International Journal of Technology Assessment in Health Care, 34:1 (2018), 46–55.

doi:10.1017/S0266462317001106

CHARACTERISTICS OF MANAGED ENTRY AGREEMENTS IN AUSTRALIA

Maxine F. Robinson
Quality Use of Medicines and Pharmacy Research Centre
maxinerobinson@mac.com

Cathrine Mihalopoulos
Faculty of Health, Deakin University

Tracy Merlin
Adelaide Health Technology Assessment

Elizabeth Roughead
Quality Use of Medicines and Pharmacy Research Centre

Objectives: Australia relies on managed entry agreements (MEAs) for many medicines added to the national Pharmaceutical Benefits Scheme (PBS). Previous studies of Australian MEAs examined public domain documents and were not able to provide a comprehensive assessment of the types and operation of MEAs. This study used government documents approved for release to examine the implementation and administration of MEAs implemented January 2012 to May 2016.
Methods: We accessed documents for medicines with MEAs on the PBS between January 2012 and May 2016. Data were extracted on Anatomical Therapeutic Classification (ATC), type of MEA (financial, financial with outcomes, outcomes, and subcategories within each group), implementation and administration methods, source of MEA recommendation, and type of economic analysis.
Results: Of all medication indication pairs (MIPs) recommended for listing, one-third had MEAs implemented. Our study of eighty-seven MIPs had 170 MEAs in place. The Government's expert health technology assessment (HTA) committee recommended MEAs for 90 percent of the eighty-seven MIPs. A total of 81 percent of MEAs were simple financial agreements: the majority either discounts (32 percent) or reimbursement caps (43 percent). Outcome-based MEAs were least common (5 percent). Ninety-two percent of MEAs were implemented and operated through legal agreements. Approximately half of the MIPs were listed on the basis of accepted claims of cost-minimization. Forty-nine percent of medicines were in ATC L group.
Conclusion: Advice from HTA evaluations strongly influences the implementation of ways to manage uncertainties while providing access to medicines. The government relied primarily on simple financial agreements for the managed entry of medicines for which there were perceived risks.

Keywords: Managed entry agreements, Pharmaceutical policy, Outcome-based agreements, Performance-based agreements

Many governments and other payers who subsidize medicines have policies to ensure timely and affordable access to medicines while addressing uncertainties or risks in an era of increasing cost and demand (1;2). These arrangements are often referred to as managed entry agreements (MEA) (3).

In Australia, the Pharmaceutical Benefits Scheme (PBS) is the national scheme for reimbursement of medicines (4). Challenges for the scheme arise due to increasing costs of the PBS for the Australian Government in concert with increasing demand for earlier access to medicines, increasing use of medicines as the population ages, and increasing requests for listing of very expensive medicines (5;6).

To list a medicine on the PBS manufacturers are required to supply evidence to support claims of health benefits gained that are acceptably cost-effective, along with estimates of the financial cost to government. This is undertaken using internationally accepted methods of health technology assessment (HTA) (7;8). The submissions are appraised by the Pharmaceutical Benefits Advisory Committee (PBAC), a government appointed independent expert group providing advice on which medicines to subsidize. The evidence within the submission may not be sufficient for the PBAC to have unequivocal confidence in the magnitude of the health benefit, the reliability of the calculated cost effectiveness, or the extent of financial cost (9–11). Lack of confidence in the evidence is often referred to as "uncertainty" and is described as a "risk" for the payer (8).

While there is always some level of uncertainty (or imprecision) in much of the scientific evidence, it is the multiple sources of uncertainty that tend to confound decisions to fund new medicines. These sources of uncertainty arise in considerations of the clinical effectiveness of the medicine (including longer term effects that are rarely measured in clinical trials), the impact of subsidizing the medicine on other health sector costs and the financial cost (9–11). Payers may decide to subsidize medicines while taking the risk of these uncertainties into account (2;11). To undertake this, the Australian Government has developed several mechanisms that can be described as MEAs (12;13).

The Health Technology Assessment International (HTAi) Policy Forum has defined MEAs as "an arrangement between a manufacturer and payer or provider that enables coverage or reimbursement of a health technology subject to specific conditions" (3). There are many different names used to describe MEAs. Some of the terms include outcome-based schemes, risk-sharing arrangements, coverage with evidence development, coverage only in research, coverage only with research,

access with evidence development, patient access schemes, conditional licensing, performance-based risk-sharing arrangements, discount schemes, pay for performance agreements, price-volume agreements, market caps, conditionally allowed specialist medicines, and dose or time capping schemes (2;14–17).

In general, MEAs have been described and assigned to one of the following three classes based on the mechanism of implementation (1;2;11;15;16;18): (i) financial agreements that reduce the payer's expenditure; (ii) financial agreements that operate with payments adjusted with reference to the collection of information on real-life health outcomes data from patients (often referred to as "pay for performance"); and (iii) agreements that collect information on outcomes (often referred to as "coverage with evidence development") with consequent effect on payments adjusted subsequent to a review of the original basis of consideration and with reference to the information collected.

Within these three groups there are a variety of mechanisms for operating MEAs that are proposed or currently implemented in different countries (1;2;10;16).

Previous studies assessing Australia's use of MEAs have relied on publicly accessible information on MEAs. Only the existence of a "hidden" discounted price, a continuation rule and an outcome-based MEA is explicitly stated in the public domain. This lack of transparency has limited assessment of the type of MEA and their operation (19–21) in Australia. In the context of the public debate concerning the need for swifter access to medicines in an era of expensive medicines (22), this study aims to provide a comprehensive assessment of the implementation and administrative operation of MEAs for PBS-listed medicines in Australia by assessing the full documentation underpinning the listing decision making.

METHODS

This study used the HTAi definition of an MEA (3). All medicines listed on the PBS that had one or more MEAs implemented between January 2012 and May 2016 were included in the study to provide the most recent experience of operation of MEAs. Medicines that were subsidized as fixed dose combination formulations were treated as one medicine in this analysis.

The PBAC makes separate recommendations for each clinical indication for a medicine, thus medicines can have one or more indications subsidized. Therefore, the data for this study were collected per indication for each medicine forming a medicine indication pair (MIP).

Approval was sought from the Australian Government Department of Health to access all materials related to the decisions of the Government and PBAC in regard to medicines listed on the PBS with an MEA in place. This includes the confidential manufacturer's application, all evaluation documents provided to the PBAC, the confidential PBAC record of the decision and the publicly released Public Summary Document that explains the decision (redacted for confidential material). Details were also sought on the documentation relating to the implementation and management of each MEA; this included the legal deed of agreement and administrative approvals for implementation and lapsing. The primary sources of information were the PBAC record of the decision and administrative approval for the deed of agreement. Approval for this access was obtained in December 2015.

The data elements extracted for this study were Anatomical Therapeutic Classification (ATC) of the medicine (23) and the year the MEA was implemented. In addition, we extracted data on the source of the recommendation for an MEA, the administrative instrument of the MEA, type of MEA, and the type of economic analysis. The type of economic analysis was classified as a cost-effectiveness analysis, including cost utility analysis, cost minimization analysis (CMA), or other (24). Because 2016 was part year, only data on medicines listed on the PBS as at June 1, 2016 were obtained (25). As MEAs are implemented at the MIP level, the number of submissions for new MIPs recommended by the PBAC was extracted (26) from the PBAC meeting records applicable to the listing period (the minimum listing time is 20 weeks following a positive PBAC recommendation) (27).

Each MEA was assigned to a typology developed from information extracted from published studies describing the actual methods used in operating MEAs (1;2;10;16;28–31). Any new types of action for an MEA identified in the study data were added to the list of actions (Table 1). Each type of action was assigned to one of the three mechanistic classes by the first author of the paper (M.F.R.). Any that were not clear were discussed with relevant government officers and a final assignation decided.

In Australia there are two administrative instruments used to operate MEAs: (i) The Government and manufacturer enter a legal deed of agreement that establishes the type and the conditions of the MEA; and (ii) A prior-approval mechanism for each prescription of the medicine covered by this MEA with a requirement for data collection from patients receiving this subsidized medicine. Prescribers provide specified information about the patient's progress while on the medicine that gives evidence of patient response to the restriction criteria as published in the PBS schedule. Prior-approval to continue is then based on the information provided by the prescribers. The manufacturer must agree to the conditions of the prior-approval before subsidy commences (12). These arrangements are referred to as "continuation rules" in PBS restrictions (32).

Material deemed or agreed to be confidential by the Government was excluded from this publication. This included the agreed prices for the medicine, expected utilization, and

https://doi.org/10.1017/S0266462317001106 Published online by Cambridge University Press

Table 1. Descriptions of Types of Actions of MEAs and Sources

Financial	
Discount on published price (F 1) The publicly released unit price is greater than the actual price and the difference is refunded to the payer.	Walker et al 2012 (15), Garrison et al 2013 (9), Stafinski et al 2010 (51)
Reimbursement if exceed cap based on a set price per unit or accepted duration of treatment (F 2). Total amount of medicine supplied is monitored and reimbursement is linked to an agreed total limit.	Ferrario & Kanavos 2013 (17)
Reimbursement if exceed a total prescription volume cap (F 3)	Ferrario & Kanavos 2013 (17)
Reimbursement if exceed expenditure volume cap (F 4). Expenditure volume is based on agreed total financial cost.	Walker et al 2012 (15), Ferrario & Kanavos 2013 (17), Jaroslawski & Toumi 2011 (28, 31), Stafinski et al 2010 (51)
Up front payment of additional administration or test costs (F 5). The manufacturer agrees to pay additional costs involved in utilisation of the new medicine. Usually applied to medicines listed on a cost minimisation basis.	Used in Australia
Reimbursement to the payer for administration or test costs (F 6). The manufacturer pays for the actual costs of additional tests or administration fees incurred by the new medicine.	Used in Australia
Reimbursement for any expenditure for treatment in combination with other specified medicines (F 7). Applied where there is a risk of use of co-administered medicines that is not considered cost-effective.	Used in Australia
Reimbursement when the price of the medicine is adjusted in relation to the volume supplied (price volume agreement) (F 8)	Walker et al 2012 (15), Ferrario & Kanavos 2013 (17)
Financial with information on medicine or patient performance required	
Reimbursement where patients do not respond, partially or completely, to an initial period of treatment (FI 1). The financial cost of continuing treatment in these patients is reimbursed.	Ferrario & Kanavos 2013 (17), Toumi et al 2016 (29), Garrison et al 2013 (9), Carlson et al 2010 (7), Jaroslawski & Toumi 2011 (31), Stafinski et al 2010 (51), Launois et al 2014 (58)
Price reduction when a patient does not respond to treatment (FI 2). The financial cost of subsidy in non-responding patients is discounted.	Walker et al 2012 (15), Garrison et al 2013 (9), Fagnani et al 2015 (30)
Reimbursement of cost of medicine if the number of treatments per patient is exceeded (F1 3). The number of treatments is tracked for each patient.	Walker et al 2012 (15), Carlson et al 2010 (7)
Reimbursement of cost of medicine if patients receive more than an agreed amount of medicine (F1 4). The total dose of medicine supplied is tracked for each patient.	Garrison et al 2013 (9), Jaroslawski 2011 (14), Walker 2012 (15)
Reimbursement linked to changes in use of other resources associated with treatment (F1 5). Utilisation of tests or services associated with the medicine are tracked and reimbursement is triggered if this use is different to pre-agreed thresholds per patient.	Used in Australia
Reimbursement ceases if patients do not meet agreed clinical measures. Information provided to a third party by the treating physician is used to monitor utilisation (FI 6)	Walker 2012 (15), Garrison et al 2013 (9), Carlson et al 2010 (7), Launois et al 2014 (58)
Outcome	
Future review of the medicine using pre-specified study protocol for all patients subsidised (O 1). The protocol determines the data collected, duration of the collection and how the results will inform the review of clinical effectiveness and cost effectiveness.	Ferrario & Kanavos 2013 (17), Garrison et al 2013 (9), Stafinski et al 2010 (51), Launois et al 2014 (58)
Future review of the medicine following additional data being provided when available from currently planned or progressing studies (O 2). Studies in progress can be identified during the evaluation of the medicine and the results expected to inform a decision to subsidise.	Garrison et al 2013 (9), Carlson et al 2010 (7)
Future review of the medicine using pre-specified study protocol from patient data provided by a sample of subsidised patients (O 3). The protocol determines the data collected, duration of the collection and how the results will inform the review of clinical effectiveness and cost effectiveness.	Ferrario & Kanavos 2013 (17), Carlson et al 2010 (7), Stafinski et al 2010 (51), Launois et al (58)

https://doi.org/10.1017/S0266462317001106 Published online by Cambridge University Press

Table 2. Characteristics of medicine-indication pairs (MIPs) with MEAs by year

Characteristic	2012	2013	2014	2015	2016[####]
Total number of MIPs recommended for subsidy by the PBAC [#]	60	52	77	65	25
Number of MIP where MEAs were implemented (% all MIPs recommended by the PBAC)[##]	13 (22%)	20 (38%)	22 (29%)	25 (38%)	7 (28%)
MIP with 1 MEA	6 (46%)	6 (26%)	6 (27%)	6 (24%)	2 (28%)
MIP with 2 MEA	6 (46%)	9 (48%)	10 (46%)	14 (56%)	1 (14%)
MIP >=3 MEAs	1 (8%)	5 (26%)	6 (27%)	5 (20%)	4 (57%)
Number of MIPs where one or more MEAs recommended by the PBAC	10 (77%)	19 (95%)	20 (91%)	22 (88%)	7 (100%)
Number of MEAs [###]	21	39	45	49	16
Administrative instrument used to support the operation of the MEA					
Prior approval with 'continuation rule'	7 (33%)	1 (2%)	3 (7%)	8 (16%)	0
Deed of Agreement	14 (67%)	40 (98%)	41 (93%)	41 (84%)	16 (100%)
Type of action for each MEA (Percentage of total MEAs)					
Financial	14 (67%)	32 (82%)	38 (84%)	41 (84%)	13 (81%)
Financial + Information	7(33%)	4 (13%)	5 (11%)	5 (10%)	3 (19%)
Outcome	0	3 (5%)	2 (5%)	3 (6%)	0
Type of economic analysis for each MIP (Percentage of MIPs)					
CEA (incl CUA)	3 (23%)	12 (60%)	14 (64%)	10 (40%)	4 (57%)
CMA	10 (77%)	8 (40%)	6 (27%)	15 (60%)	3 (43%)
Other analysis	0	0	2 (9%)	0	0

PBAC Pharmaceutical Benefits Advisory Committee, MIP medicine indication pair, MEA managed entry agreement, CEA cost effectiveness assessment, CUA cost utility assessment, CMA cost minimisation assessment, n/a not available.

[#]note 1: derived from the three meetings per year where the medicine recommended by the PBAC is likely to be listed and MEAs negotiated i.e. meetings in November 2011, March 2012, July 2012 would lead to PBS listings in 2012.

[##] note 2: MEAs usually had a duration of 5 years in this study. Thus the number active in a year at any time is cumulative.

[###]note 3: a medicine-indication pair can have more than 1 MEA.

[####]note 4: 5 months of data for 2016 available.

financial costs. All documents not in the public domain were provided by the Australian Government Department of Health for the purposes of this research.

RESULTS

Data were available for eighty-seven medicine indication pairs (MIPs) representing eighty-one medicines. Six medicines had more than one indication relating to an MEA. There were 170 MEAs for eighty-seven MIPs. Table 2 describes the characteristics of the MEAs listed.

The number of MIPs with MEAs per year increased from 2012; however, the percentage of MIPs recommended for listing as a proportion of the MIPs recommended by the PBAC was variable. Over the study period, 31 percent of new MIPs recommended by the PBAC had at least one MEA. The majority of MIPs had two or more MEAs. The most common combination (52 percent of MIPs) was a discount on the published price (F 1) and reimbursement if the total expenditure exceeded an agreed financial expenditure cap (F 4). All MIPs with an outcome-based agreement had at least one financial agreement in place and 25 percent had MEAs in the financial and financial with information groups.

For 90 percent of MIPs in the study, the PBAC advised the Government on the need for at least one MEA. The PBAC did not generally recommend a specific type of MEA, except for outcome-based MEAs. For the other nine MIPs, the Government determined that MEAs were required: seven were MIPs recommended on the basis of cost minimization to PBS-listed medicines that were already subject to a pre-existing MEA, while two had financial-based agreements implemented after the PBAC recommendation to list the medicine.

Implementation and management of the MEAs was through a Deed of Agreement for 92 percent of MEAs. A prior-approval mechanism to continue therapy was used in 9 percent of MEAs. One MEA used the prior-approval mechanism to collect information on clinical response that was specified in a clause written into the deed of agreement.

https://doi.org/10.1017/S0266462317001106 Published online by Cambridge University Press

Table 3. Analysis of MEAs by Type by Year of Implementation

	2012	2013	2014	2015	2016
Total number of types of MEA	21	39	45	49	17
Financial (F)					
Discount on published price (F1)	4	11	15	18	5
Reimbursement if exceed caps based on a set price per unit or accepted duration of treatment (F2)	0	1	0	0	1
Reimbursement if exceed prescription volume cap (F3)	0	2	1	1	0
Reimbursement if exceed expenditure volume cap (F4)	10	17	21	20	7
Up front payment of additional administration or test costs (F5)	0	0	0	0	0
Reimbursement to the payer for administration or test costs (F6)	0	1	1	1	0
Reimbursement for any expenditure for treatment in combination with other specified medicines (F7)	0	0	0	1	0
Reimbursement when the price of the medicine is adjusted in relation to the volume supplied(price volume agreement) (F8)	0	0	0	0	0
Financial with information on medicine or patient performance required (FI)					
Reimbursement where patients do not respond, partially or completely, to an initial period of treatment (FI 1)	0	1	1	0	0
Price reduction when a patient does not respond to treatment (FI 2)	0	0	0	0	0
Reimbursement of cost of medicine if the number of treatments per patient is exceeded (FI 3)	0	2	1	1	3
Reimbursement of cost of medicine if patients receive more than an agreed amount of medicine (FI 4)	0	0	0	0	0
Reimbursement linked to changes in use of other resources associated with treatment (FI 5)	0	0	0	0	0
Subsidy ceases if patients do not meet agreed clinical measures. Information provided to a third party (FI 6)	7	1	3	4	0
Outcome (O)					
Future review of the medicine according to pre-specified study protocol for all patients subsidised (O 1)	0	0	0	1	0
Future review of the medicine following additional data being provided from currently planned or progressing studies (O 2)	0	2	1	2	0
Future review of the medicine according to pre-specified study protocol in a sample of subsidised patients (O 3)	0	1	1	0	0

Half of the MEAs were implemented for medicines recommended by the PBAC on a cost minimization basis (49 percent), and the remaining half were recommended on a cost-effectiveness basis (49 percent).

The greatest numbers in our study of medicines with MEAs (49 percent) were from the class of medicines treating cancer or immune-based diseases (ATC L). This represents the largest proportion of medicines with MEAs in any class of medicines listed on the PBS: as at June 1, 2016, 137 medicines were listed in the ATC L class and forty had an MEA identified in this study. This study found lower percentages of medicines with MEAs were implemented in other therapeutic areas including 11 percent treating blood-based diseases (ATC B), 10 percent infections (ATC J), and 8.6 percent diseases of the gut (ATC A). Very low numbers of medicines (four or less) with MEAs were listed for treating cardiovascular diseases (ATC C), hormone-based conditions (ATC G), musculoskeletal conditions (ATC M), nervous system conditions (ATC N), respiratory diseases (ATC R), and eye disease (ATC S).

The descriptions and numbers of MEAs by type are reported in Table 3. Financial agreements were the most common type of MEA (81 percent). These MEAs predominantly operated as: (i) A discount on the published price that is kept hidden, that is, the negotiated "cost-effective" price is not disclosed. These are referred to as Special Pricing Arrangements in Australia. Each is usually identified by a note in the PBS schedule and in the therapeutic relativity sheets (33), both of which are publicly accessible. Examples of these MIPs include daclatasvir, lepipasvir/sofosbuvir, paritaprevir/ritonavir/ombitasvir, and sofosbuvir in hepatitis C; bortezomib in multiple myeloma, dabigatran, rivaroxaban, and apixaban in prevention of stroke in nonvalvular atrial fibrillation. (ii) An agreed percentage of payer expenditure to be reimbursed by the manufacturer if the government expenditure on the medicine for that indication exceeded agreed yearly thresholds (Table 3). The existence of these types of MEA is not explicitly provided in publicly accessible information.

https://doi.org/10.1017/S0266462317001106 Published online by Cambridge University Press

Fourteen percent of MEAs are classified as financial with information on medicine or patient performance required. The majority of this performance information was patient specific and obtained through the prior-approval mechanism established by the government (9 percent). Other performance information was obtained through the national administrative pharmacy prescription claiming data (the PBS claim dataset): for example by counting the number of times a medicine was supplied to each patient, with the manufacturer billed if the patient exceeded a specified number. Examples of MIPs in this group include MIPs where continuation rules apply such as tadalafil and epoprostenol in pulmonary arterial hypertension; mannitol, tobramycin, and ivacaftor in cystic fibrosis; and vedolizumab and infliximab in ulcerative colitis and crohn disease.

The least common forms of MEA were outcome based (5 percent). Most of these were agreements between the manufacturer and government for the PBAC to review their recommendation to list a medicine once additional outcome data were available from a clinical trial that was underway. Examples of MIPs with outcome based MEAs include critzotinib in nonsmall cell lung cancer, and ipilimumab, dabrafenib, pembrolizumab, and trametinib in melanoma.

DISCUSSION

Decision to Implement a MEA

This study found consistent use of MEAs in Australia over the study period and that the implementation of MEAs is part of the Government's decision to list for approximately one-third of new MIPs. Having two or more MEAs for an MIP is a common situation in Australia. The reasons may include having different uncertainties addressed for the same MIP or the manufacturer requesting an additional MEA to enable a higher published price over and above the MEA implemented to address an uncertainty. Reviews of MEAs in other countries have not identified this as a common practice (1;2;14;15;18). However, this conclusion is tempered by these international studies defining MEAs differently and excluding some simple financial measures, such as discounting the unit price of a medicine, from being reported in the studies (1;2). In our study, discounting to reduce the published price to that considered cost-effective was the second most common financial MEA and was combined with another type of MEA for fifty-five of these fifty-six MIPs.

For 90 percent of MIPs, the implementation of MEAs was associated with the PBAC decision about subsidy, which included identification of uncertainties (17). Current Australian Government policy allows an MEA to be requested by the PBAC, the government or a manufacturer (34). We examined each of the nine MIPs where the PBAC did not recommend an MEA. We found that each of these MIPs were listed on a CMA basis and in a therapeutic area where there was an expected large impact on the budget or where other currently subsidized MIPs had active MEAs and the new and existing MIPs would be sharing the same financial expenditure caps. The Australian Government policy is generally consistent with European countries that have similar evaluation systems for subsidizing medicines.

Ferrario et al. (2015) reviewed the policies of four European countries: Belgium, The Netherlands, Sweden, and England. Their study found that the decision-making committees in Belgium, The Netherlands and Sweden could independently propose MEAs. The decision-making committees in all four countries also advised to varying extents on the type of MEA that was implemented. However, with the exception of England, the involvement of decision-making committees from these three countries was limited to more complex types of MEA such as those described in Table 3 as financial agreements where patient information is collected or outcome agreements. Simple financial agreements were often implemented by the governments of the European countries without advice from their HTA decision-making body (14). Our findings support the extent of the PBAC's influence on the Australian Government's decisions on all types of MEAs as previously identified in a limited survey (13).

The largest numbers of MIPs in our study were in the antineoplastic and immunomodulating group of medicines (ATC L). Between 2012 and 2015 the Government added 40 medicines with MEAs in ATC L, which is 29 percent of all PBS listed medicines in this class. As one objective of MEAs can be to address concerns arising in the decision to subsidize (17), our results suggest that a larger number of these concerns arise in oncology and related therapeutic areas, and the Government is using MEAs to assist in providing access as early as practicable while managing costs for these medicines. The concerns of Australians about the high cost of medicines that treat cancers and the need to have access as early as possible was recently reported (22) and has been identified in other countries (35).

Types of MEAs Implemented

We found that in Australia the majority of MEAs were simple financial agreements with no requirement to collect individual patient information and operating by means of legal Deeds of Agreement. These agreements rely on the capacity of existing or bespoke datasets to provide information on the number of times a medicine is supplied, the dose supplied, the total cost of the medicine, and details of the prescriber type, dispenser, and patient. In Australia, the PBS claim dataset (33) is well established, reports are publicly accessible, and it provides comprehensive, auditable, reliable, and accurate data that can support the operation of MEAs (36;37). In addition, these types of datasets are simple to administer and, therefore, these MEAs are less expensive to operate than those collecting clinical patient information (37–39). There has been little reliance on bespoke data collection to provide information for MEAs.

https://doi.org/10.1017/S0266462317001106 Published online by Cambridge University Press

There were two dominant forms of financial agreements in Australia in this study period. These were reimbursement to the payer for exceeding thresholds on government expenditure and rebating a proportion of the government expenditure to reduce the unit price of the medicine. This latter type of MEA is an option to make the value of listing acceptable to the payer, that is, negotiate a lower price for the medicine to reduce the cost-effectiveness to one that the payer deems to be acceptable, while benefiting the manufacturer by having an "apparent" higher price for the product for worldwide reference pricing. This "artificial" price causes problems for countries and researchers that use external reference pricing to price new medicines (40).

In Australia, 40 percent of simple financial MEAs were implemented as a published price in the PBS schedule and a "hidden" price that remains confidential; however, the existence of a "hidden" price is not consistently available in publicly disclosed documents. The details of the "effective" price were not released, except in circumstances stated in the supporting Deed of Agreement. These types of discounts are widespread in the European Union and are also a feature in the United States systems (1;41).

Fourteen percent of MEAs were for financial agreements that relied on information about the performance of the medicine. Five percent of these operated through collection of routine administrative data (the PBS claim dataset). For example the dataset recorded the total number of treatment supplied to each patient. Nine percent used information provided by means of the operation of the prior-approval mechanism and continuation rule.

The number of MEAs using information provided by prescribers was relatively constant over time in Australia. This contrasts with the United Kingdom where there has been a move away from a reliance on prescribers. Since November 2011, 97 percent of MEAs implemented in England and Wales have relied on simple financial agreements (42). This is in further contrast to Italy where the establishment of extensive and expensive registry "infrastructure" has seen an increase in the numbers of financial-based and outcome-based MEAs using prescriber provided patient-level information (43).

The proportion of MEAs in Australia using outcome-based data was consistently low across the years studied. The most usual form of outcome-based MEA in Australia was for a review of the evidence that supports subsidy once the results of a relevant ongoing clinical trial were available. The requirement for manufacturers to provide these results was supported by a deed of agreement. In some cases, but not all, there were also agreed price changes or reimbursement clauses associated with the possible range of future results. These MEAs do not have associated implementation and administration costs for the government because the studies are already underway and manufacturers will prepare submissions for the PBAC once the relevant results are available.

Administration of MEAs

The PBS claim dataset provides a strong base for administering financial MEAs. This dataset can be used to track financial information and to provide nonclinical patient level information through tracking of patient medicine supply at the de-identified individual level. Access to, and capacity of, well established and reliable datasets, including clinical outcomes, to support MEAs is considered an important factor in the success of implementing and administering MEAs (37;41). The usefulness of the PBS claim dataset for recording details of the supplied medicines to each individual patient goes some way to explaining the apparent preference for use of simple financial agreements in Australia that rely on the amount of medicine supplied, details of other medicines supplied, and financial cost.

Some additional clinical patient information for financial agreements operated through information provided at the time prescribers sought a prior-approval to continue to prescribe. The process for prior approval is a standard administrative mechanism for obtaining access to a limited number of subsidized medicines that is operated by the government. There was one MEA to collect a measure of response with a direct financial consequence for the manufacturer and fifteen to cease subsidized supply that was not tied to a deed of agreement. In all, cases prescribers provided the required information on the extent of clinical response to a set of criteria published in the PBS schedule.

The use of clinical input as a basis for limiting continued supply of subsidized medicines to those in whom the medicine is cost-effective, that is, those who are considered responders against a set of criteria, has raised some questions about equity and efficiency in the literature (38;44;45). Prescribers and patients may regard these "rules" as interfering with decisions about patient treatment (44;45). The information required is reported separately and not integrated with the patient record. This doubling of administration has been reported in surveys conducted in other countries as "onerous" and as limiting the efficient operation of MEAs (38;46). The efficiency of the "continuation rules" as a MEA has not been extensively evaluated in Australia or elsewhere. Utilization reports in Australia, on two medicine groups, biologics for rheumatoid arthritis and cholinesterase inhibitors for dementia, compared the response rates expected in clinical trials evaluated by the PBAC at the time of recommending subsidy and the actual response rates. These studies showed that continuation rates were higher than anticipated by the PBAC (47;48), suggesting that effective use of the medicine was being achieved but there were questions about the cost-effectiveness of the subsidy.

There were a limited number of MEAs that are either outcome-based or financial-based requiring measurement of medicine or patient performance. The small number may be associated with difficulties in implementing these MEAs. These difficulties arose from a variety of sources such as lack of infrastructure to support comprehensive data collection,

https://doi.org/10.1017/S0266462317001106 Published online by Cambridge University Press

difficulty in collecting the necessary data and issues with interpretation of these data, unwillingness of manufacturers to accept price reductions and of consumers to accept disinvestment of the medicine in the cases where the results do not support the cost-effectiveness claims for subsidy (3;9;16;44;49). Electronic data systems that support collection of clinical information are considered important in facilitating operation of performance-based and outcome-based MEAs (37;41). During the study period, development of infrastructure and policies to support collection of electronic health data that would expand the PBS claim dataset through linkage to include clinical outcomes was limited in Australia.

Between 2010 and 2015 there was a Memorandum of Understanding between Medicines Australia, the representative body for the prescription medicine pharmaceutical industry, and the government, establishing a framework for operating outcome-based MEAs. The purpose of the framework was to set out how medicines could be subsidized "at a price justified by the existing evidence pending submission of evidence of cost effectiveness to support listing at a higher price" (50). Despite this framework, few outcome-based MEAs were implemented by means of this mechanism. Work on a new framework is under way (51), and this may influence preferences for the type of MEA used in the future.

Previous reviews of Australian MEAs have identified different numbers of medicines with MEAs but were unable to identify how many MEAs per medicine due to lack of access to government documentation. Measured over different periods of time and using only public sources, Vitry et al. identified seventy-one medicines (2010–2013), Lu et al. (1998–2012) ninety-five medicines, and Robertson et al. (2004–09) seventy-three medicines (19–21), but these studies were unable to identify all of the MEAs.

It is clear from the current study that there are many more MEAs operating for each medicine than previously reported, and that the majority are simple financial agreements. Greater transparency through acknowledging the existence of all MEAs implemented, while excluding exact details of the costs, may reassure other stakeholders in the Australian health system that government and manufacturers are proactively supporting the ongoing viability and sustainability of the PBS and are facilitating early access to potentially cost-effective medicines.

Limitations of the Study

All MIPs examined were those where an MEA was put in place. Therefore, a limitation of this study was that it was not possible to examine if the characteristics associated with MIPs with an MEA differ from medicines considered and recommended by the PBAC without an MEA, or considered and not recommended by the PBAC, or MIPs where the PBAC recommended an MEA and the Government did not implement the PBAC recommendation. The characteristics were ATC classification, the type of economic analysis, the type of MEA implemented, and the implementation method.

A complete list of all MIPs included in this study and the types of MEA cannot be published owing to confidentiality considerations.

The MIPs included in the study were the MIPs that proceeded to listing on the PBS. The count of all MIPs recommended by the PBAC in Table 2 may include a small number of MIPs that did not proceed to listing in the study period owing to limitations in information available to check if all these MIPs proceeded to list on the PBS. Therefore, the denominator selected for this study was MIPs recommended for listing without separating out the reasons for a medicine with a PBAC recommendation not proceeding to list on the PBS or implementing an MEA.

Conclusion

The cost of the PBS is increasing as the population ages and the prevalence of chronic disease increases (5). At the same time, consumers continue to have expectations for access to new medicines, some of which are expensive, and lead to significant cost to taxpayers (6). MEAs provide a mechanism to ensure access to medicines, and to manage concerns for the government raised before listing, including during the evaluation of these medicines.

Australia has many more of these MEAs implemented than has previously been reported but the majority are simple financial agreements using the PBS claim dataset to operationalize them. Use of more complex MEAs remains low. The question remains as to whether the MEAs identified in this study were an efficient and effective way of managing the government's concerns.

CONFLICTS OF INTEREST

Dr. Robinson reports personal fees from Department of Health, personal fees from Research Training Scheme: Australian postgraduate award, outside the submitted work. Dr. Mihalopoulos reports personal fees from Department of Health and Aging, Commonwealth of Australia, outside the submitted work. Prof. Merlin reports other financial interests, outside the submitted work, due to being commissioned by the Australian Government Department of Health to perform evaluations of medicines for the Pharmaceutical Benefits Advisory Committee. Dr. Roughead has nothing to disclose.

REFERENCES

1. Ferrario A, Kanavos P. Managed entry agreements for pharmaceuticals: The European experience. European Commission EaI. http://eprints.lse.ac.uk/id/eprint/50513 (accessed November 22, 2017).
2. Garrison L, Towse A, Briggs A, et al. Performance-based rish sharing arrangements - Good practices for design, implementation, and

https://doi.org/10.1017/S0266462317001106 Published online by Cambridge University Press

evaluation: Report of the ISPOR Good Practices for Performance-Based Risk-Sharing Arrangements Task Force. *Value Health*. 2013;16: 703-719.
3. Klemp M, Fronsdal K, Facey K. What principles should govern the use of managed entry agreements? *Int J Technol Assess Health Care*. 2011;27:77-83.
4. Australian Government. About the PBS. [updated 1 July 2015]. http://www.pbs.gov.au/info/about-the-pbs (accessed November 22, 2017).
5. Parliamentary Library. Pharmaceutical benefits scheme budget review 2015–16: Commonwealth of Australia. [updated May 2015]. http://www.aph.gov.au/About_Parliament/Parliamentary_Departments/Parliamentary_Library/pubs/rp/BudgetReview201516/PBS (accessed November 22, 2017).
6. Australian Health Department. New breast & lung cancer drugs available from today. [updated July 1, 2015]. http://www.health.gov.au/internet/ministers/publishing.nsf/Content/health-mediarel-yr2015-ley083.htm (accessed November 22, 2017).
7. Australian Government. PBAC Guidelines for submissions: Commonwealth of Australia. http://www.pbac.pbs.gov.au/ (accessed November 22, 2017).
8. Moberg J, Alonso-Coello P, Oxman A. GRADE Evidence to Decision (EtD) Frameworks Guidance. The GRADE Working Group 2015 May 2015. Report No. 1.1. https://ietd.epistemonikos.org/#/help/guidance (accessed July 13, 2016).
9. Carlson JJ, Garrison LP Jr, Sullivan SD. Paying for outcomes: Innovative coverage and reimursement schemes for pharmaceuticals. *J Manag Care Pharm*. 2009;15:683-687.
10. Carlson J, Sullivan S, Garrison L, Neumann P, Veenstra D. Linking payment to health outcomes: A taxonomy and examination of performance-based reimbursement schemes between healthcare payers and manufacturers. *J Health Policy*. 2010;96:179-190.
11. Towse A, Garrison L. Can't get no satisfaction: Will pay for permformance help? *Pharmacoeconomics*. 2010;28:93-102.
12. Australian Government. Procedure guidance for listing medicines on the Pharmaceutical Benefits Scheme. Department of Health; 2016. Report No. 1.0. http://www.pbs.gov.au/info/industry/listing/listing-steps (accessed November 22, 2017).
13. Makino K, Tilden D, Kamei M, Shibata K. Risk-Sharing agreements in Australia: Attitude towards risk-sharing arrangements with the Department of Health for the PBS listing of pharmaceuticals. *Value Health*. 2014;17:A801.
14. Ferrario A, Kanavos P. Dealing with uncertainty and high prices of new medicines; A comparative analysis of the use of managed entry agreements in Belgium, England, the Netherlands and Sweden. *Soc Sci Med*. 2015;124:39-47.
15. Jaroslawski S, Toumi M. Market access agreements for pharmaceuticals in Europe: Diversity of approaches and underlying concepts. *BMC Health Serv Res*. 2011;11:259-266.
16. Walker S, Sculpher M, Claxton K, Palmer S. Coverage with evidence development, only in research, risk sharing, or patient access scheme? A framework for coverage decisions. *Value Health*. 2012;15:570-579.
17. McCabe C, Stafinski T, Edlin R, Menon D. Access with evience development schemes: A framework for descriptions and evaluation. *Pharmacoeconomics*. 2010;28:143-152.
18. Coulton L, Annemans L, Javier J, Brown R, Keskinaslan A, eds. *Risk-sharing schemes worldwide: A landscape analysis of health outcomes-based reimbursement agreements*. ISPOR 4th Asia-Pacific Conference; 2010; Phuket, Thailand.
19. Vitry A, Roughead E. Managed entry agreements for pharmaceuticals in Australia. *Health Policy*. 2014;117:345-452.
20. Lu C, Lupton C, Ralowsky S, Babar Z-U-D, Ross-Degnan D, Wagner A. Patient access schemes in Asia-pacific markets:current experience and future potential. *J Pharm Policy Pract*. 2015;8:6.
21. Robertson J, Walkom E, Henry D. Transparency in pricing arrangements for medicines listed on the Australian Pharmaceutical Benefits Scheme. *Aust Health Rev*. 2009;33:192-199.
22. Commonwealth of Australia. Availability of new innovative and specialist cancer drugs in Australia. The Senate, Committee CAR. [updated September 17, 2015]. http://www.roche-australia.com/content/dam/roche_australia/en_AU/policy/2015-02%20Senate%20Inquiry.pdf (accessed November 22, 2017).
23. WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Methodology [updated December 15, 2016]. https://www.whocc.no (accessed November 22, 2017).
24. Drummond M, Sculpher M, Torrance G, O'Brien B, Stoddart G. Methods for the economic evaluation of health care programmes. 3rd ed. New York: Oxford University Press; 2005.
25. Australian Government. PBS text files. www.pbs.gov.au/info/publication/schedule/archive (accessed November 22, 2017).
26. Australian Government. PBAC Outcomes Australia: Department of Health; [updated April 22, 2016]. http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes (accessed November 22, 2017).
27. Turkstra E, Comans T, Gordon L, Scuffham P. ISPOR global health care systems road map: Australia – Pharmaceutical. [updated February 20, 2017]. https://www.ispor.org/HTARoadMaps/Australia_Pharm.asp (accessed November 22, 2017).
28. Toumi M, Jaroslawski S. Patient access schemes in UK are driven by health technology assessment. *Value Health*. 2011;13:A246.
29. Toumi M, Jaroslawski S, Sawada T, Kornfeld A. The use of surrogate and patient-relevant endpoints in outcomes-based market access agreements: Current debate. *Applied Health Econ Health Policy*. 2017;15:5-11.
30. Fagnani F, Pham T, Claudepierre P, et al. Modeling of the clinical and economic impact of a risk-sharing agreement supporting a treat-to-target strategy in the management of patients with rheumatoid arthritis in France. *J Med Econ*. 2016;19:812-821.
31. Jaroslawski S, Toumi M. Design of patient access schemes in the UK. *Appl Health Econ Health Policy*. 2011;9:209-215.
32. Lu C, Williams K, March L, Sansom L, Bertouch J. Access to high cost drugs in Australia. *BMJ*. 2004;329:415-416.
33. Australian Government. The Pharmaceutical Benefits Scheme A-Z medicine listing. [updated 1 July 1, 2016]. http://www.pbs.gov.au/browse/medicine-listing (accessed November 22, 2017).
34. Australian Government. Deeds of Agreement. [updated September 23, 2013]. http://www.pbs.gov.au/info/industry/listing/elements/deeds-agreement/b-background (accessed November 22, 2017).
35. Espin J, Rovira J, Garcia L. Experiences and impact of European risk-sharing schemes focusing on oncology medicines. Granada, Spain: Andalusian School of Public Health; 2011.
36. Edmonds D, Dumbrell D, Primrose J, Birkett D, Demirian V. Development of an Australian Drug Utilization Database: A report from the Drug Utilization Subcommittee of the Pharmaceutical Benefits Advisory Committee. *Pharmacoeconomics*. 1993;3:427-432.
37. Briggs A, Ritchie K, Fenwick E, Chalkidou K, Littlejohn P. Access with evidence development in the UK: Past experience, current initiatives and future potential. *Pharmacoeconomics*. 2010;28:163-170.
38. van de Vooren K, Curto A, Freemantle N, Garattini L. Market-access agreements for anti-cancer drugs. *J R Soc Med*. 2015;108:166-170.
39. Williamson S. Patient access schemes for high-cost cancer medicines. *Lancet Oncol*. 2010;11:111-112.

https://doi.org/10.1017/S0266462317001106 Published online by Cambridge University Press

40. Conter H. Financial risk-sharing agreements: Using options to make marginal benefits cost effective. *J Clin Oncol*. 2016;34(Suppl):41.
41. Garrison L, Carlson J, Bajaj P, et al. Private sector risk-sharing agreements in the United States: Trends, barriers and prospects. *Am J Manag Care*. 2015;21:632-640.
42. Maguire P, Gibson E. Patient access schemes within the UK: A retrospective analysis. *Value Health*. 2015;18:A335-A766.
43. Tettamanti A, Urbinati D, Noble M. Market access entry agreements in the Italian market between January 2006 and April 2015. *Value Health*. 2015;18:A334-A766.
44. Atkinson W. The impact of CED on private payers. *Biotechnol Healthc*. 2007;4:24-30.
45. Lu C, Williams K, Day R. Access to tumour necrosis factor inhibitors for rheumatoid arthritis treatment under the Australian Pharmaceutical Benefits Scheme: Are we on target? *Intern Med J*. 2006;36: 19-27.
46. Garattini L, Curto A, van de Vooren K. Italian risk-sharing agreements on drugs: Are they worthwhile? *Eur J Health Econ*. 2015;16:1-3.
47. Australian Government. Review of Pharmaceutical Benefits Scheme Anti-dementia Drugs to Treat Alzheimers Disease: Department of Health. [updated May 28, 2012]. http://www.pbs.gov.au/info/reviews/anti-dementia-drugs (accessed November 22, 2017).
48. Australian Government. PBAC Review of bDMARDs for the treatment of severe active rheumatoid arthritis: Department of Health. [updated Februrary 19, 2010]. http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2009-12/pbac-psd-bdmards-dec09 (accessed November 22, 2017).
49. Bishop D, Lexchin J. Politics and its intersection with coverage with evidence development: A qualitative anlaysis from expert interviews. *BMC Health Serv Res*. 2013;13:88-98.
50. Australian Government. Framework for the introduction of a Managed Entry Scheme for submissions to the Pharmaceutical Benefits Advisory Committee. [updated February 23, 2011]. http://www.pbs.gov.au/info/publication/factsheets/shared/framework-for-introduction-of-managed-entry-scheme-for-PBAC-submissions (accessed November 22, 2017).
51. Australian Government. Access to Medicines Working Group (AMWG) Communique: Department of Health. [updated September 8, 2016]. http://www.pbs.gov.au/info/general/amwg-files/amwg-april-2016 (accessed November 22, 2017).

https://doi.org/10.1017/S0266462317001106 Published online by Cambridge University Press