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An integrative review of Managed Entry Agreements – chances and limitations

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(Accepted for publication *PharmacoEconomics*)

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Abstract

Introduction: Managed Entry Agreements (MEAs) consist of a set of instruments to reduce the uncertainty and the budget impact of new high priced medicines; however, there are concerns. There is a need to critically appraise MEAs with their planned introduction in Brazil. Accordingly, the objective is to identify and appraise key attributes and concerns with MEAs among payers and their advisers, with the findings providing critical considerations for Brazil and other high- and middle-income countries. **Methods:** An integrative review approach was adopted. This involved a review of MEAs across countries. The review question was 'What are the health technology MEAs that have been applied around the world?' This review was supplemented with studies not retrieved in the search known to the senior level co-authors including key South American markets. Afterall, involved senior level decision makers and advisers providing guidance on potential advantages and disadvantages of MEAs and ways forward. **Results:** 25 studies were included in the review. Most MEAs included medicines (96.8%), focused on financial arrangements (43%), and included mostly antineoplastic medicines. Most countries kept key information confidential including discounts or had not published such data. Few details were found in the literature regarding South America. Our findings and inputs resulted in both advantages including reimbursement and disadvantages including concerns with data collection for outcome-based schemes. **Conclusion:** We are likely to see a growth in MEAs with the continual launch of new high priced and often complex treatments, coupled with increasing demands on resources. Whilst outcome based MEAs could be an important tool to improve access to new innovative medicines there are critical issues to address. Comparing knowledge, experiences and practices across countries is crucial to guide high- and middle-income countries when designing their future MEAs.

Key words: Risk Sharing Arrangements, Managed Entry Agreements, New Medicines

Key-points for decision makers:

1. Managed Entry Agreements (MEAs) are in operation around the world and they can be an important tool to address uncertainties related to new medicines/health technologies including their potential budget impact
2. MEAs can provide several benefits including reimbursing new medicines where this would have been difficult and managing increasing demand for medicines within available resources benefitting all countries. Decision-makers should also consider their limitations and challenges before adopting different schemes including those with outcome-based schemes
3. This paper provide a worldwide vision of MEAs including their advantages, disadvantages and key considerations to support decision makers for the future

1. Introduction

1.1 Rationale behind managed entry agreements (MEAs)

Providing efficient, safe, equitable and accessible health services to all citizens is the goal of many countries, especially those with universal healthcare systems (1, 2). Initiatives and activities to achieve this goal across countries has been enhanced by the constant monitoring of their progress to achieve Sustainable Development Goal (SDG) 3, i.e. ensuring healthy lives and promoting well-being for all at all ages (3, 4). However, this is becoming more challenging with ageing populations across many countries, increasing the prevalence of chronic non-communicable diseases (NCDs), instigation of single disease model guidelines and policies along with the continual launch of new higher priced medicines to address areas of unmet need (2, 5-16). There are now concerns that even high income countries are failing to provide high quality services as resource pressures grow (17-19), leading to delays to their funding and utilisation (20-22). This builds on limited utilisation of biological medicines to treat patients with immunological diseases among middle-income European countries versus higher income countries in view of their costs and co-payment issues (15, 23, 24). Similarly, there is greater availability of cancer medicines and those for orphan diseases among higher income European countries versus lower income ones again due to a number of reasons including issues of costs, affordability and other priority demands (25-27). However, funding and co-payment concerns may be eased by the increasing availability of oral generic cancer medicines and biosimilars along with aggressive discounting by originator manufacturers to secure procurement and utilisation once originators lose their patents (28-33). Currently for instance, a course of standard treatment for early stage HER2 positive breast cancer including doxorubicin, cyclophosphamide, docetaxel, and trastuzumab, would cost approximately 10

years of average annual wages in South Africa; however, costs are expected to fall appreciably with the availability of biosimilar trastuzumab alongside generic doxorubicin, cyclophosphamide, and docetaxel (27, 34, 35).

The increasing prevalence of patients with NCDs, with an associated increase in medicine use, as well as high requested prices for new medicines for patients with cancer and orphan diseases (36-40), has increased the focus on medicines and their expenditures in recent years. We have seen the price per life year gained for new cancer medicines rising up to four fold during the past years after adjusting for inflation (39, 41), alongside high requested prices for new medicines for orphan diseases (5, 40). In view of this, coupled with increasing prevalence rates, expenditure on medicines for cancer now dominate pharmaceutical expenditure in high income countries (42-44). In Europe, total expenditure on medicines for cancer doubled from €14.6 billion in 2008 to €32 billion in 2018 (in 2018 prices and exchange rates) (45), with the cost of cancer care accounting for up to 30% of total hospital expenditure driven by the increasing cost of medicines (46-48). Overall, world-wide sales of medicines for oncology are estimated to reach US\$200 billion by 2022, up from US\$133 billion in 2017, despite the increasing availability of biosimilars and low cost oral generics (44). There are also concerns with rising expenditure on medicines for orphan diseases with worldwide sales envisaged to be over US\$178 billion in 2020 (8, 49, 50); potentially offset by increasing use and availability of low cost generics and biosimilars (50).

The emotive nature of cancer and orphan diseases has enhanced their potential for funding and reimbursement in high income countries at high prices despite the limited health gain of a number of new medicines (40, 51-57). However, as mentioned, this has resulted in their variable and limited funding in lower income countries, similar to the situation seen with immunological diseases (15, 25, 26). The focus on medicines can also distort funding decisions as seen with considerable funding for immunotherapeutic regimens in a number of middle-income countries; however, on average only 22% of patients have access to safe, affordable and timely cancer surgery in these countries (58). There is likely to be a similar challenges with funding new Advanced Therapy Medicinal Products (ATMPs), as well as regenerative medicines, given current requested prices, the number of these medicines in development, and the degree of uncertainty surrounding them, which is leading to new models being proposed for their funding including performance based annuity payments (13, 59 – 65).

Typically, the decision to reimburse and fund new higher priced medicines is often hampered by numerous uncertainties that exist regarding their effectiveness, safety, and cost-effectiveness, as well as their potential budget impact in routine clinical care (2, 66-69). This can cause concern especially in patients with cancer where there is a high failure rate with turning promising Phase II data into positive findings in later studies, i.e. Phase III and beyond (70-75). Having said this, new medicines for patients with hepatitis C have achieved the desired reductions in viral loads and statins have achieved the desired reduction in cardiovascular events post launch (76-78).

On the other hand, truly innovative and valued technologies are not necessarily receiving appropriate funding limiting patient access once launched (7,15,79,80). Potential ways to address this include creating budgetary space through encouraging the use of low cost generics and biosimilars where pertinent, improving the competitiveness of the off-patent market for orphan drugs as more medicines for orphan diseases lose their patents building on examples in Europe including imatinib, which was initially launched as an orphan disease medicine, developing new models for pricing considerations especially for orphan diseases including multicriteria decision models, which can also be used for priority setting, as well as developing fair pricing models (32, 56,81-92). There has also been a growth in managed entry agreements (MEAs) across countries to help with reimbursement and funding of new valued medicines. These agreements are principally aimed at enhancing the affordability and value of new medicines at launch and post launch given their frequent substantial budget impact and clinical uncertainty in routine clinical care at the time of their launch (9,18, 67,69,93-109). This is particularly the case of new medicines for oncology and orphan diseases (68,93,104,110-115).

1.2 Definition of MEAs

According to Ferrario & Kanavos (94), MEAs typically consist of “a set of instruments used to reduce the impact of uncertainty and high prices when introducing a new medicine”, providing access to new typically higher priced, but considered cost-effective, technologies under pre-established conditions between both parties (67,94,97,116). Numerous terms have been used to describe such schemes, including risk sharing arrangements, risk sharing schemes, MEAs, managed entry schemes, performance-based risk sharing

schemes, performance-based risk sharing arrangements, outcome-based MEAs, outcome-based contracting and patient access schemes (2,5,69,95-97,104,117-124). These agreements or schemes typically use different methodologies to reduce uncertainties related to the technology, especially its value and budget impact, and are typically tailored to a given situation and country (95,121,122,125).

MEAs are now the generally used term rather than “risk sharing scheme”. The Health Technology Assessment International (HTAi) society defines MEAs as “*an arrangement between a manufacturer and payer or provider that enables coverage or reimbursement of a health technology subject to specific conditions*” (69,122,126,127). According to the taxonomies developed by Adamski *et al.* (97), Ferrario *et al.* (93), the World Health Organization (WHO) and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), such agreements can be subdivided into payments that are linked to health outcomes or, alternatively, the financial considerations, where the price is defined considering quantitative measures such as the estimated consumption of the technology in question (68,94,97,104,121,128 – 130). The design of these agreements does differ across countries suggesting that different cultures, systems, and goals, may require different programs and approaches. However, the rationale is often similar. Table 1S (Supplementary Material) gives illustrative details of the different schemes and examples that have existed or are still ongoing across countries. Insurance companies in the United States (US) are also now entering into value-based contracts with hospitals to share the risk (132).

1.3 Challenges and benefits from MEAs

There is a general consensus that outcome based schemes are more challenging than financial-based schemes in view of the necessary infrastructure involved (93,96,104,112,124,125,132). There are also concerns whether outcome based schemes actually achieve a shift in resource allocation to more effective medicines and/or patient populations (133). This can potentially be seen with the use of surrogate markers in outcome based schemes especially in patients with solid tumours as these may not necessarily translate into improved outcomes (53,134-137). Other concerns regarding outcome-based agreements include a belief that ending reimbursement when conditional schemes for new medicines fail to demonstrate the necessary value can be more difficult in practice than starting such schemes (138). On the other hand, reimbursed prices are not increased when the value of a new medicine is shown to increase as more data becomes available. However, we believe such situations are rare in practice with Phase II and III studies principally including selected patients compared with routine clinical care and there can be concerns with turning positive trends in surrogate markers into similar improvements in outcomes (53, 75,136). Principal concerns regarding financial based agreements include the lack of transparency with respect to discounts and rebates (57,93). This is of critical concern among countries that rely on external reference pricing for their deliberations and where patient co-payments are based on list rather than discounted prices (57,139). Appropriate redaction of publicly available documents is one way forward in addition to growing calls for increased transparency (117,140,141). There are concerns though with appropriate incentives for pharmaceutical companies if prices continue to fall and there is price fixing at lower costs with increased transparency (142). However, increasing discussions regarding fair pricing approaches for new medicines will necessarily involve increased transparency (85,86,90,143).

Having said this, there can be considerable benefits with MEAs. These include reimbursing and funding new medicines where this would have been difficult to achieve; demonstrating negotiated outcomes can be achieved in practice, as seen with the statins in the United Kingdom and new medicines for hepatitis C in Sweden; only paying for agreed outcomes, as seen with new treatments for hypercholesterolaemia in US; increasing the use of biomarkers to better target treatments and resources, as seen with medicines for multiple myeloma; and finally, keeping within agreed budgets through discounts and rebates (9,76,97,106,144,145). In Italy, there were concerns with the effectiveness of donepezil and other treatments for patients with Alzheimer’s Disease when first launched, resulting initially in 100% co-payment for these medicines (97). However a study undertaken among 500 Alzheimer Evaluation Units (CRONOS study) in Italy demonstrated similar health gain in patients with mild to moderate AD in routine care compared to those seen in the clinical trials, which resulted in the Italian NHS subsequently fully funding these medicines (‘A’ classification) provided patients were treated in specialist outpatients clinics (97, 146).

These examples of MEAs can be seen as part of a general approach within healthcare systems to monitor the effectiveness, safety and value of new medicines where possible especially where there are concerns initially with their effectiveness, safety and value in routine clinical care (144,147-156). In addition, be part of a general move away from a policy model of one-time evaluation regarding the incorporation of a new technology into health care systems towards a model of multiple evaluations of new health technologies over time. Such

activities are likely to grow with the emergence of electronic health records and information systems across countries (14,157).

The potential savings in terms of cost avoidance from financial based MEAs can be appreciable. In the Netherlands, savings from financial based agreements in 2017 was €150million and €203million in 2018 (9), equating to 4.4% of total pharmaceutical sales in 2017 (158). In Belgium, after adopting MEAs, the total extent of discounts under the various MEAs was €23.7million in 2013 rising to €273.4million in 2017, again equating to 4.4% of total pharmaceutical sales (158). A similar situation was seen in France in 2015 where the following rebates occurred under agreed MEAs (9):

- Price-volume agreements: €573 million
- Budget caps (medicines for orphan diseases): €139 million
- Outcome based agreements: €98 million
- Discounts: €94 million
- Cost/patient (based on an agreed treatment scheme and average daily costs): €82 million
- Others (not specified): €29 million

In Colombia, the Colombian Ministry of Health and Social Protection through Pan American Health Organization (PAHO) was able to make a centralized purchase for new treatments for Hepatitis C cutting the price by nearly 80% (159). By the end of October 2018, the centralized purchase had benefited 1,069 patients with a healing rate of 96.2% (159). In Brazil, the Ministry of Health recently published a performance evaluation guideline to provide continuous assessment of technologies incorporated in the National Health System (SUS) (160). The first evaluation in the country was made for intramuscular beta interferon 1a, attesting its inferiority compared to other beta interferons already incorporated by the SUS (161).

1.4 Objectives of the paper

In 2019, the Brazilian Minister of Health announced that a new modality of technology acquisition would be adopted through risk sharing agreements for relevant high-price medicines (162,163). However, there was an identified need to learn from the experiences in other countries. As a result, we undertook a combined approach to provide guidance to the authorities in Brazil. This included an integrative review, documenting a range of international experiences with MEAs, along with information on MEAs from other South American countries. In addition, appraising the principal issues and concerns among health authority personnel and their advisers from multiple countries, including middle-income countries, involved in the design and implementation of MEAs.

Consequently, the overall aim of this paper is to provide a basis for critical considerations surrounding the implementation of future performance-based agreements among the authorities in Brazil. Such considerations may also be pertinent for other middle-income and higher-middle income countries going forward as they refine existing MEAs as well as appraise new MEAs for their markets.

2. Methods

2.1 Combined approach

An integrative review approach was adopted to achieve the objective. The first stage involved a review of MEAs across countries. The review question was 'What are the health technology managed entry agreements that have been applied around the world?' We were aware that a number of reviews have been conducted and published regarding MEAs (93-95,97,104,106,164-166); however, we wanted to consolidate these and expand to include Latin America. This review was supplemented with published studies not retrieved in the search, coupled with other sources from the senior level co-authors regarding ongoing arrangements within key South American markets (Second stage), since only limited published information were found. The countries included Argentina, Brazil, Colombia and Uruguay,

The third stage involved senior level health authority personnel, their advisers, and academics from a range of high- and middle-income countries involved with implementing and/ or researching MEAs, coupled with senior level personnel from PAHO and the World Bank, providing guidance on potential advantages and disadvantages, as well as key considerations, that the authorities in Brazil should consider as they progress with MEAs. This was based on the literature review, combined with their own experiences and activities. The

contextualising of the findings from the multiple approaches was principally from a payer (national or regional health authority or health insurance company) perspective, as this was the main emphasis of the paper.

This three-part approach was adopted because of the limited information regarding the implementation of MEAs and their impact, especially outcome based schemes, available in the published literature (5,9,93,94). . These combined approaches have been successfully used before when providing guidance and feedback to key stakeholder groups in disease areas and situations of interest (8,83,93,97,167-172)..

2.2 Search design for the literature review

Search strategies were designed for PubMed, EMBASE, LILACS and Cochrane Library databases on March 5th, 2019. The literature search used the strategy outlined by the Cochrane guideline, considering the population, intervention/exposure, comparator and in some cases the outcomes (clinical results) (PICO) (173). This review considered: problems, topics of interest and outcomes:

- Problem: Managed Entry Agreements;
- Topic of interest: Medicines or health technologies;
- Outcomes: Experiences, processes, performances, and efficiency of MEAs.

Descriptors and words were extracted from the three main controlled vocabularies according to Cochrane, Medical Subject Headings (MeSH) for Medline database and others, including the Emtree thesaurus for EMBASE database and Health Sciences Descriptors (DeCS) for Latin America databases. Some synonymous and key words were also added to the search on all text. The search strategies used in each database are detailed in the Supplementary Material (Table 2S).

2.3 Inclusion and exclusion criteria for the literature review

This review included the following eligibility criteria for potential studies:

- *Inclusion*: papers in Portuguese, English or Spanish concerning payment for performance and/or risk-sharing agreements and/or MEAs experiences across countries and suppliers for medicines or health technologies, including systematic or integrative reviews, as well as abstracts published in annals.
- *Exclusion*: dissertations or theses; editorials; news; commentaries; letters to the editor; guidelines; studies that did not identify the payment for performance/risk-sharing agreements/MEA.

The eligibility of potential studies was assessed by two researchers (MSC and ALP), using the Rayyan® web app. They undertook the initial screening of the studies by reading the titles and abstracts. Disagreements were solved by a third researcher (CZD). Subsequently, the articles selected were analyzed by reading the full text. Articles were subsequently included in the review if they met the inclusion criteria. Disagreements were assessed by a third reviewer (MMG). Grey literature was also considered as an important strategy to recover eligible studies in this review as we believed a number of MEAs may be contained in the grey literature and not published. This was conducted via a manual search of the references in the first selected papers, additional search in google/google academics, as well as with suggestions from the co-authors and others working in this field. Any conflict was also resolved by another researcher (CZD), who made the final decision.

2.4 Analysis of the results from the literature review

The data extracted from the publications were analysed by country through a descriptive analysis approach. The variables considered were: year, type of agreement, type of technology/medicine, clinical condition and the payers and providers involved. Relevant additional publications known to the co-authors that were not covered in the literature search were also included to add depth and robustness to the paper.

3. Results

3.1 Literature review

2299 articles were retrieved from the systematic literature review conducted among the four databases. Seventy-four articles remained after removing duplicates and reading the titles and abstracts. After a full

reading of the papers and the inclusion of manual and grey literature, 25 studies remained, addressing 446 agreements (Figure 1 in Supplementary Material).

Out of these, 432 agreements included medicines and only 14 included other technologies or procedures. Most of the arrangements were financial, including discounts and volume (43%), followed by performance-based schemes (36%). More than half of the agreements involved antineoplastic medicines. Among the pharmaceutical companies involved in such arrangements, Novartis, Roche and Pfizer were the most cited. Table 3S (Supplementary material) presents the main characteristics of the MEAs identified in the studies.

The agreement categories: “outcomes”, “impact results” and “other aspects” were typically not fully addressed in the included studies, which meant we could not deeply analyze the results and performance of the agreements. Most countries kept key information, such as discounts or rebates, confidential or have not published such data in journals or conferences (103,106,132). This is a concern, particularly regarding publicly funded healthcare systems as this information cannot be used to guide pricing considerations in other countries as identified in a number of publications and reviews (5,93,174,175). . Having said this, care is needed in order to still incentivize companies to invest in new medicines whilst maintaining the sustainability of healthcare systems (142). Such deliberations will continue with growing calls for fair pricing for new medicines among key stakeholder groups (85,90,143,176), with the WHO arguing that improving price transparency should be encouraged on the grounds of good governance with no conclusive evidence on its downside (27). Figure 2S in the Supplement depicts which countries are already practicing MEAs, according to the literature.

3.2 Summary of studies broken down by continent and country

Table 4S (Supplementary material) provides the details of the MEAs among selected countries found from the literature review and supplemental data, building on the information presented in Table 3S. Overall, we see financial based MEAs as the principal type of MEA in a number of European countries. Until the end of 2015, in Poland, for example, the most common types of MEAs for new medicines included discounts (43.6%) and other schemes (34.5%), which typically involved free supplies and payback arrangements (21.8%). There were no outcome schemes in operation at this time (177).

By the end of 2018, there were over 100 MEAs established in NHS Scotland that are part of the Patient Access Schemes (119). The vast majority were simple discount schemes (discount at the point of invoice). Less than 10% of the MEAs involved more complex financial schemes and only one was an outcome-based scheme. There are likely to be similar arrangements in England and Wales. However, the situation may change in the United Kingdom (UK) with criteria for ring-fencing monies to fund new cancer medicines where there are concerns with their cost-effectiveness now changed with the requirement that new applications be part of an agreed managed access scheme that includes the collection of health service utilization data to inform subsequent funding decisions alongside ongoing debates on this subject (178,179).

In Canada, MEAs are principally financial-based schemes involving the pan-Canadian Pharmaceutical Alliance (pCPA) for publicly funded drug programs and patients (116). Currently, outcome-based schemes are seen as challenging due the lack of integrated real world data sources in Canada (116). As new medicines increasingly target niche populations, it may require data from more than one country to combine their real world data in order to gain enough patients to assess meaningful findings (125,180). . Table 5S summarizes the types of MEAs found in a number of different countries with a range of geographies, gross domestic product (GDP) and financing of healthcare systems.

3.3 MEAs in key South American countries

The literature review retrieved few information regarding agreements in South American countries. In this way, when consulting other sources (suggested by co-authors from these countries) regarding ongoing arrangements within key South American markets, some activities, including planned agreements, and the funding of medicines were summarized (Table 1).

Table 1 – Synopsis of activities surrounding MEAs and funding medicines in key South American countries

Country	Summary of current and planned MEAs
Argentina	<ul style="list-style-type: none"> • MEAs are just starting in Argentina, but these efforts are hampered by fragmentation of the healthcare system. • Currently, there appears to be only one value-based agreement in operation (for bevacizumab), which started in 2017 and involved a single health insurer and a pharmacy. However, there are no published details. The situation is likely to change with the introduction of biosimilars for bevacizumab in Argentina combined with ongoing pharmacovigilance programmes (181).
Brazil	<ul style="list-style-type: none"> • The first performance evaluation was taken for intramuscular beta interferon 1a, to treat multiple sclerosis. CONITEC (the Brazilian Health Technology Assessment Agency) recommended the disinvestment of the technology. The recommendation affected the purchase price paid by the government (161,182). • As mentioned, in 2019 the Minister of Health of Brazil announced the intention to initiate a risk sharing agreement for certain high priced medicines (162). • CONITEC also recently recommended the incorporation of two high priced medicines for rare diseases (eculizumab and nusinersen) under performance evaluation (162,183).
Colombia	<ul style="list-style-type: none"> • Because of increasing litigation in the country, the Ministry of Health was compelled to cover technologies without any further assessment or management of their entry onto the benefits plan. • In 2017, the enactment of the law 1751 of 2015 (184) entered into force any medicine granted registration by the National Food and Drug Surveillance Institute is considered as included in the Health Benefits Plan and must be reimbursed by the government. Consequently, any high-cost medicine must now be paid by the government. The costs of all agreed medicines on the market must be covered by the public insurance except explicit exclusions. Law 1751 contains the criteria for excluding technologies (which define legitimate limits of the human right to health), but the Constitutional Court amended such criteria and prohibited exclusions based on cost-effectiveness assessments. • Currently (up to 2019), the Government in Colombia has no agreed MEAs; however, it is currently negotiating two under strict confidentiality. In a context though where coverage is obtained automatically following marketing authorization from the National Food and Drug Surveillance Institute, there seem to be limited incentives for pharmaceutical companies to negotiate MEAs since reimbursement is guaranteed once the technology enters the market. The sole incentive would probably be to get a special payment scheme (up-front, for example) to gain more rapid access; however, the government has no incentive for this. • Nonetheless, there are a few MEAs between pharmaceutical companies and insurers, which are confidential and are typically offered by pharmaceutical companies to gain a competitive advantage and get doctors to prescribe their new medicines. However, there are no published details.
Uruguay	<ul style="list-style-type: none"> • Uruguay has a National Health System financed by the National Health Fund. Besides the National Health Fund, there is the National Resources Fund (<i>Fondo Nacional de Recursos - FNR</i>) that finances highly specialized medical procedures and high cost medicines for the users based on approved coverage protocols. • The FNR has some confidential trading agreements with pharmaceutical companies including volume, fixed monthly payments, and discounts/rebates based on agreed performance metrics to help ease budgetary pressures. Some examples of these agreements include: <ul style="list-style-type: none"> ○ Erlotinib for the treatment of advanced non-small cell lung cancer. Typically, patients have on average 12 months survival after starting treatment. As part of the agreement, the costs of subsequent doses after 12 months are covered by the pharmaceutical company. ○ Iloprost for the treatment of pulmonary hypertension. The recommended dose is six to nine sprays per day, with patients typically being treated with no more than 4.5 per day. The FNR buys the first three boxes of a monthly treatment, the fourth box is a bonus, and the next three boxes are provided by the company at no cost to FNR. This is repeated every month as long as the patient remains in treatment and follow-up. There is a monthly follow-up of patients. ○ The agreement for financing breast cancer treatment, since 2016, includes medicines for HER2+ patients and is based on published clinical trials. ○ Since July 2019, there is a flat tariff agreement to finance adalimumab for rheumatic and other diseases.

3.4 Key considerations for MEAs from a payer's perspective

There are a number of considerations that need to be carefully considered when starting MEAs, especially among middle-income countries. These can be divided into their potential advantages (Box 1) and disadvantages (Box 2), as well as key areas to consider during initial negotiations with pharmaceutical

companies and their implementation (Box 3). These have been identified from the literature (Tables 1 as well as Supplementary Tables 1S, 3S and 4S), supplemented by the considerable experiences of the co-authors. There is a concern though that middle-income countries will end up paying more for their medicines than higher-income countries. This is because higher income countries potentially have greater economic power when discussing and debating confidential discounts and rebates in MEAs for new medicines (139, 185-189), potentially unbalancing the international market. However, we have seen purchasing consortia forming to address this as seen with PAHO and treatments for Hepatitis C in South America (159). A number of cross boarder Pan-European Groups have now formed including BeNeLuxA, Nordic and Valletta groups undertaking joint activities including Horizon Scanning and HTA activities (190-193), and these are likely to continue. However, joint reimbursement negotiations are at an earlier stage given differences between the reimbursement and legal systems in each country (194).

Box 1 – Potential advantages of MEAs from a payer’s perspective

Potential advantages of MEAs from a payer’s perspective
<p><u>General advantages</u></p> <ul style="list-style-type: none"> • May provide access to new medicines where affordability is an issue and where there are concerns with the uncertainty of the effectiveness or cost-effectiveness of a new medicine when introduced into wider routine clinical care. This is particularly important in situations where there are only a limited number of treatment choices currently available and resources are scarce with many competing demands. • May suggest to pharmaceutical companies key areas and outcome measures to consider during the future development of new medicines to address areas of unmet need. This includes the development of biomarkers and other approaches to better target the patient population where health gain will be greater. • Can enhance the use of medicines in a more predictable, transparent and rational way. Consequently, prompting and potentially expediting the use of agreed prescribing guidelines among all key stakeholder groups which may help to reduce differences in utilization patterns for reimbursed medicines seen across countries despite positive reimbursement and funding decisions (45). This is in addition to differences in patient characteristics between countries. • Offer flexibility in terms of their value and potential budget impact when considering new and often high priced medicines characterised by appreciable levels of uncertainty compared with existing funded treatments. This flexibility surrounding pricing and funding will become even more important as more biological medicines seen as standards lose their patent and become available as lower cost biosimilars. An example of this is the case of pertuzumab+trastuzumab for the treatment of HER2-positive early breast cancer in England and Wales, where NICE would recommend reimbursement if the manufacturer would reduce their requested price now that biosimilar trastuzumab is available at appreciably lower prices than the originator (195).
<p><u>Advantages of Financial Schemes</u></p> <ul style="list-style-type: none"> • Easier to implement than outcome-based schemes, and can help contain costs and keep expenditure within agreed limits. This is especially important in countries such as middle-income countries with restricted budgets alongside increasing demands on available resources. • Potential for cross product agreements with particular pharmaceutical companies, which involve reducing the price of an older medicine to gain reimbursement for a new medicine. This is a form of financial agreement in existence in New Zealand and similar overall to the types of agreements in France to keep annual increases in pharmaceutical expenditure to agreed limits (168, 196). This can potentially have multiplying financial effects if internal reference pricing is being used in a country as the price of an entire cluster can potentially be reduced. However, such arrangements are potentially against antitrust regulations especially in Europe. • Can improve the cost-effectiveness of new medicines by lowering the incremental cost-effectiveness ratio (ICER) levels, thereby aiding reimbursement and funding decisions as seen in the UK and other countries in the decisions by health authorities to reimburse new medicines under patient access schemes (57,117).
<p><u>Advantages of Outcome schemes/Performance agreements</u></p> <ul style="list-style-type: none"> • May provide treatment to those patients most likely to benefit from the new medicine in routine clinical care. Such schemes enhance the value of the new medicines and hence the potential for reimbursement alongside payback/rebates schemes for non-responders. This is important as patients in Phase II or III trials typically include selected patients that may show improved results versus patients typically seen in routine care which may be more co-morbid and older (7, 147). • Can provide evidence about a health technology in different populations as not all patient groups are included in clinical trials including patients with greater co-morbidity. In addition, provide more information on patient outcomes with well-designed studies. • Can help update guidelines within a country on appropriate medicine use. • May potentially be part of agreed post marketing schemes or current registry schemes to reduce the burden of data collection as part of improved information technology (IT) infrastructures among to generally improve data collection/ patient information. This was seen in the UK with the Systemic Anti-Cancer Therapy (SACT) database in England and potentially the Cancer Medicines Outcome Programme (CMOP) in Scotland (124,197,198).

Potential advantages of MEAs from a payer's perspective

- Can prolong the time for capturing data on the effectiveness, safety and cost-effectiveness of a new medicine in a more restricted environment with clinicians adhering to agreed protocols and no off-label use. Consequently, when the findings are analysed, a decision can be made on more robust data with less confounders regarding their value and potential reimbursed price in routine clinical care.

Box 2 – Potential disadvantages and concerns with MEAs from a payer's perspective

Potential disadvantages and areas of concern with MEAs from a payer's perspective

Financial based schemes

General considerations:

- Lack of transparency with confidential discounts and rebates. However, this has to be balanced against providing incentives and competition for the development of new medicines and new indications with discounts/ rebates not necessarily linked to value. Agreed variable discounts by volume may be one way forward to incentivise research into multiple indications as typically administrative databases do not contain indication data given current concerns with indication-based pricing (8,199).
- They do not necessarily ensure that the most appropriate patients receive the new medicine – especially when agreed budgets have been exceeded. However, demand-side measures could potentially be incorporated to guide physician prescribing aiming to reduce potential inequities. This though would depend on the healthcare system with some healthcare systems more able to instigate demand-side measures than others (83,108,168,196).
- Patient co-pays will be higher in ambulatory care (as opposed to hospital care) if these are based on list rather than actual prices, which could affect utilisation in practice. However, balanced against wholesalers, distributors and retail pharmacists typically paid on list rather than actual prices which would mean re-designing the remuneration scheme and making discounts more transparent.

Pricing and discount issues

- Pharmaceutical companies could ask for higher prices initially – especially if they believe discounts are inevitable. Robust Health Technology Assessment (HTA) systems can help to address this.
- The confidential nature of discounts and rebates can enable manufacturers to maintain a high list price if the designated country is a reference priced country for external reference pricing purposes to the detriment of some countries.
- Launching of medicines first in a high income country with higher threshold levels especially if they are an external reference-priced country knowing that prices may well fall with aggressive negotiations during reimbursement discussions; however, the list price has been established as a reference for other countries. This is a concern for countries with less economic power and where there are high patient co-payments; however, a reflection of current pricing schemes in a number of countries based on external reference pricing. The formation of purchasing consortia especially in Europe (progressing) and South America via PAHO (as seen with new medicines for Hepatitis C) may help to address this.

Outcome schemes/Performance agreements

General Issues

- Typically, more costly and ambitious than financial based schemes.
- Pharmaceutical companies could ask for higher prices initially – especially if they believe patient populations will be more restricted once effectiveness data becomes available. Instigation of robust HTA systems can help address this.
- Fragmentation of healthcare services/structure and limited capacity within some countries can make it difficult to undertake outcome-based schemes in practice.
- Potentially high administrative and transaction costs, including:
 - (i) Data entry costs, especially if the technology under assessment demands separate registries rather than using existing electronic health records/systems and it is necessary to develop electronic health records or other systems to assess whether the agreed outcomes are being achieved under the performance agreement (acknowledging this will become less of a barrier with increasing availability of electronic health records across countries);
 - (ii) Additional efforts may be required to make new medicines available to patients especially in outcome based schemes including the additional time needed for negotiations alongside monitoring patient responses.
- In multiple-payer healthcare systems, data tracking is challenging for payers when members move from one plan to another.
- Early approval decisions for new medicines based on preliminary data may be considered by physicians and patients as improvements compared to current standards.

Potential disadvantages and areas of concern with MEAs from a payer's perspective

- MEAs using surrogate markers requires caution since these do not necessarily translate into appreciably improved outcome measures, e.g. survival times (greater than 3 to 6 months) compared with similar times for progression-free survival (8,53,135,136,200). Greater dialogue between payers, regulators, HTA personnel and clinicians could help to address this.
- Information collected in outcome-based schemes may not enhance the evidence base beyond self-certified validation of appropriate prescribing for reimbursement purposes as currently seen in Italy (132).
- Patient accessibility may be compromised in situations where under an MEA, particularly outcome-based schemes; the new medicine may only be available in a limited number of reference centres.
- The temporary nature of certain agreements could make manufacturers cautious about progressing with them, exacerbated if the studies subsequently demonstrate that the reimbursed patient population is smaller than originally thought reducing potential sales.

Confidentiality issues:

- The confidential nature of any data captured especially during outcome based MEAs adds to the difficulties with transparency when analysing the findings with typically strict criteria within health authorities on access to patient level data under governance and data ownership agreements.
- Confidential data can also add to the difficulties for fully assessing the cost-effectiveness of the new medicine in routine clinical care, with confidentiality adding to the complexity for independent parties, e.g. researchers, evaluating MEA results.
- Issues of transparency can also be important in discussions with patients about the temporary nature of any funding for new medicines under outcome based MEAs.

Re-evaluation including potential price adjustments

- Concerns with how long outcome-based schemes will last before evaluation, and who pays for the medicine during the evaluation period. The length of time is especially important in rapidly changing disease areas where new technologies or generics/ biosimilars become available by the time the outcome-based scheme is finished.
- Concerns regarding 'who is to blame if outcomes are not being achieved' which will impact on the value of new technologies. The outcomes definition and/or performance indicators measured are critical issues. Key issues to consider in routine clinical care alongside the assessment of any outcome-based scheme include the potential for suboptimal persistence/adherence unless fully addressed, inadequate diagnosis and off label use. The collected data could reflect actual effectiveness and safety in routine clinical care, which could differ from clinical trials where everything is more controlled and typically patient populations are likely to be less co-morbid, unless addressed in the design of the outcome-based MEA.
- Another concern is that pharmaceutical companies may not fully compensate health authorities in payback schemes when the new medicine is not as effective or cost-effective in real life as expected. Companies know that it is more difficult for health authorities to delist medicines due to cost rather than safety reasons.

There are a number of key considerations that payers especially those in middle- and higher-middle income countries need to take into account when assessing potential MEAs especially as new high-cost medicines including more complex treatments will continue to enter the market on a regular basis.

Box 3 – Key considerations for payers when discussing possible MEAs for new medicines

Key considerations of MEAs for new medicines in the payer perspective

General considerations

- The current healthcare system and its capacity to undertake financial and/ or outcome based MEA with multiple pharmaceutical companies given the fragmentation of most healthcare systems. This includes the number of personnel to monitor financial based MEAs among pharmaceutical and other companies as well as the necessary infrastructure to undertake and monitor any outcome based scheme.
- MEAs must be clearly constructed with clear aims and objectives as well as outcomes, and agreed by all parties. This includes a robust plan for the analysis to address concerns that any agreement, especially for outcome-based schemes, can deliver the desired data despite patient heterogeneity including likely co-morbidities and ages in routine care. In addition, an agreed well defined exit strategy for a new medicine if new evidence fails to demonstrate its value in routine clinical care.
- Addressing concerns with asymmetry of information as manufacturers will typically know more about the new technology than the competent authority. Companies must be questioned when further trial data becomes available, especially in cases of early entry of new medicines following Phase II studies.
- Any MEA must be fully appraised beforehand regarding all the factors involved with arranging them including any potential performance metrics. This is particularly important for outcome-based schemes and includes likely administrative times as well as the time, expertise, and costs, necessary to enter and analyse the data in electronic databases.
- Realistic timelines for any MEA.

Key considerations of MEAs for new medicines in the payer perspective

- For specialized medicines such as those for cancer and orphan diseases, it is important to restrict MEAs to agreed centres of excellence to improve data collection as well as early assessment.

Additional considerations for Outcome based schemes

- Will any proposed outcome based MEA be effective in addressing current areas of uncertainty, e.g. making sure that any proposed surrogate marker has been shown to have a robust correlation to longer term outcome measures of interest? In addition, in what way can any MEA being considered improve the scientific base for new innovative technologies in addition to potentially providing early access to patients?
- Carefully consider what is the most appropriate time frame for any outcome evaluation, and what are the optimal markers/ outcome measures to be able to fully assess performance when engaging in outcome-based agreements.
- Instigating appropriate governance measures to help ensure that the evidence from observational data collected is strong enough to assess comparative effectiveness in any outcome-based scheme. This includes assessing whether a control group is needed. If so, adequately addressing how will this be handled including any necessary patient concerns.
- The timeframe for observing the outcome must be clearly defined as part of good governance. Responsibility for collection and payment for evidence generation during this period must be agreed and transparently communicated between all relevant parties before instigating any MEA.
- Assessing whether it is possible to develop milestone contracts using population risk pooling and predictive modelling approaches within the healthcare system, which could potentially involve spreading payments over multiple years and tying each payment to the achievement of agreed performance measures. This could be based on benchmarks in other situations within the healthcare system if this exists as this departure is different from current annual budget arrangements for pharmaceuticals. However, may be applicable for new expensive equipment within hospitals. Staged payments not necessarily tied to milestones can potentially soften the initial impact of new high cost therapies.
- Assess whether evidence-gathering efforts can be shared among countries in order to improve information quality and completeness and to counter potential information bias. This can be part of general considerations to assess whether the outputs of any patient level research can be shared among countries, especially with increasingly targeted conditions with small patient volumes, to reduce the time interval for data collection.

4. Discussion

Based on the literature review, 97% of MEAs identified involved medicines, typically medicines for oncology, with financial based schemes the most prevalent. This is perhaps not surprising in view of the complexities typically involved in outcome-based schemes as well as the necessary infrastructure to undertake such schemes (Boxes 2 and 3). Moreover, in reality, financial based schemes have been perceived as easier to undertake as seen by different recommendations by NICE in England and Wales for the different approaches (201). In addition, financial-based agreements are generally seen as a more effective means whereby health services can monitor and influence their outlay on expensive medicines. However, this is not universal considering the developments in outcome based contracting for medicines and diseases areas among managed care organisations in the US (Table 1S, Supplementary Material). In addition, the UK is now linking the collection of clinical data with funding for new oncology medicines within the cancer drug fund (178).

In our literature review, we found MEAs in most continents. In North America, the United States is notable for the large number of agreements particularly involving several payers (Tables 1S, 4S and 5S). As mentioned, this high number of payers is related to the model of their health system with a considerable number of patients covered by different health insurance providers with 67.2% of patients currently covered by private insurance schemes in the USA and 37.7% by government coverage (202). In South America, Marin *et al.* (2015) referred to Colombia as a pioneer in MEAs (203). However, a greater understanding of the healthcare system in Colombia with its current challenges would appear to contradict this (Table 1). Whilst no studies were found in the literature review reporting Uruguayan experiences with MEAs, a number of these are now in operation (Table 1) (204). In Oceania, both New Zealand and Australia have MEAs, and in Asia there are MEAs in existence in China, the Philippines, Singapore, Indonesia, Korea, and Taiwan (69,101,164).

There are a number of reasons why MEAs have now become widespread across countries. These include, as previously mentioned, progress in science involving more complex treatments. Reasons also include the launch of advanced therapies with typically high associated prices and an associated budget impact, uncertainty and costs of new treatments as seen with new medicines for cancer and orphan diseases, and the increasing prevalence of chronic NCDs with aging populations with implications for appreciably increased use and costs of medicines (8,39,40,61,93,205,206). As a result, we are likely to see the number of MEAs grow alongside other potential measures for funding new medicines (8). However, there are concerns that there is limited information to date regarding the results of MEAs to guide future activities (5,9,93,99,108). This is

complicated by the decision of many countries to preferentially adopt confidential discounts for new and existing medicines as part of any MEA especially within public healthcare systems. This has resulted in increasing calls for transparency; however, this has to be balanced against appropriate incentives for pharmaceutical companies to develop new medicines to address areas of unmet need as well as price fixing considerations (57,93,140,142). Moreover, the traditional methods of health technology assessment used to support decisions may not be enough by themselves in this context. As a result, more robust and innovative models including multicriteria decision analysis (MCDAs) may be required to aid decision making although there have been concerns with MCDAs which are being addressed (8,91,115, 207-210).

However, despite the many potential benefits of MEAs (Box 1) there are considerable concerns that need to be considered in countries such as Brazil as they seek to implement additional MEAs (Box 2). These include concerns with the extensive adoption of confidential price contracts. This means that no one country can really determine if they are getting optimal discounts compared with their neighbouring countries (Box 2). In addition, high income countries with appreciable greater populations may use their economic power to negotiate aggressive confidential discounts which may well not be available to smaller countries to the detriment of their citizens especially if there are patient co-payments in the country. However, the number of outcome-based schemes may well grow to address uncertainty with a number of new medicines, especially in patients with cancer, being launch and approved by regulatory authorities on the basis of small clinical trials, with pressure on health authorities to fund them as more evidence is generated (75,211).

Typically, a number of requirements are needed before MEAs can become a realistic option in middle-income countries. These include (i) a flexible legislative framework, (ii) an adequate infrastructure for data collection within the country to facilitate data entry and enhance the evaluation of all agreed schemes, (iii) potential for integration between the different current databases within a country to aid analysis, (iv) strengthening of current healthcare structures where pertinent to facilitate pertinent data entry and analysis as well as monitoring any agreement especially for outcome based schemes, (v) and good alignment of the objectives between health authorities, clinicians and pharmaceutical companies including pertinent incentives for all key stakeholder groups. The outcome-based schemes, in particular, can be costly and necessitate in advance agreements regarding the funding for data entry, collection, analysis, medicines during data collection and supervision. Moreover, for allocation decisions publicly funded health care systems need to consider reassessment of currently funded interventions and their value whenever new technologies enter the market (212).

Which type of MEA to choose when entering into negotiations with pharmaceutical and other companies, as well as the key factors to consider when developing these agreements, are part of a number of key issues that health authorities need to consider going forward (Box 3). This is particularly important in priority disease areas such as cancer and rare diseases since new medicines are typically needed in these areas but have commanded high prices despite often limited health gain (40,55,108,213). These agreements can be performed to improve scientific knowledge regarding new innovative technologies alongside providing early access to patients. However, this has to be balanced against issues of affordability and sustainability of the whole health system. New approaches or funding new medicines are, however, outside of the scope of this paper and may be followed up in future research projects (8). Alternative access schemes for pharmaceuticals have also recently been collated and discussed by Löblová and colleagues (214), and such discussions will continue.

We are aware of the limitations of this paper regarding the formatting of data and the presentation of the results from the published articles due to a lack of information regarding the nature of MEAs. This includes defining the parameters used in such agreements as well as the evaluation of the outcomes of any MEA. In addition, not all MEAs as well as not all countries with MEAs are included in this review due to publications not meeting the inclusion criteria. We are also aware that some agreements found in the literature are likely to have expired by now. However, they have been included as examples going forward especially in countries where there are limited outcome based schemes to date. Despite these limitations, we believe our findings and their implications are robust providing direction to those planning MEAs.

5. Conclusion

We are likely to see a growth in MEAs in the future with the continual launch of new premium priced medicines including new Advanced Therapy Medicinal Products. Alongside this, ageing societies demanding new complex treatments to address unmet needs further increase demands on available resources especially among high- and upper middle-income countries. MEAs are a potential way forward to address funding

pressures alongside other financing approaches. However, MEAs can be complex to administer and require critical appraisal among all key stakeholders before initiation alongside issues of affordability and sustainability for the health care system as a whole. However, this has to be balanced against such agreements improving the knowledge base for new innovative technologies as well as providing early access to patients for potentially innovative therapies.

The financial-based agreements are easier to perform, enabling health care systems to reduce their outlay for new expensive medicines especially where there are considerable uncertainties surrounding the value of a new medicine in routine clinical care. Nevertheless, as mentioned, the extensive adoption of confidential price contracts across many countries generates market failures. Such discounts mean that no country can really determine if they are getting the best discounts jeopardizing the overall goal of reducing the cost of new medicines. However, this has to be balanced against ensuring necessary incentives for companies to develop new technologies to address areas of unmet need. The specificities and peculiarities of each country should also be taken into account when seeking to initiate MEAs alongside adequate infrastructures. These include whether there are robust information systems in place for data collection rather than instigating single registries for each new medicine.

MEAs can potentially be important tools to improve the scientific capacity and knowledge within countries alongside providing access to new innovative and high cost medicines whilst seeking to minimize the opportunity costs of the decisions. Incorporating international knowledge and practice can be a crucial strategy to guide countries such as Brazil as they design MEAs for new innovative medicines. We will be researching this further as Brazil starts to introduce MEAs.

Compliance with ethical standards

Data Availability

Further data will be available on request.

Funding

No funding was received to conduct the research or write up this paper.

Informed consent

There was no need for informed consent or ethical approval since the senior level personnel providing advice and contextualising the findings from the literature review were the co-authors.

Conflicts of interest

The authors have no relevant conflicts of interest to declare although most of the co-authors are employed by health authorities or are advisers to health authorities.

Authors contribution

- C. Z. Dias, B. Godman, L. P. Gargano, P. S. Azevedo, M. M. Garcia, M. S. Cazarim, L. L. N. Pantuzza, A. L. Pereira, F. A. Acurcio, J. Alvares-Teodoro, A. A. Guerra-Junior participated in the conception of the paper, design of the search strategy, data and information collection including the systematic review, writing of the first and subsequent drafts as well as endorsed the content of the submitted paper.
- R. Iunes, T. Pippo, R. C. Hauegen, C. Vassallo, T. L. Laba, S. Simoens, S. Márquez, C. Gomez, L. Voncina, G. W. Selke, L. Garattini, H. Y. Kwon, J. Gulbinovic, A. Lipinska, M. Pomorski, L. McClure, J. Furst, R. Gambogi, C. H. Ortiz, S. Jan, D. V. Araújo, and V. Canuto work for health authorities and/or are advisers to them as well as engaged in implementing/ reviewing managed entry agreements in their countries. They all contributed to the writing and design of the section “Key considerations for MEAs from a payer’s perspective” and commented on successive drafts. They also endorsed the final submission. In addition, a number of these co-authors also participated in the conception of the paper.
- V. E. Araujo N. G. Ribeiro-Junior, I. F. Zuppo, and M. C. Borin contributed to the design and conducting of the search strategy, successive drafts and the final review of the paper.

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