achieved through this tool.

KEYWORDS

managed entry agreements, pharmaceutical prices, risk-sharing agreements

1 | INTRODUCTION

Managed entry agreements (MEAs), often referred to as *risk-sharing agreements*, are being increasingly adopted by payers to manage the tension between ensuring the largest number of patients can benefit from access to new, possibly innovative, medicines and adhering to strict budget constraints.[1] MEAs can take simple forms, such as financial discounts, or involve more complex contracts, regulating the relationship between the payer and the manufacturer. The typical taxonomy distinguishes between the *financial-based* agreement (FA) and the *performance-based* agreement (PA). Each category comprises several types of contract. *Cost and volume* agreements, whereby discounts are applied for units bought by the payer over a given threshold, are an example of a FA. Similarly, with *cost-sharing* agreements, no payment is made to the manufacturer for a certain number of doses when the treatment of a patient is started. Other types of FA include simple discounts and straight caps on total expenditure on a certain medicine. PAs may make the payment dependent on the existence of a patient response to the treatment, or may use a rule to adjust the price based on additional evidence the manufacturer is mandated to provide. In this paper, we adopt the broadest definition of MEA, which also includes a third category of agreements in addition to FAs and PAs, with no direct financial implications. Agreements in this third group, sometimes called *appropriateness agreements* (AAs), aim to enhance the appropriateness of prescriptions through the management of patient registries (Jommi & Minghetti, 2015).

Several authors have discussed the risks and opportunities of MEAs. While the immediate consequence of these agreements is an expected reduction in pharmaceutical expenditure, the literature has investigated other impacts, such as patient access to innovation (Stafinski, McCabe, & Menon, 2010) and the incentive to invest in research and development (R&D) (Cook, Vernon, & Mannin, 2008; Levaggi, Moretto, & Pertile, 2017). The present paper focuses on the impact of

[1]Overviews of the use of MEAs in various countries can be found, for example, in (Ferrario & Kanavos, 2013), (Carlson, Chen, & Garrison, 2017), (Ferrario et al. 2017) and (Pauwels, Huys, Vogler, Casteels, & Simoens, 2017).

MEAs on list prices, that is, prices before any deduction due to the agreement. Understanding whether MEAs affect list prices is essential to be able to correctly quantify financial savings on pharmaceutical expenditure due to these agreements, the main reason for their introduction from the payers' perspective. This is because a correct estimate of the financial savings requires knowledge of the counterfactual price, that is what the price would be without the agreement, which is clearly unobservable. If the introduction of an MEA leads to higher (lower) list prices, ignoring this impact may lead to an overestimate (underestimate) of financial savings.

The implicit assumption that list prices are the same with or without an MEA is common in the policy debate[2] and is also often made in some theory-based papers (e.g., Zaric & O'Brien, 2005; Gavious, Greenberg, Hammerman, & Segev, 2014; Zhang & Zaric, 2015). However, manufacturers might anticipate the presence of an MEA and respond by increasing list prices to reduce the revenue loss resulting from the agreement (Towse, 2010; Pita Barros, 2011).

Despite the enormous attention given to the implementation of MEAs, there is still little information on the quantitative impact of their introduction. One exception is Russo et al. (2010), who find that, for oncology products in Italy, the time for patient access tends to be shorter if there is an agreement. Van de Vooren et al. (2015) and Navarria et al. (2015) estimate the amounts reimbursed by pharmaceutical companies in Italy as a result of PAs. However, this literature tends to investigate correlations based on case studies in specific countries. A major challenge for the assessment of the impact of MEAs is the confidential nature of the contents of the agreements; in some cases, it is not even known whether an agreement exists. A recent overview of the literature concludes that assessment of MEAs 'requires not only more published data but also models to understand and estimate the advantages of such agreements and to enable the consequences of these agreements to be compared with those in situations without them' (Antonanzas, Juárez-Castelló, Lorente, & Rodríguez-Ibeas, 2019, p. 1479).

The present paper aims to contribute to the filling of this gap. At the theoretical level, we build on the existing literature [3] to include the analysis of other types of agreement and several policy scenarios. In particular, we extend the analysis to cases where the introduction of an MEA is stochastic. Empirically, we provide the first estimate of the impact of MEAs on list prices based on a comparatively large set of medicines and several countries. Our empirical analysis uses information from six European countries for which it was possible to retrieve precise information about the adoption of MEAs, exploiting the fact that, in general, an MEA for one drug may exist in some countries, but not in others. We combine information on the presence of an agreement and the type of agreement with data on list prices for 156 medicines as of December 2016. The identification strategy exploits differences between countries in products covered by an MEA to estimate the average treatment effect on the treated of MEAs at the level of list prices.

The theoretical results show that, unless the manufacturer acts myopically or prices are determined mechanically through a mechanism of external reference pricing (ERP), the expected impact of the introduction of an MEA is an increase in the list price. Ignoring this impact may lead to an overestimation of the savings achieved through the MEA. The theoretical finding that, under most price setting regimes, the introduction of an MEA leads to a higher list price is supported by the empirical results: in the baseline specification, list prices are on average 5.9% higher with MEA. Further analysis distinguishing between different types of MEA suggests the impact is mainly driven by FAs. Due to some conservative assumptions that we make, we believe our estimates can be considered a lower bound of the true impact.

The remainder of the paper is organised as follows. Section 2 investigates the theoretical impact of the introduction of an MEA on list prices in a number of settings. Section 3 presents the data and the empirical specification, with results set out in Section 4. Section 5 concludes and discusses policy implications.

2 | INTRODUCING MEAS IN DIFFERENT SETTINGS

The aim of this section is to contribute to the existing theoretical literature on the impact of MEAs on prices and to provide a theoretical background for the interpretation of the empirical analysis in Section 3. The two theoretical contributions closest to ours are those of Pita Barros (2011)[4] and Antonanzas et al. (2011). Our theoretical analysis differs from theirs in various ways. Firstly, our focus is specifically on the impact of MEAs on prices.[5] Another difference is that Pita Barros

[2] For example, this assumption is fundamental for the argument that some of these agreements lead to *shifting* (from the payer to the manufacturer), rather than to *sharing* of risk (Towse & Garrison, 2010).
[3] See Antonanzas et al. (2019) for an overview.
[4] For a recent development of the model in Pita Barros (2011), see Mahjoub et al. (2018).
[5] Pita Barros (2011) considers additional factors such as the welfare implications of the introduction of an MEA, whereas in Antonanzas et al. (2011), the focus is on the conditions under which a health authority would propose an MEA to a manufacturer.

(2011) and Antonanzas et al. (2011) focus on PAs, whereas we extend the analysis to the impact of FAs and AAs. Finally, both contributions focus on a specific framework in terms of pricing regulation: in Pita Barros (2011), the price is set by a profit-maximising firm, while in Antonanzas et al. (2011), it is the result of Nash bargaining. We consider these two frameworks as well as others that may be relevant in the real world. In particular, we also consider a framework where the introduction of an agreement is stochastic.

Let a new medicine be available for the treatment of a population of patients, whose size is normalised to one. The new treatment provides either a benefit e, with probability π, or no benefit. The probability of success is distributed in the population with density $f(\pi)$. It is also assumed that the treatment is only provided to patients for whom the probability of success exceeds a minimum threshold, $\underline{\pi}$. Unless otherwise stated, we assume $\underline{\pi}$ to be exogenous and based exclusively on clinical criteria.

The process of price determination involves a payer and a manufacturer, aiming at the maximisation of the net expected value of health benefits (S) and of expected profit (R), respectively:

$$S = \int_{\underline{\pi}}^{1} (\pi\ \lambda\ e - p) f(\pi)\ d\pi\ ;\ R = \int_{\underline{\pi}}^{1} (p - c) f(\pi) d\pi, \tag{1}$$

where p is the price, c the marginal cost[6] and λ the monetary value per unit of effectiveness. The definition of $S(\cdot)$ means that the effectiveness of any therapeutic alternative for the same indication is normalised to zero, which allows us to disregard the corresponding variables for the existing treatment. The rules under which the payer and the manufacturer interact to determine the price of the new treatment depend on the specific regulatory framework for price setting.

The three types of agreement are modelled as follows:

1. FA: we model a simple financial discount, that is, the simplest form of agreement, which also turns out to be most common in the data used for the empirical analysis. Using superscripts to denote the type of MEA (f: FA, p: PA, a: AA), the resulting objective functions are

$$S^f = \int_{\underline{\pi}}^{1} (\pi\ \lambda\ e - p(1 - m)) f(\pi)\ d\pi\ ;\ R^f = \int_{\underline{\pi}}^{1} (p(1 - m) - c) f(\pi) d\pi, \tag{2}$$

   where m is the rate of reduction of the price due to the MEA. In what follows, p indicates the *list price* (gross price) and $p(1 - m)$ the *net price*.
2. PA: the treatment is paid only if the patient responds. Hence,

$$S^p = \int_{\underline{\pi}}^{1} \pi(\ \lambda\ e - p) f(\pi)\ d\pi\ ;\ R^p = \int_{\underline{\pi}}^{1} (\pi\ p - c) f(\pi) d\pi. \tag{3}$$

3. AA: in this case, it is less obvious how to model the agreement, because an AA is not intended to have direct financial implications. Because the aim is to reduce the number of inappropriate treatments, that is, those with a low probability of success, we assume that an AA increases the lower limit of the probability of success from $\underline{\pi}$ to $\underline{\pi}(1 + k)$, where k is a parameter that depends on how strict the rules for prescription and use are under the agreement. The resulting objective functions are

$$S^a = \int_{\underline{\pi}(1+k)}^{1} (\pi\ \lambda\ e - p) f(\pi)\ d\pi\ ;\ R^a = \int_{\underline{\pi}(1+k)}^{1} (p - c) f(\pi) d\pi. \tag{4}$$

   It is important to note a significant difference between an AA and the other two types of agreement. While FAs and PAs have immediate financial consequences, with AAs, these consequences depend on whether or not the introduction of a registry leads to a lower number of treatments. In principle, prescription behaviour is likely to comply with appropriateness criteria even without an AA, in which case, there is no financial impact (equivalent to $k = 0$).

The remaining part of this section is a theoretical analysis of the impact of the introduction of an agreement on the list price in the following price regulation frameworks:

[6] This does not include the R&D component, as it is sunk at this stage.

- Nash bargaining;
- Uncertainty about the introduction of a MEA;
- External Reference Pricing.

Although real-world pricing policies may be a combination of more than one approach, the analysis of these frameworks allows to clarify how economic agents react to the introduction of an MEA and the resulting impact on list prices. Understanding whether the introduction of an MEA has an impact on list prices is essential from the policy perspective, because the answer to this question determines whether or not the approach typically adopted to estimate the financial savings arising from these agreements is reliable. The usual approach is to compute financial savings by considering the impact of the agreement on the net price or on the number of treatments, given the observed list price. We refer to this approach as to naïve calculation of savings. The correct estimate, however, requires knowledge of the counterfactual price, that is, the list price without an MEA, which is unobservable. The naïve calculation leads to an overestimate (underestimate) of true savings if the list price observed under an agreement is higher (lower) than the counterfactual price.

2.1 | Nash bargaining

Assuming that the disagreement pay-off is zero for both parties, and denoting with α and $1-\alpha$ the bargaining power of the payer and the manufacturer, respectively, for the case of no MEA, the maximisation problem is[7]

$$\underset{p_n}{\operatorname{argmax}} \left[S(p_n)\right]^{\alpha} \cdot \left[R(p_n)\right]^{1-\alpha}, \tag{5}$$

which leads to the following first-order condition (FOC):

$$(1-\alpha)\int_{\underline{\pi}}^{1}(\pi\ \lambda\ e - p_n)f(\pi)\ d\pi = \alpha\int_{\underline{\pi}}^{1}(p_n - c)f(\pi)d\pi. \tag{6}$$

It is worth observing that, if $\alpha = 0$, at the optimum, expected revenues equal the monetary value of the expected health benefits, that is, the price is value-based and the whole rent goes to the manufacturer. This is also the price the manufacturer would set if faced with a maximum threshold of the incremental cost-effectiveness ratio (ICER) equal to λ, above which no reimbursement is granted.[8] Hence , valued-based prices and the existence of a maximum cost-effectiveness threshold may be seen as special cases of the bargaining solution. At the opposite extreme, with $\alpha = 1$, the price equals the marginal cost and the payer retains the whole rent.

In the presence of an FA, the FOC becomes

$$(1-\alpha)\int_{\underline{\pi}}^{1}(\pi\ \lambda\ e - p_n^f(1-m))f(\pi)\ d\pi = \alpha\int_{\underline{\pi}}^{1}(p_n^f(1-m) - c)f(\pi)d\pi. \tag{7}$$

It is immediate to see that the solution in Equation (7) is a rescaling of the one in Equation (6), with no impacts in real terms: the equilibrium price with no MEA (p_n) equals the net price with an FA, ($p_n^f(1-m)$). Hence, in this case, we expect an increase in the list price ($p_n^f > p_n$) as a result of the introduction of an FA, such that the net price is unaffected. Hence, the naïve calculation of savings due to the agreement leads to an overestimation.[9]

Under a PA, the FOC defining the equilibrium price is

$$(1-\alpha)\int_{\underline{\pi}}^{1}\pi(\lambda\ e - p_n^p)f(\pi)\ d\pi = \alpha\int_{\underline{\pi}}^{1}(\pi\ p_n^p - c)f(\pi)d\pi. \tag{8}$$

The comparison with the case without an MEA is similar to that of an FA. Revenues in Equation (6) (i.e., $\int_{\underline{\pi}}^{1} p_n\ f(\pi)\ d\pi$) are replaced with a lower value ($\int_{\underline{\pi}}^{1}\pi\ p_n^p\ f(\pi)\ d\pi$) in Equation (8). With PA, the resulting price is such

[7] Below, subscripts of the equilibrium price are used to denote the relevant framework, whereas superscripts still define the type of MEA, if any.

[8] See, for example, Levaggi and Pertile (2020). In this case, a value of expenditure (revenues) equal to $\lambda\int_{\underline{\pi}}^{1}\pi\ e\ f(\pi)\ d\pi$ implies an ICER equal to λ, meaning that this is the highest value of expenditure (revenues) that ensures reimbursement under this regime.

[9] In this case, the actual saving would be zero.

that $\int_{\underline{\pi}}^{1} \pi\ p_n^p\ f(\pi)\ d\pi = \int_{\underline{\pi}}^{1} p_n\ f(\pi)\ d\pi$. Therefore, as in the case of an FA, the expected impact is an increase in the list price, such that the expected expenditure for the payer is the same as with no MEA. Again, the naïve computation of the savings leads to an overestimate.

Finally, for an AA, the FOC is

$$(1-\alpha)\int_{\underline{\pi}(1+k)}^{1}(\pi\ \lambda\ e - p_n^a)f(\pi)\ d\pi = \alpha\int_{\underline{\pi}(1+k)}^{1}(p_n^a - c)f(\pi)d\pi. \tag{9}$$

In this case, we are interested in the analysis of the impact of an increase in k on the price that solves Equation (9). The implicit function theorem can be used to show that the sign of $\frac{dp_n^a}{dk}$ is the same as the sign of

$$(1-\alpha)\underline{\pi}\lambda e \geq 0. \tag{10}$$

Hence, the introduction of an MEA leads to a higher list price, unless $\alpha = 1$. The intuition for this result is that, unless $\alpha = 1$, the price grows with the monetary value of the health benefit. Moving from $k = 0$ (i.e., no agreement) to a strictly positive value of k means that, on average, the treated population has higher probability that the treatment is successful, which means a greater expected effectiveness and therefore a higher price. Unlike for FAs and PAs, here, savings may be positive. Nonetheless, the positive impact of the agreement on the list price means that the naïve calculation leads to an overestimate.

2.2 | Uncertainty about the introduction of an MEA

In the previous subsection, we assumed that the manufacturer knows whether or not an MEA exists before setting or negotiating the price. However, this information may not be available. Here, we study the situation where the manufacturer may propose a price and the payer, given the proposed price, may decide to introduce an MEA.

If the manufacturer is myopic, that is, it sets or negotiates the price without taking into account that the payer might introduce an MEA, the MEA would have no impact on the list price, and the naïve estimate of savings would coincide with the true value.

A more interesting case arises if the manufacturer is forward looking, meaning that in proposing the price, it anticipates the possibility of an MEA being introduced. For this case to be different from the Nash bargaining framework, the decision whether or not to introduce an MEA is assumed to be nondeterministic. Situations where this might be relevant are those where decisions are based on the comparison between an ICER and a maximum acceptability threshold, whose level is not known with certainty to the manufacturer (Jobjörnsson, Forster, Pertile, & Burman, 2016). Hence, the manufacturer knows that the payer might introduce an MEA whenever the ICER deriving from the proposed price exceeds the unknown threshold.[10] From the perspective of the manufacturer, the acceptability threshold is given by the random variable W, with cumulative distribution function F_W. With no MEA, the manufacturer sets the price at the value that maximises the expected profit, that is, it solves

$$\underset{p_u}{\text{argmax}} \quad \left[1 - F_W(ICER(p_u))\right]\int_{\underline{\pi}}^{1}(p_u - c)f(\pi)d\pi, \tag{11}$$

where

$$ICER(p_u) = \frac{\int_{\underline{\pi}}^{1} p_u\ f(\pi)d\pi}{\int_{\underline{\pi}}^{1}\pi\ e\ f(\pi)d\pi}.$$

Jobjörnsson et al. (2016) show that, under mild conditions for the characteristics of F_W, Equation (11) has a unique maximum corresponding to a finite value of p_u. Intuitively, the manufacturer equalises the marginal benefit of an increased price in terms of additional revenues with the marginal cost, due to the increased probability of obtaining no reimbursement.

[10] The threshold might not be known with certainty because, for example, some characteristics of the drug or the disease affect the payer's willingness to pay although the threshold does not explicitly depend on them.

Let us assume now that the payer introduces an MEA whenever the price set by the manufacturer is such that the ICER exceeds the true acceptability threshold, which is only known to the payer. In the case of an FA, we assume that if an agreement is introduced, it is such that the net price, $p_u^f(1-m)$, is set at the maximum value such that the condition is satisfied, that is,

$$\frac{\int_{\underline{\pi}}^{1} p_u^f(1-m)f(\pi)d\pi}{\int_{\underline{\pi}}^{1} \pi\ e\ f(\pi)d\pi} = W. \tag{12}$$

The manufacturer maximises

$$\begin{aligned}\underset{p_u^f}{\operatorname{argmax}}\ \left[1-F_W(ICER(p_u^f))\right]\int_{\underline{\pi}}^{1}(p_u^f-c)f(\pi)d\pi+\\ F_W(ICER(p_u^f))\int_{\underline{\pi}}^{1}(E[W|W<ICER(p_u^f)]\pi e-c)f(\pi)d\pi.\end{aligned} \tag{13}$$

The MEA allows to obtain reimbursement irrespective of the proposed price because m is set so the maximum acceptability threshold is met (see Equation 12). Thus, there is no reason for the manufacturer to opt for a low price due to the risk of setting a price that is lower than the true willingness to pay. Hence, in principle, in this case, the optimal price to propose is unbounded. Although this is clearly an extreme case, it highlights the risk that using an MEA to meet the acceptability threshold prevents the threat of no reimbursement from playing a role in extracting rent from the manufacturer. Therefore, we would expect list prices to be higher in a framework where MEAs are allowed than in one where they are not. An important difference with the cases previously studied is that, in this case, the possibility of having an MEA may increase all prices, including those that, in the end, are reimbursed without an MEA.

Similarly, we assume that PAs are introduced if the ICER exceeds the maximum acceptability threshold. The difference with an FA is that, in this case, no parameter can be adjusted to meet the maximum acceptability threshold. Hence, even after a PA has been introduced, the new treatment may not be cost effective and therefore may not be reimbursed. The resulting objective function is

$$\begin{aligned}\underset{p_u^p}{\operatorname{argmax}}\ \left[1-F_W(ICER(p_u^p))\right]\int_{\underline{\pi}}^{1}(p_u^p-c)f(\pi)d\pi+\\ +F_W(ICER(p_u^p))\left[1-F_W(ICER^{pa}(p_u^p))\right]\int_{\underline{\pi}}^{1}(\pi p_u^p-c)f(\pi)d\pi,\end{aligned} \tag{14}$$

where $ICER^{pa}$ is the value of the ICER resulting from the implementation of the PA:

$$ICER^{pa}(p_u^p) = \frac{\int_{\underline{\pi}}^{1} \pi\ p_u^p\ f(\pi)d\pi}{\int_{\underline{\pi}}^{1} \pi\ e\ f(\pi)d\pi}.$$

Unlike in the case of an FA, now the optimal price is bounded because an excessively high price would involve an ICER higher than the maximum acceptability threshold even after the introduction of the PA. Nonetheless, the agreement leads to an increase in the list price ($p_u^p > p_u$), by reducing the marginal cost for the manufacturer of a price increase.

As for the other types of agreement, we assume that an AA is introduced if the price originally proposed is such that the maximum acceptability threshold is exceeded. In particular, in this case, k is set at the minimum value such that the ICER does not exceed the threshold. The value that satisfies this condition (k^{aa}) is implicitly defined by the equation

$$\frac{\int_{\underline{\pi}(1+k^{aa})}^{1} p_u^a\ f(\pi)d\pi}{\int_{\underline{\pi}(1+k^{aa})}^{1} \pi\ e\ f(\pi)d\pi} = W. \tag{15}$$

Note that, if the value of p_u^a is particularly high, there exists no k^{aa} such that $\underline{\pi}(1+k^{aa}) < 1$. The situation is therefore similar to the case of a PA, with three ranges of p_u^a, leading to reimbursement and no MEA, reimbursement with an

appropriately defined MEA (Equation 15) and no reimbursement. The objective function can be written as

$$\begin{aligned}\underset{p_u^a}{\operatorname{argmax}} \ & \left[1 - F_W(ICER(p_u^a))\right] \int_{\underline{\pi}}^{1} (p_u^a - c) f(\pi) d\pi + \\ & + F_W(ICER(p_u^a)) \max \left\{ 0 \ , \ E_W \left[\int_{\underline{\pi}(1+k^{aa})}^{1} (p_u^a - c) f(\pi) d\pi | W < ICER(p_u^a) \right] \right\}. \end{aligned} \tag{16}$$

Also in this case, the introduction of an MEA leads to a higher list price because the agreement reduces the marginal cost of an increase in price. However, the optimal price is bounded, due to the possibility that the product is not reimbursed.

As highlighted above, in the situation where the payer, given the proposed price, may decide to introduce an MEA (of whatever type), list prices are higher than in a framework where MEAs are not allowed. This means that in this situation, the naïve calculation of the savings due to an agreement leads to an overestimation.

2.3 | External reference pricing

Let us consider the purest form of ERP, that is, where the domestic price is determined solely as a function of prices previously set in a defined group of other countries.[11] Because the list price is fixed, given the ERP rule, the subsequent introduction of an MEA can only affect the net price. It is immediate to see from Equations (2) to (4) that the introduction of an agreement reduces the payer's expenditure and the manufacturer's profit. In this case, the counterfactual price equals the list price observed in the presence of an MEA, and the naïve estimate is unbiased.

2.4 | Summary of theoretical findings

The main results of the theoretical analysis can be summarised as follows:

- In the frameworks considered, list prices are higher in the presence of an MEA, unless the manufacturer is myopic or prices are mechanically determined by ERP.
- Under the assumptions of Section 2.2, the prices of products for which no MEA exists may also increase.
- A necessary condition for an AA to have an impact on list prices is that its introduction changes prescription behaviour.
- A positive impact of the MEA on list prices means that a naïve calculation of savings from agreement leads to an overestimation, by overestimating the counterfactual price.[12]

In the following sections, we use the fact that for a given product, an MEA may exist in some countries but not in others, to investigate whether the introduction of an MEA has an impact on the list price. We interpret the impact, if any, as evidence that the list price with an MEA differs from the counterfactual price, meaning that the naïve calculation of savings due to the agreement is biased.

3 | METHODOLOGY

3.1 | Data

A major hurdle in conducting empirical analysis on the impact of MEAs is the need to have precise information on the existence and type of agreement for a given medicine. Although this information is often unavailable, we were able to retrieve it for December 2016 in six European countries (Belgium, England, Greece, Italy, the Netherlands and Norway). The availability of information on the content of agreements in the countries that use them varies greatly. For Belgium and the Netherlands, we only know that all the MEAs in place in December 2016 were FAs (Vogler, Haasis, Dedet, Lam, & Bak Pedersen, 2018). For England and Italy, the information is much more detailed. However, the size of financial

[11] However, in most countries, ERP is supplementary to other pricing policies (Vogler, Zimmermann, & Haasis, 2019).

[12] In this section, we have modelled one sole type of FA, a simple discount. The economic implications are the same for other types of agreements such as *cost & volume* or *cost sharing*. The extension of the results to the case of an *expenditure cap* is less obvious. However, even in this case, there is a risk of overestimating the savings due to the agreement if the MEA has a positive impact on the price. Assuming a binding expenditure cap, a naïve estimate of the financial saving is $\int_{\underline{\pi}}^{1} p^e f(\pi) d\pi - EC$, where p^e is the price set where an MEA based on an expenditure cap exists and EC is the value of the expenditure cap. If the counterfactual price is lower than p^e, this estimate exceeds the value of the actual saving. However, it should be noted that, in this case, the overestimate of financial savings may be at least partly offset by the benefit of a reduced financial risk.

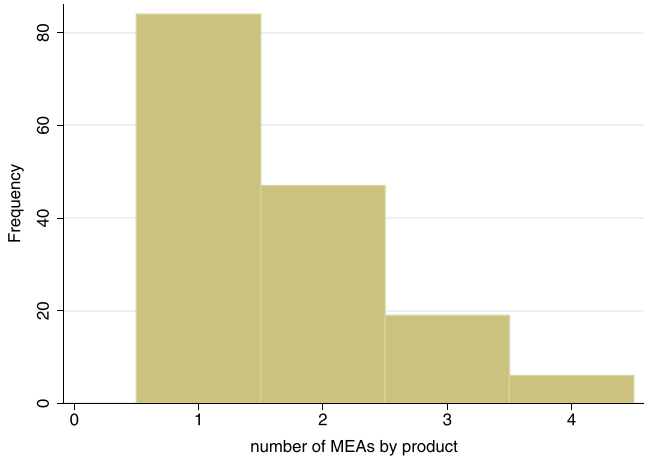

FIGURE 1 Number of managed entry agreements (MEAs) by product [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Products covered by a managed entry agreement by Anatomical Therapeutic Chemical (ATC) code (December 2016)

ATC1 code	Number	Percentage
A: Alimentary tract and metabolism	26	17
B: Blood and blood forming organs	6	4
C: Cardiovascular system	5	3
D: Dermatologicals	2	1
G: Genitourinary system and sex hormones	0	0
H: Systemic hormonal preparations, excluding sex hormones and insulins	1	1
J: Antiinfective for systemic use	9	6
L: Antineoplastic and immunomodulating agents	90	58
M: Musculo-skeletal system	3	2
N: Nervous system	6	4
P: Antiparasitic products, insecticides and repellents	0	0
R: Respiratory system	3	2
S: Sensory organs	3	2
V: Various	2	1
Total	156	100

discounts is unknown in all cases. Because in Greece and Norway, no MEA existed before 2017,[13] these two countries can be used as controls.

Information concerning the existence and type of agreement was retrieved from the relevant authorities in each country. The source of information for Belgium is the Social Health Insurance institute (INAMI), accessed through the Belgian Healthcare Knowledge Centre (KCE), while data for the Netherlands were provided by the Dutch Ministry of Health. For England, the National Institute for Health and Care Excellence website [14] documented the situation as at December 2016, specifying the type of each agreement. Finally, up-to-date information on active and previous agreements in Italy, the date they came into effect and/or ended, as well as the type of agreement, is provided on the National Agency for Medicines (Agenzia Italiana del Farmaco) website.[15]

Our initial sample includes all 191 medicines that in December 2016 had an MEA in at least one of these countries. We then excluded all products for which it was possible to retrieve the price in less than three countries. This reduced our sample to 156 medicines, including 84 with an MEA only in one country, 47 in two countries, 19 in three countries and 6 in four countries (see Figure 1). [16] Interestingly, 58% of products in our sample are antineoplastic and immunomodulating agents (see Table 1). A large number of MEAs also refer to treatments for the alimentary tract and the metabolism.

[13] This was confirmed by a representative of the Greek National Organization for the Provision of Healthcare Services, on January 14, 2019, and of the Norwegian Medicine Agency, on November 15, 2018.
[14] https://www.nice.org.uk/about/what-we-do/patientaccess-schemes-liaison-unit/list-of-technologies-with-approvedpatient-access-schemes, accessed on February 20, 2019.
[15] https://www.agenziafarmaco.gov.it/content/lista-aggiornata-dei-registri-e-dei-piani-terapeutici-web-based, accessed on February 12, 2019. For products where MEAs were updated after December 2016, as specified on the national pharmaceutical authority website, we retrieved the information concerning the type of agreement as at December 2016 from the Italian Official Gazette (*Gazzetta Ufficiale*).
[16] The list of active ingredients for medicines in our sample is set out in Table S1. An active ingredient may be used in several products.

TABLE 2 Number and type of MEAs by country (December 2016)

	Belgium			Italy			Netherlands			England		
	PA			PA			PA			PA		
FA	No	Yes	Total	No	Yes	Total	No	Yes	Total	No	Yes	Total
No	87	0	87	109*	21	130	139	0	138	95	1	96
Yes	69	0	69	18	8	26	17	0	17	57	3	60
Total	156	0	156	127	29	156	156	0	156	152	4	156

Abbreviations: FA, financial-based agreement; MEA, managed entry agreement; PA, performance-based agreement.

* For 65 of these products, appropriateness agreements are in force.

Table 2 summarises the number and type of agreements in each of the four treated countries. As of December 2016, for the 156 products in our sample, there were 172 FAs, 33 PAs, and 65 AAs. Each product can be covered by an agreement in more than one country: the products with an FA, PA and AA totalled 112, 31 and 65, respectively. Although PAs attracted enormous attention in policy and academic debates, in our sample, they exist almost exclusively in Italy. Another peculiarity of Italy is that, to our knowledge, it is the only country that uses agreements based purely on registries (AAs) to ensure the appropriateness of prescribing and use of the medicines. In other countries, registries accompany MEAs.

Country-specific prices per unit for each product were retrieved through the Pharma Price Information (PPI) service (Vogler, 2018) of the Austrian National Public Health Institute, which uses national administrative price databases. For each product, a single presentation (i.e., a medicine in a specific pharmaceutical form, strength and pack size) is selected, based on clinical relevance, evaluated on the basis of the recommended dose indicated in the summary of product characteristics and/or the defined daily doses assigned by the Oslo WHO Collaborating Centre for Drug Statistics Methodology. As a secondary criterion, data availability was used, selecting presentations with the most available price information.

For 18 medicines, where no price data were available for the selected presentation, the price of a presentation with the same pharmaceutical form and strength, but a different pack size, was included. Because the analysis is run on the price per unit, this does not affect our results. Price data for the relevant presentation in one or more countries could not be retrieved for 35 products,[17] leading to the loss of 44 observations. Therefore, the final sample consists of 892 observations, instead of the expected 936 (i.e., $156 \cdot 6$).[18]

We use official list prices, as published by pricing authorities,[19] at the ex-factory level. In the Netherlands, Norway and England, official ex-factory prices are not regulated and therefore are not published. Because prices are set at the wholesale level, wholesale price data are available. For these countries, ex-factory prices are calculated from wholesale prices and average margins in 2016, as provided by the PPI service. Price data are expressed in the national currency and have been converted into US$ purchasing power parity (PPP) using the PPP for 2016 sourced from the Organisation for Economic Co-operation and Development.[20]

The top portion of Table 3 shows descriptive statistics for the sample analysed, separating PPP prices and prices without a PPP adjustment. The bottom portion of the table shows the same information for products for which price data are available in all countries. This avoids the potentially confusing effect of differences between countries in the composition of the relevant sample. Interestingly, differences between countries are much smaller for nominal than for PPP prices.

It is important to mention that in some cases, MEAs exist only for some indications of a medicine. Because information on specific indications to which the MEA applies is not available for every country, a conservative approach was adopted: an MEA is attributed to a product in a given country whenever an agreement exists for at least one indication. Because for some of these products, there may be other indications not affected by the agreement, our estimate of the impact of MEAs on list prices may be biased downward.

3.2 | Empirical specification

We exploit the fact that, in general, for a given product, an MEA exists only in some countries, to estimate the impact of MEAs on list prices. Our baseline empirical specification is

$$ln[price_{ic}] = \alpha + \beta FA/PA_{ic} + \gamma AA_{ic} + \delta_p + \zeta_c + \epsilon_{ic}, \quad (17)$$

[17] Active ingredients of these products are marked with an asterisk in Table S1.

[18] This might determine a potential problem of sample selection if missing observations are not randomly distributed. We address this point by estimating the same model on a restricted sample, which includes only products for which the price is available in all countries (see Table 5).

[19] Official prices do not include any discounts or clawbacks.

[20] https://data.oecd.org/conversion/purchasing-power-parities-ppp.htm#indicator-chart, accessed on June 6, 2019.

TABLE 3 Average ex-factory price per unit (December 2016) in the full (upper part) and restricted sample (lower part)

		US$ PPP		US$	
Country	**Obs.**	**Average price**	**SD**	**Average price**	**SD**
Full sample					
Belgium	143	969.5	2,498.4	811.6	2,091.5
Greece	148	1,097.7	2,721.6	694.4	1,721.7
Italy	151	1,075.3	2,592.7	809.5	1,951.7
Netherlands	148	944.7	2,281.6	806.8	1,948.4
Norway	151	626.6	1,540.8	750.3	1,844.9
England	151	813.2	2,130.2	710.0	1,859.8
Restricted sample: products for which price data are available for all countries					
Belgium	121	1,079.5	2,661.2	903.7	2,227.8
Greece	121	1,263.4	2,951.6	799.2	1,867.1
Italy	121	1,218.2	2,815.6	917.0	2,119.5
Netherlands	121	1,086.2	2,480.7	927.6	2,118.5
Norway	121	707.6	1,673.4	847.3	2,003.7
England	121	925.2	2,325.6	807.8	2,030.5

Abbreviation: PPP, purchasing power parity.

where the dependent variable is the natural logarithm of the PPP price for product i in country c and FA/PA is a binary variable taking value 1 if there is either a PA or an FA. Hence, this dummy variable identifies the presence of any type of agreement that fits the most standard definition of MEA. Because it is debatable whether AAs should be considered part of the category of MEAs and the introduction of this type of agreement would have no financial implications if prescription behaviour is consistent with appropriateness criteria even without the MEA, we introduce a separate dummy variable for this type of agreement. δ_i is a product fixed effect, the inclusion of which is intended to capture the dependency of the price on drug's quality and therapeutic advances, both of which are unobserved. A product fixed effect is also essential because the standard course of treatment varies between drugs. ζ_c is a county fixed effect, needed to account for unobserved heterogeneity among countries due, for example, to differences in reimbursement policies. Finally, ϵ_{ic} is the idiosyncratic error term.

The empirical literature on the determinants of pharmaceutical prices has investigated the role of a number of additional covariates, such as gross domestic product per capita, health expenditure, the policy framework, how innovative the product is and its therapeutic advantages (see, among others, Cabrales & Jiménez-Martín, 2013; Kanavos & Vandoros, 2011; Kyle & Qian, 2014; Puig-Junoy & González López-Valcárcel, 2014; Benda, Mallory, & Lu, 2004; Lu & Comanor, 1998; Ekelund & Persson, 2003). Because our analysis is not longitudinal, most of these potential determinants are constant at the country or product level. Hence, by including fixed effects both at the country and product level, we substantially reduce the risk of bias due to omitted variables.

4 | RESULTS

Table 4 presents the results. Column (1) shows the impact of MEAs as defined by the standard definition, that is, including agreements that are either FAs or PAs, and column (2) shows the results of the estimation of Equation (17). The subsequent columns present the results of alternative specifications aiming to provide information on the role of the type of agreement, by distinguishing between FAs and PAs (columns (3) and (4)), and to analyse heterogeneity in the effect at the country level (columns (5) and (6)). Because the inclusion of fixed effects generally does not control for all of the within-cluster correlation of the error (Arellano, 1987), standard errors are clustered at the country level in all specifications. To account for the low number of clusters G, the $T(G-1)$ distribution for critical values is adopted (Cameron & Miller, 2015).

In line with the theoretical result that, under most policy frameworks, list prices are higher with than without an MEA, the results for our main econometric specification (column (2)) shows that, on average, prices are 5.9% higher if an FA or a PA exists. The coefficient for the dummy variable of interest is significant at the 5% level (p value = 0.026). On the other hand, the coefficient for the dummy for AAs is not statistically significant. Other things being equal, PPP prices in Greece, Italy, and the Netherlands are higher than in Belgium (our reference country) and are lower in Norway and England. It is worth emphasising that, in this case, the fact that a country has higher list prices on average does not mean that the

TABLE 4 Results

	(1)	(2)	(3)	(4)	(5)	(6)
PA/FA	0.054**	0.059**			0.053*	0.052*
	(0.016)	(0.019)			(0.026)	(0.025)
AA		0.033		0.030		0.040
		(0.029)		(0.033)		(0.041)
Greece	0.189***	0.191***	0.189***	0.190***	0.188***	0.188***
	(0.007)	(0.009)	(0.008)	(0.008)	(0.012)	(0.012)
Italy	0.167***	0.154***	0.170***	0.156***	0.169***	0.144***
	(0.003)	(0.010)	(0.008)	(0.017)	(0.008)	(0.025)
Netherlands	0.044***	0.046***	0.045***	0.045***	0.041**	0.041**
	(0.007)	(0.008)	(0.008)	(0.008)	(0.013)	(0.013)
Norway	−0.378***	−0.376***	−0.378***	−0.377***	−0.378***	−0.379***
	(0.009)	(0.010)	(0.009)	(0.009)	(0.013)	(0.013)
England	−0.131***	−0.131***	−0.131***	−0.131***	−0.130***	−0.130***
	(0.004)	(0.004)	(0.004)	(0.004)	(0.014)	(0.014)
PA			0.022	0.035		
			(0.021)	(0.031)		
FA			0.055**	0.057**		
			(0.018)	(0.018)		
PA/FA_Italy					−0.007	0.018
					(0.012)	(0.028)
PA/FA_Netherlands					0.027	0.028
					(0.034)	(0.035)
PA/FA_England					−0.001	−0.002
					(0.026)	(0.027)
Product FE	Yes	Yes	Yes	Yes	Yes	Yes
N	892	892	892	892	892	892

Note. Cluster standard errors (at the country level) in parentheses.
Abbreviations: AA, appropriateness agreement; FA, financial-based agreement; PA, performance-based agreement.
* $p < 0.10$.
** $p < 0.05$.
*** $p < 0.01$.

expenditure per patient is higher, due to the role of MEAs in reducing net prices in the countries where they are adopted and the differences in the number of MEAs (Table 2).

The results of columns (3) and (4) suggest that the impact of MEAs as previously reported is driven mainly by FAs. The estimated coefficient for PAs is still positive, but smaller and not statistically significant. [21]However, it should be observed that the number of PAs (33) is substantially lower than that of FAs. The results concerning the differences in prices between countries previously illustrated still apply.

The analysis of Section 2 shows that the policy setting may be crucial in determining the impact of MEAs on list prices. The complexity of real-world pricing policies is such that no country can be associated with a single framework as presented in Section 2. However, we can investigate the heterogeneity in the impact of MEAs between countries by including interaction terms among the variable *PA*/*FA* and country dummies (columns (5) and (6)). According to column (5), prices in Belgium (reference category) are 5.3% higher with an MEA. The impact of the agreements in the other countries is not statistically different from Belgium. Looking at the linear combination of the coefficient for *PA*/*FA* and of the interaction term, the impact of *PA*/*FA* is 4.6% for Italy ($p = 0.041$), 8.0% for the Netherlands ($p = 0.054$) and 5.2% for England ($p = 0.013$). Once the control for AAs is included (column (6)), the effect for Italy increases to 7.0%, although it is no longer statistically significant ($p = 0.120$). The other results are basically unaffected when the dummy for AAs is added to the specification. The inclusion of the interaction terms also shows that PPP prices in Italy and the Netherlands are statistically higher than in Belgium both for products covered by *FA*/*PA* (as highlighted by the linear combination of the coefficient for the country and of the interaction term) and for products not covered. On the other hand, irrespective of the existence of an agreement, PPP prices in England are statistically lower than in Belgium. [22]

[21] If the variable PA is omitted from the model, the coefficient for FA and its level of significance are virtually unaffected.
[22] This result is in line with previous findings for the comparative analysis of cancer drug prices (see, e.g., Vogler, Vitry, & Babar, 2016).

TABLE 5 Results for the sample of products available in all countries

	(1)	(2)	(3)	(4)	(5)	(6)
PA/FA	0.071***	0.075**			0.081**	0.080**
	(0.016)	(0.020)			(0.025)	(0.025)
AA		0.026		0.025		0.041
		(0.024)		(0.029)		(0.037)
Greece	0.219***	0.221***	0.217***	0.218***	0.223***	0.223***
	(0.007)	(0.009)	(0.008)	(0.008)	(0.012)	(0.012)
Italy	0.178***	0.168***	0.178***	0.167***	0.181***	0.157***
	(0.002)	(0.007)	(0.008)	(0.017)	(0.007)	(0.020)
Netherlands	0.074***	0.075***	0.073***	0.073***	0.076***	0.076***
	(0.006)	(0.007)	(0.006)	(0.006)	(0.012)	(0.012)
Norway	−0.354***	−0.352***	−0.356***	−0.355***	−0.350***	−0.350***
	(0.007)	(0.009)	(0.008)	(0.008)	(0.012)	(0.012)
England	−0.111***	−0.111***	−0.112***	−0.112***	−0.097***	−0.096***
	(0.000)	(0.000)	(0.001)	(0.001)	(0.011)	(0.011)
PA			0.047	0.057		
			(0.029)	(0.040)		
FA			0.068**	0.069**		
			(0.017)	(0.017)		
PA/FA_Italy					−0.004	0.020
					(0.014)	(0.026)
PA/FA_Netherlands					0.010	0.011
					(0.042)	(0.042)
PA/FA_England					−0.031	−0.031
					(0.023)	(0.024)
Product FE	Yes	Yes	Yes	Yes	Yes	Yes
N	726	726	726	726	726	726

Note. Cluster standard errors (at the country level) in parentheses.
Abbreviations: AA, appropriateness agreement; FA, financial-based agreement; PA, performance-based agreement.
* $p < 0.10$.
** $p < 0.05$.
*** $p < 0.01$.

Restricting the analysis to the 121 products for which price data are available for all countries, the quality of the results is unchanged, whereas the magnitude of the impact of MEAs and its statistical significance tend to be slightly greater (Table 5).

There may be several explanations for the fact that AAs appear to have no impact on prices. Referring to the theory, we clarified that a necessary condition for this type of agreement to have a financial impact is that its introduction leads to a lower number of treatments provided, which would not be the case if prescription behaviour is appropriate even without an MEA. Moreover, the impact on list prices vanishes in the limit case $\alpha = 1$. These findings may be seen as supporting the view that AAs should not be considered as an MEA. Had we taken this narrower definition of MEA, our sample would have excluded 65 products for which there is an AA. As a robustness check, we replicate the analysis on the restricted sample of products covered by a PA or FA (91 products, 524 observations). Table 6 shows the results, which are qualitatively similar to those of the baseline analysis. In this case, the estimate of the average impact of MEAs on list prices increases to 7.9%.

Finally, we investigate heterogeneity across therapeutic areas. The therapeutic class with the highest number of MEAs is for antineoplastic and immunomodulating agents. Once these products are excluded from the sample (leaving 66 products and 368 observations), the effect of FA/PA increases to more than 13% (see Table 7). Moreover, regarding these 66 products, both FA and PA have a significantly positive effect on prices, not observed for AA. The quality of the results concerning country fixed effects is the same as for the full sample. Similarly, there are no statistically different impacts of agreements between countries.

One aspect of our analysis that deserves discussion is whether the positive association between the existence of an MEA and the level of prices is consistent with our interpretation, that is, manufacturers raising prices to reduce at least part of the financial loss due to the MEA. In principle, it could be argued that the introduction of an MEA might be a reaction by the payer to a comparatively high price proposed by the manufacturer. In this case, the positive association would be due

TABLE 6 Results for the sample of products covered by an FA or a PA

	(1)	(2)	(3)
PA/FA	0.079*		0.085*
	(0.032)		(0.034)
Greece	0.240***	0.237***	0.243***
	(0.016)	(0.016)	(0.018)
Italy	0.187***	0.192***	0.195***
	(0.001)	(0.010)	(0.017)
Netherlands	0.105***	0.103***	0.097***
	(0.015)	(0.014)	(0.020)
Norway	−0.336***	−0.338***	−0.332***
	(0.018)	(0.018)	(0.020)
England	−0.084***	−0.085***	−0.062**
	(0.002)	(0.002)	(0.024)
PA		0.040	
		(0.030)	
FA		0.074*	
		(0.030)	
PA/FA_Italy			−0.015
			(0.032)
PA/FA_Netherlands			0.112
			(0.059)
PA/FA_England			−0.044
			(0.046)
Product FE	Yes	Yes	Yes
N	524	524	524

Note. Cluster standard errors (at the country level) in parentheses.
Abbreviations: FA, financial-based agreement; PA, performance-based agreement.
* $p < 0.10$.
** $p < 0.05$.
*** $p < 0.01$.

to reverse causality. Although our data do not allow this question to be addressed empirically, an analysis of the different frameworks introduced in Section 2 may shed some light on this issue.

A necessary condition for the problem of reverse causality to arise is that the introduction of an MEA is decided by the payer, knowing the price. This rules out the framework analysed in Section 2.1, but not those of Sections 2.2 and 2.3. However, in Section 2.2, we found that a rational manufacturer would react to the possibility of an MEA being introduced by raising the proposed price of all products, some of which may end up having no MEA. Hence, the opportunity for the payer to introduce an MEA, given the proposed price, causes an increase in the list price.

The last case is that of ERP. As long as the set of countries whose prices are referenced is the same for all products, differences between countries would be captured by the relevant fixed effect. However, the sequence of entries to different national markets, and hence the countries whose prices contribute to the determination of the domestic price, may change from one drug to another. If the price were mechanically determined through ERP and MEA were introduced if the resulting domestic price were comparatively high, then reverse causality might arise. We believe there are several reasons why this possibility is unlikely to affect our results significantly. First, England, which is the second country in our sample in terms of the number of FAs and PAs, does not use ERP. Moreover, in many countries, ERP is often just one among several criteria for price determination (Leopold et al. 2012; Ruggeri & Nolte, 2013; Vogler et al. 2019).

5 | DISCUSSION AND CONCLUSION

Although MEAs have been used extensively for several years in a number of countries, a great deal remains to be understood about their economic implications. It has been argued that their effect might be to shift the risk from the payer to the manufacturer, rather than to lead to risk sharing. However, who gains and who loses from the introduction of MEAs, as well as the size of gains and losses, depends on economic factors that go beyond the formal content of the agreement. Our theoretical analysis of the introduction of different types of MEA in a number of frameworks for price determination shows that in most situations, list prices are higher with than without an agreement. We test this hypothesis empirically

TABLE 7 Results for the sample of products excluding antineoplastic and immunomodulating agents

	(1)	(2)	(3)	(4)	(5)	(6)
PA/FA	0.132***	0.133***			0.143**	0.141**
	(0.031)	(0.030)			(0.043)	(0.042)
AA		0.025		0.026		0.032
		(0.043)		(0.044)		(0.058)
Greece	0.245***	0.246***	0.245***	0.245***	0.252***	0.250***
	(0.016)	(0.016)	(0.017)	(0.016)	(0.022)	(0.022)
Italy	0.198***	0.187***	0.198***	0.185***	0.203***	0.185***
	(0.014)	(0.027)	(0.014)	(0.028)	(0.018)	(0.037)
Netherlands	0.112***	0.113***	0.112***	0.112***	0.125***	0.124***
	(0.015)	(0.014)	(0.015)	(0.015)	(0.028)	(0.028)
Norway	−0.328***	−0.327***	−0.328***	−0.328***	−0.322***	-0.323***
	(0.016)	(0.016)	(0.017)	(0.016)	(0.025)	(0.025)
England	−0.111***	−0.111***	−0.111***	−0.111***	−0.107***	−0.108***
	(0.010)	(0.010)	(0.010)	(0.010)	(0.022)	(0.020)
PA			0.142***	0.155***		
			(0.034)	(0.030)		
FA			0.132***	0.133***		
			(0.032)	(0.031)		
PA/FA_Italy					−0.000	0.019
					(0.030)	(0.055)
PA/FA_Netherlands					−0.043	−0.041
					(0.055)	(0.057)
PA/FA_England					−0.003	−0.002
					(0.062)	(0.061)
Product FE	Yes	Yes	Yes	Yes	Yes	Yes
N	368	368	368	368	368	368

Note. Cluster standard errors (at the country level) in parentheses.

Abbreviations: AA, appropriateness agreement; FA, financial-based agreement; PA, performance-based agreement.

* $p < 0.10$.

** $p < 0.05$.

*** $p < 0.01$.

on a sample of 156 products from six countries. We construct a dataset that combines data on pharmaceutical list prices with information on whether an agreement existed or not for the specific medicine in a given country. Our results suggest that the presence of an FA or a PA drives up prices on average by more than 5%. This result is essentially driven by FA. To the best of our knowledge, this contribution is the first evidence that MEAs may be associated with higher list prices.

We believe that ours can be considered a conservative estimate of the true impact of MEAs on list prices for three reasons. First, we assign an MEA to a product whenever the agreement is relevant for at least one indication, although there may be several other indications for which it is not implemented. Moreover, we find a stronger effect (7.9%) when we exclude from the sample products for which only an agreement based on a patient registry exists. This result is relevant because there is still debate on whether these agreements should be classified as MEAs. Finally, we show theoretically that scenarios may exist where the possibility of using MEAs leads to an increase of all prices, including those of products for which no MEA is implemented.

A relevant policy implication of our results is that payers may overestimate the savings that can be achieved through an MEA by ignoring the fact that the list price may be higher where an agreement exists. It should be noted that, in principle, at least part of the increase in list prices might be to offset some shifting of risk from payers to manufacturers (Lilico, 2003). In this case, we would still have an overestimate of financial savings, but this could at least partially be compensated by the benefit to a risk-averse payer. However, not all agreements have this characteristic. Those for which this is most important are probably PAs for which, incidentally, we find no statistically significant effect. These considerations suggest that there may be a potential advantage, from the payer's perspective, in the use of PAs compared with FAs. However, given the comparatively small number of PAs in our sample and their concentration in Italy, further empirical analysis conducted on a larger sample of PAs from multiple countries would be extremely valuable. In any case, it is important to

remark that any conclusion on whether, or not, from the payer's perspective, an MEA should be used is beyond the scope of the our contribution.

A limitation of our analysis is that it refers to a single point in time. Exploiting the longitudinal dimension would strengthen our results. However, this would probably also involve a substantial reduction in the sample size because, with few exceptions, the publicly available information does not include the exact date when an agreement came into effect or expired.

ORCID

Simona Gamba https://orcid.org/0000-0002-5538-2873
Paolo Pertile https://orcid.org/0000-0002-6555-5491
Sabine Vogler https://orcid.org/0000-0003-4853-4397

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Gamba S, Pertile P, Vogler S. The impact of managed entry agreements on pharmaceutical prices. *Health Economics*. 2020;29(S1):47-62. https://doi.org/10.1002/hec.4112