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Strategies for Sustainable Access: Unpacking Managed Entry Agreements (MEAs) and Innovative Medicine Access

In recent years, significant advancements in science and technology including novel pharmaceuticals, have emerged (1). These innovative medicines not only extend life expectancy but also hold the potential to **improve the quality of life and save lives.** However, the soaring prices of these groundbreaking medications, coupled with the increasing prevalence of non-communicable diseases (NCDs), such as cancer, and rare diseases, have become a cause for global concern. Governments worldwide are grappling with the financial burden of funding these high-cost medicines (2). Additionally, reimbursing them has several challenges with traditional funding and pricing models (1,3). This predicament becomes even more pronounced for low and middle-income countries (LMICs), where healthcare resources are limited and prioritizing healthcare expenditure is paramount to achieve affordable, equitable, and sustainable access to these life-changing medicines (4).

The high cost of innovation places significant budget constraints within the healthcare systems. Challenges such as higher rates of inflation, increasing prices and limited initial evidence of new therapeutic benefit, present daunting hurdles for both payers and manufacturers. For countries with commitment to Universal Health Coverage (UHC) (5), reimbursement decisions are based on value which is a function of clinical and cost effectiveness. However, the high cost makes it difficult for the payer to prioritize. This challenge has led to many developed high income countries exploring alternative funding models and one such mechanism to facilitate reimbursement is through **Managed Entry Agreements (MEAs)** (6,7,8).

MEAs aim at early access to high-cost innovative medicines at pre-determined terms that can ensure the financial sustainability of healthcare systems. However, their successful adoption hinges on a consideration of various factors to address the unique challenges faced by different nations.

The aim of this document is to explore the concept of MEAs, understanding insights from existing literature regarding their benefits and challenges. Additionally, it seeks to formulate overarching recommendations for the implementation of MEAs in LMICs.

Understanding Managed Entry Agreements (MEAs):

The concept of MEAs is relatively new and therefore subject to varying interpretations in terms of both concept and terminology. Broadly defined as "Conditional agreements between the producer/manufacturer and the payer/provider," MEAs facilitate access through coverage or reimbursement of health technologies under predefined conditions (9).

Depending on the nature of the agreement, several mechanisms exist to manage uncertainties related to cost-effectiveness/or clinical effectiveness in a real-world setting leading to uncertainty in adoption, or its impact on the overall health system budget.

policy brief

MEAs can be broadly categorized into two main types:

Financial-Based Agreements (FBAs): These primarily focus on cost containment, considering factors such as the cost of the medicinal product or the overall cost of treatment. In FBA, the financing of a product falls on both the manufacturer and the payer. For example, a payer may agree to pay for a specified amount of the population over a given period of time, with the remainder of the treatment required to be paid for by the manufacturer.

Performance-Based Agreements (PBAs): PBAs are centered on the effectiveness of a product. When a novel, innovative product is under contract for a PBA, evidence is often limited, and payers' concerns focus on uncertainty as to whether the product will perform as beneficial in the real world. In these agreements, usually, a pact is established between the payer and the pharmaceutical company, enabling the collection of real-world data to determine payment based on observed clinical results.

In addition to these two primary types, a newer model of MEAs known as service-based agreements (SBAs) has gained prominence and importance although it has not been extensively studied.

For a comprehensive understanding of MEAs, Kanavos et al. proposed a taxonomy framework. This framework classifies MEAs based on a) The objectives they aim to achieve; b) The subject matter being monitored; c) The instruments used for their implementation; and d) The impact they can potentially bring about. **Figure 1,** adapted from Ferrario and Kanavos (2013) (9), provides a visual representation of this taxonomy framework, aiming to classify and analyze the impact of MEA. The most frequent types of FBAs and PBAs are detailed in **Table 1.**

Figure 1 MEA Taxonomy

(as adapted from Ferrario and Kanavos)

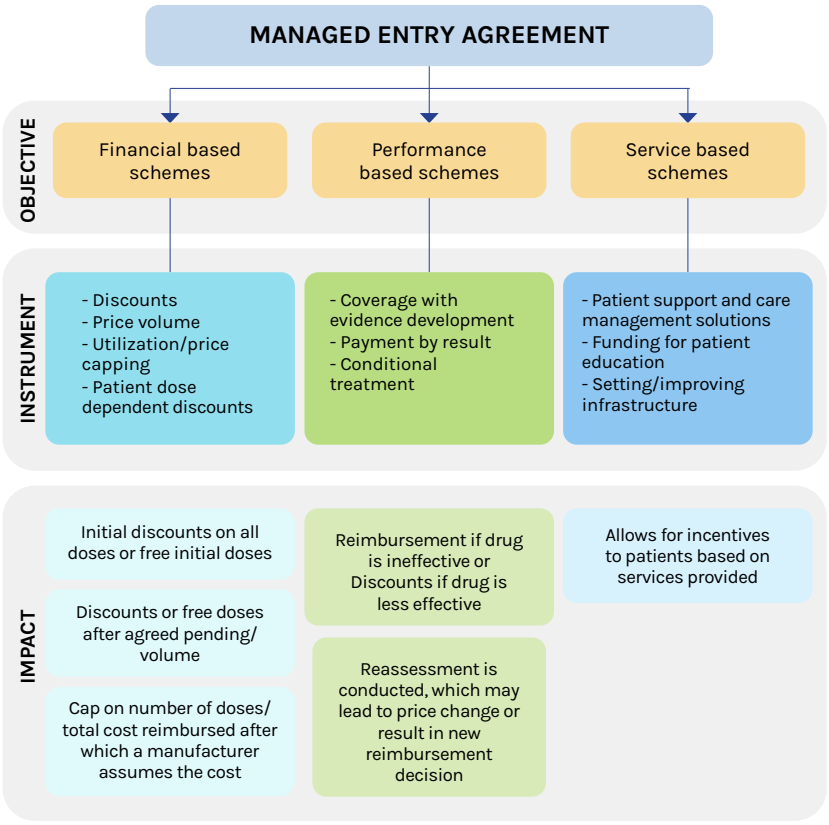

Table 1: Detailed description of different types of Finance and Performance-based agreements

Finance-Based Agreements	Rebates	Payments refunded by the manufacturer to the payer driven by incremental cost-effectiveness ratio (ICER) or simply determined during negotiations.
	Discounts	Price reductions granted to payers to improve market access, usually confidential, without affecting the drug list price. Discounts may also be agreed on manufacturer's portfolio in exchange for better price/access for another product.
	Price-volume agreement	Price drugs are reduced based on sales volume. Alternatively, depending on the total sales volume, the price will be discounted for all units sold, according to a predefined scheme.
	Utilization cap	At patient level, it aims at capping the yearly price/ yearly treatment course reimbursed. Additional treatment courses are provided by the manufacturer for free. At population level, beyond the cap, manufacturers may have to reimburse the full/ part retail price/ex-factory price, depending on the agreement.
	Fund-based payment	Such as national silo fund for specific conditions (e.g., the Cancer Drugs Fund in the UK that pays for new cancer drugs rejected by the NICE).
	Cost-Sharing	Manufacturers share in the cost with Payers of introducing a product on to the market on an agreed upon basis, amount, rate, duration, etc.
	Free Initiation Treatment	Manufacturers will provide free initiation of treatment to share the financing of a product with the payer. After an agreed upon duration or number of treatments, payers assume responsibility of financing the products.
Performance -Based Agreements	Payment by result	Manufacturer pays rebate / refund to the payer if pre-determined clinical goals are not met during actual usage (Pay-for-performance, P4P).
	Conditional treatment / Discounted treatment initiation	Treatment initiation is provided for free or at a discount for all patients; payers pay full price of further therapy for responders.
	Coverage with evidence development	Product reimbursed for set period. After that time, additional evidence gathered will determine whether coverage should be expanded, withdrawn, or continued as is. A rebate may also be required if evidence is unfavourable.

Source: Dabbous M, Chachoua L, Caban A, Toumi M. Managed Entry Agreements: Policy Analysis From the European Perspective. Value in Health. 2020;23(4):425-33.

Use, Adoption, and Trends in MEA

There has been a notable surge in the implementation of MEAs over the years, particularly in high-income countries (more than 95% of all MEAs are in HICs) (4). Specifically, MEAs have been implemented mainly in European countries, while such utilization remains less common in low-income nations. Among the various types of MEAs, experience with financial-based agreements is extensive, whereas experience with outcome-based agreements remains relatively limited. Among financial schemes, price/volume agreements and discounts stand out as the most frequently employed instruments (4).

LMICs that have documented the use of MEAs have predominantly reported utilizing financial MEAs, primarily in the form of discounts. The diseases that are commonly covered under either type of MEA are NCDs, particularly cancers, chronic melogenic leukemias, osteoporosis, diabetes, and rare diseases such as multiple sclerosis (4).

To understand the situation of MEA in high-income countries we purposively looked at selecting three countries with developed Health Technology Assessment (HTA) systems. Table 2 below provides an overview of different types of MEA implemented in Australia, England and South Korea.

Table 2: Summary of types of MEAs implemented in select countries.

Country	MEA used	Medicines reimbursed
Australia	The risk sharing arrangement is captured through a legal deed of agreement ('deed') that is negotiated between the sponsor and the government. Some financial risk share arrangements can be class deeds where sponsors share the risk based on market share.	A financial risk share was mentioned for 24 medicines in the most recent public summary documents.
England	National Health Service (payer) and manufacturers have an agreement and one of the functions of Cancer Drug Fund (CDF) is managed access fund providing conditional funding for cancer drugs where uncertainty is addressed through data collection. Dominantly financial MEAs in form of discounts are used, but outcome-based MEAs are also used.	England has approved 42 medicines since introduction of CDF.
South Korea	Four types of MEAs: i) Coverage with additional evidence; ii) expenditure cap refund; iii) Utilization cap per patient; and iv) Refund/expenditure cap	As of 2019, 39 medicines had been reimbursed under RSA.

Source: Authors Analysis

Advantages and limitations of MEAs as an effective risk management tool

MEAs offer numerous benefits including reducing budget impact while ensuring early access to innovative technologies by minimizing uncertainty in clinical and cost-effectiveness data thus potentially lowering payer risks. Financial MEAs i.e., FBAs aim to enhance the financial stability of health plans and equitably allocate resources within finite budgets, achieving cost control and ensuring broader patient coverage plans (10,11,12). Payers consider that the FBAs are a resource rationing tool. Reducing the cost pressure in terms of price reduction allows coverage of a maximum number of patients and certainty of medicine budget. For outcome-based or PBAs are crucial in areas with high clinical unmet needs, small patient populations, challenging data collection, and market access uncertainty. PBAs enable both payers and patients to gain valuable experience with the medication and address clinical data uncertainty through real-world data collection, aiding collaboration between pharmaceutical companies and payers. Manufacturers employ to differentiate their products and demonstrate effectiveness against competitors (13).

Despite these advantages, MEA's implementation poses challenges, necessitating careful consideration by policymakers. A primary challenge with FBAs is the inclination of manufacturers to establish them with payers from larger market shares and higher purchasing power, thereby placing a disproportionate burden on smaller, less affluent markets. Moreover, the confidentiality of discounts and rebates to payers often obscures the actual list price of medicines, affecting External Reference Pricing (ERP), because prices are set based on official listed prices rather than on the actual net ones (14, 15). Additionally, a central issue revolves around defining the objectives of MEAs and assessing the sufficiency of evidence for informed decision-making.

For PBAs, although designed to collect real-world clinical outcome data, establishing the infrastructure for such data collection is resource-intensive and costly. Payers face challenges related to administrative burdens, resource demands, execution costs, and the complexity of implementing and executing these agreements. The intricate nature of such agreements and the associated costs can slow down access.

A case study from Italy, which has one of the oldest PBA systems, revealed that the return to payer accounted for 5% of the total expenditure in setting up the PBA scheme (16, 17). Another significant criticism is related to the outcome uncertainty in clinicaltrials, either because of theirshort duration orthe use of surrogate endpoints that may not accurately represent true endpoints, thereby undermining the very purpose of outcome-based agreements, which is to address uncertainty (18, 19, 20). Critics express concerns that MEAs may become quick fixes or ad hoc solutions. Predictability for manufacturers concerning listing and future rewards imposes constraints. For Coverage with Evidence Development (CED)-based MEAs, reversing reimbursement coverage decisions is typically challenging, further contributing to payer resistance towards conditional coverage. Lastly, from the patient's perspective, there is a fear of premature withdrawal of effective treatments if predefined criteria are not met (8, 14, 21).

Policy Implications

MEAs hold a great potential in facilitating early access to innovative medicines while addressing financial challenges.The policy recommendations outlined in this brief aim to guide healthcare policymakers from LMICs towards informed decision-making, fostering a sustainable and equitable healthcare system that meets the evolving needs of its population.

1. MEA not a quick fix - MEA should only be used when the traditional reimbursement model like health technology assessment identifies issues to coverage decisions and requires further evidence on either clinical effectiveness or cost. MEA should be seen as a last resort and particularly as a mechanism for price negotiation.

2. Establishment of a National MEA Framework: Countries may consider establishing clear and coherent guidance for MEAs, outlining the roles and responsibilities of all stakeholders, including government agencies, pharmaceutical companies, and healthcare providers.

3. Robust Evaluation an dMonitoring Mechanism: It is crucial to develop a robust evaluation and monitoring mechanism for MEA's to assess their impact on patient outcomes, healthcare costs, and overall healthcare system sustainability. Regular assessments will enable evidence-based adjustments and improvements to the agreement terms.

4. Stakeholder Collaboration: Collaboration among all stakeholders is essential for the successful implementation of MEAs. Engaging healthcare experts, patient advocacy groups, and pharmaceutical industry representatives in the decision-making process will lead to fair and transparent agreements that prioritize patient welfare.

5. Continued knowledge exchange and Capacity Building: Initiating knowledge exchange programs and capacity-building initiatives for healthcare professionals, policymakers, and stakeholders will foster a better understanding of MEAs and their potential benefits. This will help build expertise and ensure effective negotiation and implementation of agreements.

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Author

Dimple Butani,
Project Associate,
International Unit, HITAP

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For the list of references, please visit
https://www.hitap.net/en/research/188013

Contact: hiu@hitap.net

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