# HTAi 2023 Latin America Health Technology Assessment Policy Forum

# How can managed entry agreements can contribute to coverage decisions?

VIII Latin America Health Technology Assessment Policy Forum (Latam Policy Forum). Chile, August 2023.

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## Overview of the 2023 Latam Policy Forum

Managed entry agreements (MEAs) encompass different types of agreements between stakeholders such as drug manufacturers, payers, and patients to share the risks and benefits associated with the reimbursement of a particular treatment. These agreements are tools that are increasingly to address challenges in access to innovative and high-cost therapies.

In the Spanish language, the terminology around these agreements can sometimes have different meanings, and there is also the term “risk-sharing agreements” (RSAs) that can be used interchangeably.

The potential utility of such agreements in Latin America will be explored, with consideration to the challenges in access to medicines, health system financial sustainability, and the need to guarantee access to innovative and high-quality treatments. A description of how these agreements work will be presented along with examples of their implementation in the region and elsewhere in the world.

This background paper provides information to decision makers, policy makers, and technology manufacturers to enable greater participation of participants in the 2023 Latam Policy Forum to be held in Chile.

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## 1. Introduction

Both healthcare payers and technology manufacturers have the shared interest to enable rapid access to technologies after they receive market authorization. However, in some situations there is uncertainty about the true benefit of technology or the health system budget impact of a technology. To address such situations of uncertainty, managed entry agreements (MEA) can be used, also known as risk-sharing agreements, to establish a contract between the manufacturers and payers that allow risks associated with this uncertainty (about clinical benefit or budget impact) to facilitate technology coverage.[1] These agreements can help mitigate the

[1] Garrison, L. et al. (2013), "Performance-Based Risk-Sharing Arrangements—Good Practices for Design, Implementation, and Evaluation: Report of the ISPOR Good Practices for Performance-Based Risk-Sharing Arrangements Task Force", Value in Health, Vol. 16/5, pp. 703-719, http://dx.doi.org/10.1016/j.jval.2013.04.011.

consequences of making coverage decisions when there is uncertainty about the effects of a new treatment. Making inappropriate decisions can result in poor health outcomes, waste resources, and reduce the credibility of the decision-making processes.

These agreements can be used to set payment schedules and reimbursement terms that are fair and equitable to healthcare payers and providers as well as technology manufacturers, while ensuring access to quality care.

These types of agreements have been used for those technologies with the potential for high budget impact in reimbursement where the uncertainty (either budgetary or clinical performance) can be reduced. This type of agreement aims to "share" the risks associated with the reimbursement of technologies between the payer and manufacturer in situations where, due to the characteristics of the particular pathology, there is elevated uncertainty about the evidence quality or the budget impact after adoption.

In other words, they represent a strategy to share risk between the manufacturer of drugs, devices or diagnostic tests, and the payers, whether they are health systems, social security providers or private insurers.

These agreements are used to provide access to innovative technologies and, in some cases reduce the cost of treatment, mainly in situations where there is insufficient certainty about outcomes or whether the technology will have positive results in the real world similar to what is shown in clinical studies.

The **objective** of the eighth annual Latin American Health Technology Assessment (Latam) Policy Forum will be to consider the **potential utility of using managed entry agreements (MEA) including risk sharing agreements (RSA)** in the reimbursement of health technologies. The Forum will analyze the **characteristics of these agreements including the barriers and facilitators** that different stakeholders encounter in their use, and to define a series of **key principles and actions** to guide choices in their implementation.

## What is health technology assessment (HTA)?

Health technology assessment (HTA) is a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle.[2] The purpose is to inform decision-making in order to promote an equitable, efficient, and high-quality health system. The information is used by health systems to make resource allocation decisions such as whether or not to grant coverage to a particular health technology or to incorporate it into a benefits package.

Today health technologies are an indispensable part of health systems and their use has increased over recent decades. The introduction of new technologies has generally brought

[2] O'Rourke B, Oortwijn W, Schuller T; International Joint Task Group. The new definition of health technology assessment: A milestone in international collaboration. Int J Technol Assess Health Care. 2020 Jun;36(3):187-190.

significant benefits in terms of safety, illness prevention, improvements in health and quality of life, or a reduction in adverse effects. However, in situations of limited resources, ensuring the appropriate reimbursement and diffusion of technologies has become a challenge and, in some cases, a serious problem.

The rapid pace of new technologies coming to market and the increase in the volume of available evidence are currently faced by all health systems. The delivery of health services involves making decisions about: which interventions are to be made available (and implicitly or explicitly which are not); how the health system is to be organized; who will pay for these interventions; and, how they should be provided and by whom. The challenge is to achieve adequate health outcomes with the resources available, having also considered the social values, expectations, and demands of the population.

Many countries have committed to achieving universal health coverage (UHC) for their population, which is one of the objectives prioritized by the World Health Organization (WHO). The WHO emphasizes that to achieve UHC, a strategy for the prioritization of interventions is essential, and that this is to be based on the best available evidence and conducted in a deliberative process that takes into account social values.[3] [4] In this endeavour, healthcare decision-makers have increasingly needed reliable and detailed information that enables them to make transparent and legitimate decisions when setting priorities, with a view to maximizing the benefits realized through limited budgets. The development and growth of HTA mirrors this increasing demand for robust and transparent information to support decisions about the development, reimbursement, and diffusion of health technologies.[5] HTA began in the 1970s in light of the growing concern about the diffusion of new and expensive health technologies and the limitations of health systems to finance their use. The discipline of HTA grew from these beginnings over forty years ago to become today a multidisciplinary specialty with the purpose of retrieving and synthesizing available evidence to support healthcare decision-makers, professionals, and patients to understand the relative value of technologies.

The development of HTA has been especially notable in the last 20 years and it is now an essential component of health systems in many countries. In the Latin American and Caribbean (LA) region several such initiatives have emerged. Argentina, Brazil, Colombia, Chile, Mexico and Uruguay have HTA agencies that are members of INAHTA (acronym for the International Network of HTA Agencies), and several Latin American countries use HTA, to different a extent, to support resource allocation decision-making. Most of these initiatives in the region are grouped in RedETSA, the health technology assessment network of Latin America (http://redetsa.org/), coordinated by the Pan American Health Organization (PAHO).

[3] Terwindt F, Rajan D, Soucat A. Priority-setting for national health policies, strategies and plans. In: Schmets G, Rajan D, Kadandale S, eds. Strategizing national health in the 21st century: a handbook: World Health Organization (WHO); 2015:71

[4] World Health Organization (WHO). Making fair choices on the path to universal health coverage. Final report of the WHO Consultative Group on Equity and Universal Health Coverage 2014: http://apps.who.int/iris/bitstream/10665/112671/1/9789241507158_eng.pdf?ua=1. Accessed 11- 3-2016

[5] Gabbay J, Walley T. Introducing new health interventions. BMJ. 2006;332(7533):64-65.

HTA can be a very useful tool for decision-makers. However, if it is not conducted and used appropriately, it runs the risk of poorly informing decisions that can lead to inefficient resource allocation by: reimbursing interventions of little or no benefit; impeding or delaying patient access to useful health technologies; exposing patients to unnecessary risks; and, sending the wrong messages to technology manufacturers, among others.[6] Furthermore, HTA is not purely a technical exercise and the decision-making process must take into account increasingly broad dimensions. The decisions made based on the HTA process have the potential to affect a large number of people and institutions and therefore a series of basic principles have been proposed for HTA. These principles include aspects such as transparency in the HTA implementation and decision-making processes; the involvement of relevant stakeholders; the presence of explicit mechanisms to decide which technologies to be assessed; and, the existence of a clear link between the assessment and decision-making.[7] [8] [9] Many of these aspects were addressed in previous years of the Latam Policy Forum. [10] [11] [12] [13] [14] [15]

## 2. Background and Objectives of the Forum

The Health Technology Assessment Policy Forum was founded in 2004 by Health Technology Assessment International (HTAi) to provide a neutral space for strategic discussions on the development and current state of HTA, along with related implications for health systems, industry, patients, and other stakeholders. It brings together representatives of three main groups: 1) decision makers responsible for coverage, reimbursement, and pricing of drugs and devices used in the health system; 2) organizations that carry out HTA in support of these decisions; and, 3) biomedical companies that produce technologies. The main Policy Forum has been operating

[6] Wilsdon T, Serota A. A comparative analysis of the role and impact of health technology assessment. London:UK: Charles River Associates; 2011.http://www.phrma.org/sites/default/files/pdf/hta_final_comparison_report_13_may_2011_stc1.pdf

[7] Daniels N, Sabin J. Setting limits fairly: learning to share resources for health. 2nd ed. New York: Oxford University Press; 2008

[8] Drummond MF, Schwartz JS, Jönsson B, Luce BR, Neumann PJ, Siebert U, Sullivan SD. Key principles for the improved conduct of health technology assessments for resource allocation decisions. Int J Technol Assess Health Care. 2008. Summer;24(3):244-58; discussion 362-8

[9] Pichon-Riviere A, Augustovski F, Rubinstein A, Martí SG, Sullivan SD, Drummond MF. Health technology assessment for resource allocation decisions: Are key principles relevant for Latin America? Int J Technol Assess Health Care. 2010 Oct;26(4):421-7

[10] Pichon-Riviere A, Soto NC, Augustovski FA, García Martí S, Sampietro-Colom L. Health techonolgy assessment for decision making in Latin America: good practice principles. Int J Technol Assess Health Care, 34:3 (2018), 1-7

[11] Pichon-Riviere A, Soto NC, Augustovski FA, Sampietro-Colom L. Stakeholder involvement in health technology assessment process in Latin America. Int J Technol Assess Health Care, 34:3 (2018), 1-6

[12] Pichon-Riviere A, GarciaMarti S, Oortwijn W, Augustovski F, SampietroColom L (2019). Defining the Value of Health Technologies in Latin America: Developments in Value Frameworks to Inform the Allocation of Healthcare Resources. International Journal of Technology Assessment in Health Care 35, 64–68

[13] Pichon-Riviere A, Augustovski F, García Martí S, Alfie V, Sampietro-Colom L (2020). The link between health technology assessment and decision making for the allocation of health resources in Latin America. International Journal of Technology Assessment in Health Care 36, 173–178

[14] Pichon-Riviere A, Augustovski F, García Martí S, Alcaraz A, Alfie V, Sampietro-Colom L (2021). Identification and selection of health technologies for assessment by agencies in support of reimbursement decisions in Latin America. International Journal of Technology Assessment in Health Care 1–8

[15] Alcaraz A, Pichon-Riviere A, García-Martí S, Alfie V, Augustovski F, Castro H. Deliberative processes in decision making informed by health technology assessment in Latin America. Int J Technol Assess Health Care. 2022 Dec 16;38(1):e86.

for 17 years with a focus on Europe and the United States; and for the past 10 years, a Policy Forum has been running in Asia. In 2016, the Policy Forum began in Latin America, with 2023 being the eighth Latam Policy Forum conducted.

An Organizing Committee composed of the Forum President and representatives of the participating institutions (three representatives from the public sector and three from technology manufacturers) developed the topic, agenda, and logistical details of the Forum. The Institute of Clinical Effectiveness and Health Policy in Argentina (IECS – www.iecs.org.ar) served as the Scientific Secretariat.

The process to select the topic of this eighth Forum began during the previous year's event and included the following steps:

1. A list of topics was prepared based on suggestions from the members of the Latam Policy Forum, and a vote was held during the closing of the 2022 Forum to identify the highest priority topics for 2023 based on this list.

2. The prioritized topics were sent to the Organizing Committee for their comments/suggestions.

3. The final topic was selected through a deliberative process by the Organizing Committee.

As a result of this process, the topic selected for the Latam Policy Forum was, "How can new access schemes, including risk sharing agreements, contribute to coverage decisions?".

This eighth edition of the Latam Policy Forum follows from the previous seven. The first Forum was held in Costa Rica in 2016 where the good practice principles in the application of HTA in decision-making in Latin America were discussed. During this Forum the principles prioritized as most relevant to promote the application of HTA in the Latin American region were:

- Transparency in the HTA processes and communication of HTA results
- Involvement of relevant stakeholders in the HTA process
- Existence of mechanisms for appeal
- Existence of clear mechanisms for establishing HTA priorities
- Existence of a clear link between HTA and decision making

The 2017 Latam Policy Forum was held in Lima, with the central theme being the involvement of different stakeholders in the HTA process, which was identified as a priority topic during the 2016 Forum.

In 2018, the Forum was held in Montevideo where HTA value frameworks were discussed.

In 2019, the Forum went to Buenos Aires where the topic was to look at the relationship between HTA and decision making.

During the years of the Covid-19 pandemic, the Forum was conducted online, and in 2020 the Forum examined the mechanisms used by HTA agencies to the prioritize topics for assessment, and in 2021 they discussed the role of deliberative processes in HTA.

In 2022, the Forum returned to being in-person and that year it was held in Brasilia on the topic of the use of real-world evidence in the HTA process.

(The results of discussions held during the most recent five Latam Policy Forums are available in a series of publications: Pichon-Riviere et al. 2018-2022).

The main objectives of the eighth Latam Policy Forum are to:

- Understand the current state of MEA/RSA use in HTA and reimbursement processes in Latin America
- Explore the benefits and limitations/barriers/risks to using MEA/RSA along with opportunities for their implementation in the region.
- Discuss and identify the main aspects in the regional context that should be taken into account when implementing MEA/RSA, as well as good practice principles for their conduct.
- Consider the potential to apply different models used elsewhere in the world to Latin American health systems, and to create a set of recommendations to guide the implementation of MEA/RSA related to HTA in the region.

The objective of this background document is to provide information as a starting point for the discussions that will take place in the HTAi 2023 Latin America Policy Forum that will take place in-person on 14 and 15 August in Santiago, Chile. The information is derived from a literature search focused on MEA/RSAs and HTA and from the review of agency and health system websites.

# 3. Managed entry agreements

## *a. Definition and Taxonomy*

There are several varieties of MEA with no standard classification that encompasses all types of agreements. However, two main categories can be identified: financial-based agreements and those based on health outcomes.[16] Both aim to share risk between the payer and the manufacturer in conditions of uncertainty regarding technology reimbursement. However, they address different areas of uncertainty: financial agreements aim to reduce uncertainty about the budget impact of acquiring new health technologies, while performance-based agreements seek

[16] Carlson, J. et al. (2010), "Linking payment to health outcomes: A taxonomy and examination of Health Policy, Vol. 96/3, pp. 179-190, http://dx.doi.org/10.1016/j.healthpol.2010.02.005.

to reduce uncertainty regarding the effectiveness and cost-effectiveness (or performance) of innovations.[17]

**Financial-based agreements (FBAs)** aim to manage uncertainty around the budget impact of a new technology. They are not linked to clinical outcomes and do not require health outcomes data to be analyzed. FBAs are contractual agreements that may establish the price, discounts, or reimbursement levels along with other terms and conditions associated with the procurement and/or use of a health technology.

**Agreements based on clinical outcomes (COAs)** are established between a payer and a manufacturer to set prices, discounts, or reimbursement levels for a product based on the achievement of predefined clinical outcome targets. They require that clinical outcomes be analyzed and monitored for patients involved in the agreement. They also have a financial objective, but this is specifically related to the clinical outcomes.

Table 1 presents the different types of agreements organized according to their taxonomy.

**Table 1. Taxonomy of agreement types**

| |
|---|
| FINANCIAL-BASED AGREEMENTS |
| Discounts |
| Price/volume agreements |
| Budget capping (subscription) agreements |
| Utilization capping agreements |
| CLINICAL OUTCOME-BASED AGREEMENTS |
| Performance-based agreements |
| Coverage with evidence development agreements |

## *Financial-Based Agreements*

Described below are four commonly used types of financial-based agreements.

**Discounts**. It should be noted that this type of agreement does not correspond to what is typically considered risk sharing. While it could be argued that a discount is the manufacturer assuming some of the risk, since this is applied in situations of certainty, it does not constitute a risk allocation in itself. The redistribution of risk can be applied to costs that have already been discounted. However, there are the simplest and most common type of agreement, they involve providing a price discount for the drug or other health technology based on various factors. For

[17] Wenzl, M. and S. Chapman (2019), "Performance-based managed entry agreements for new medicines in OECD countries and EU member states: How they work and possible improvements going forward", OECD Health Working Papers, No. 115, OECD Publishing, Paris, https://doi.org/10.1787/6e5e4c0f-en.

example, there may be a discount based on the volume of product purchased or based on the duration of the contract.

**Price/volume agreements** are based on a sliding scale of prices for the drug or health product based on the volume of sales. For example, if a certain number of units is purchased, the price per unit will be lower. This type of agreement is beneficial for the supplier, since there is an incentive to stimulate increased sales of the product, and also for the buyer, who can obtain a lower price per unit if certain purchase levels are reached.

**Budget capping agreements** are where a pre-established spending limit is set for a specific drug or health product. The objective is to ensure that the budget allocated to a technology does not exceed a certain level, which can help control health system costs. Sometimes this type of agreement is called a subscription model (Netflix model) since the producer provides the required number of treatments for a fixed amount of money.

**Utilization capping agreements** involve setting a limit on the number of patients or doses per patient to receive a drug or health technology. The goal here is to limit the use of the technology only to patients who are expected to benefit from it, i.e., those within its approved indication.

In summary, FBAs are useful tools to control costs and promote access to health technologies. The four types of agreements described above are commonly used to control spending in clinical practice and they are much easier to implement compared to clinical outcomes-based agreements.

### *Clinical Outcomes-Based Agreements*

Clinical outcomes-based agreements can be classified as follows:

**A. Performance-based agreements**: In these agreements, reimbursement is linked to the effectiveness of the drug or technology in the real world, meaning that specified criteria must be met for full or partial reimbursement. The goal is to assess the value of technology in a real-world healthcare environment. This type of arrangement can be beneficial to both the payer and manufacturer, as the payer only pays for drugs that work, while the producer receives greater financial certainty.

There are different variations of this type of agreement. They can be **based on the process of care**, whereby reimbursement is specified *a priori* and depends on the clinical decision-making process. For example, payment can be linked to provider adherence to clinical guidelines or selection of individual patients based on a biomarker, such as a genetic test.

In other cases, agreements can be **based on outcomes** where reimbursement occurs *a posteriori* through measuring intermediate or clinical endpoints. These may include measures of efficacy, safety, and/or cost-effectiveness. An "outcomes guarantee" can be implemented, for

example, the manufacturer agrees to provide a partial or full refund if the drug or technology does not perform as expected. In other situations, the "conditional continuation of treatment" is negotiated, that is, the payment for the continued use of the therapy is made based on the patient outcomes realized.

Regarding the monitoring of **clinical endpoints**, **patient risk-sharing agreements** can be implemented. In these agreements, patients take and active role in the management of their disease and the monitoring of their response to treatment. The agreement may include incentives for the patient to adhere to the treatment regimen and to report outcomes to healthcare providers. The agreement may also include a partial or full refund if the patient does not respond adequately to the treatment. **Healthcare provider risk sharing agreements**, on the other hand, involve healthcare providers in the financial risk of treatment. In these cases, the manufacturer agrees to provide the therapy at a reduced price or with a partial refund, and healthcare providers agree to monitor and report treatment outcomes. If these outcomes are not as expected, the manufacturer provides an additional refund.

**B. Coverage with evidence development (CED) agreements:** These agreements – the most complex to implement - provide coverage for a new drug or medical technology while additional clinical studies are carried out to confirm the product's effectiveness and safety. The goal is to allow patient access to the technology while additional data is collected. These agreements link payment or reimbursement at the population level with prospective data collection from individual patients. The agreement may affect all patients eligible to receive the technology (called 'only with research' agreements) or only those patients who are voluntarily included in a clinical trial (called 'only in research' agreements).

These agreements provide coverage for a drug or technology for specific patients based on certain conditions. For example, coverage may be limited to patients with certain characteristics or at certain stages of the disease. Coverage is reviewed regularly and may change based on the results of additional clinical trials.

Presented below are some examples of the various agreement types:[18]

## Financial-based agreements

- Budget limit agreements
  *Antivirals for Hepatitis C in Australia (since 2015). The government allocated an annual budget for these drugs and above this budget limit the technology manufacturer reimbursed the total cost.*

- Utilization limit agreements

[18] Wenzl, M. and S. Chapman (2019), "Performance-based managed entry agreements for new medicines in OECD countries and EU member states: How they work and possible improvements going forward", OECD Health Working Papers, No. 115, OECD Publishing, Paris, https://doi.org/10.1787/6e5e4c0f-en.

*Lenalidomide for the treatment of myelodysplastic syndromes in the UK. The government pays for up to 26 cycles of treatment, and for those patients who require more than 26 cycles, these are provided by the technology manufacturer at no cost.*

### Clinical outcome-based agreements

- Reimbursement agreements linked to outcomes (payment by results)
  *Alfaglucosidada Alfa for Pompe disease with late onset in Estonia. Payment is only made to those patients with a positive outcome confirmed by a panel of 4 specialist doctors.*

- Coverage with evidence development agreements
  *Axicabtagene ciloleucel (Yescarta®) for B-cell lymphoma in England. The drug is covered by the Cancer Drug Fund (CDF) on the condition of generating more evidence of survival estimates. The evidence includes a phase II trial and the creation of a cancer registry. At the end of the agreement, the drug is reassessed and if there is insufficient evidence or the drug is deemed not to be clinically or economically effective, it may be removed from the CDF and no longer available from the NHS. In such a case, patients will continue to receive the medication but it must be paid for by the manufacturer until the prescribing physician deems discontinuation of therapy appropriate.*

## *b. Differences between financial-based and clinical outcomes-based agreements*

**When to choose a financial-based or clinical outcomes-based agreement**

The main difference between financial- and performance-based agreements is their focus. Financial agreements aim to share uncertainty about the financial risk and how a treatment will be paid for to permit health systems to more precisely manage their budgets. On the other hand, performance-based agreements address the clinical effectiveness of a therapy and how the quality of patient care can be improved.

Agreements based on financial results are easier to implement than agreements based on clinical outcomes as they require less data collection and are generally less difficult to monitor.

The choice of using a risk agreement based on clinical outcomes (performance) or a financial agreement will depend on the specific objective, the uncertainty of clinical information, and the cost of the technology.

Risk sharing agreements based on clinical outcomes are used when clinical or health outcomes are unclear or uncertain, and the intent is to share the risk between the manufacturer and the payer. These agreements are generally used for new or innovative products, or in situations where outcomes are unpredictable.

Financial agreements, on the other hand, are used to achieve specific savings or cost management objectives. They are often used for products that have a known history health and clinical outcomes.

The choice between a risk sharing agreement based on clinical outcomes and a financial agreement will depend on the specific objectives to be achieved, as well as the nature and history of the drug or treatment in question.

## *3.3 Description of recent uses*

In 2019, Castro et al. published a literature review of managed entry agreements.[19] Of the total found (n=285), 95% had been implemented in high-income countries (23 European countries, 6 Asian countries, 2 North American countries, 2 in Oceania and 1 in Africa). Financial-based agreements were more frequent than those based on clinical outcomes (50.2% vs. 44.9%, respectively). FBAs were the most common worldwide, while PBAs were most common in North America. This is consistent with other investigations into the different types of agreements utilized, where financial agreements are generally more frequent than those based on clinical outcomes.[20] [21]

One example of a FBA is used by the United Kingdom's National Institute for Health and Care Excellence (NICE), which negotiates with manufacturers to achieve acceptable levels of cost-effectiveness for the drugs that are covered.[22] [23] The incremental cost-effectiveness ratio (ICER) range generally considered acceptable by NICE is £20,000-30,000 per quality-adjusted life year (QALY) gained and up to £51,000/QALY gained for end-of-life treatments. A much higher ICER range of £100,000-£300,000 was introduced in 2017 for ultra-orphan drugs that are assessed through the Highly Specialized Treatments pathway. NICE has patient access schemes that consist of simple discounts or trade agreements based on performance or on evidence generation. The discount range negotiated by NICE is typically between 30% and 60%, with most discounts being between the 45% to 50% range. Common situations where NICE would sign such agreements include where there is a lack of proven cost-effectiveness due to uncertainty of clinical or other data for economic analysis, as well as uncertainty related to relative efficacy and the need to collect more evidence on long-term outcomes and adverse effects of treatment. For cell and gene therapy (known as highly specialized therapied (HST)) drugs agreements are based on financial and clinical assessment, as cost-effectiveness is always uncertain due to data limitations encountered in rare diseases. In addition to the Cancer Drugs Fund negotiations,

[19] Castro, Hector & Malpica-Llanos, Tanya & Musila, Ruth & Konduri, Niranjan & Amaris, Ana & Sullivan, Jennifer & Gilmartin, Colin. (2019). Sharing knowledge for policy action in low- and middle-income countries: A literature review of managed entry agreements. Medicine Access Point of Care. 3. 239920261983424. 10.1177/2399202619834246.

[20] Ferrario, A. and P. Kanavos (2013), Managed entry agreements for pharmaceuticals: The European experience, EMiNet, Brussels.

[21] Wenzl, M. and S. Chapman (2019), "Performance-based managed entry agreements for new medicines in OECD countries and EU member states: How they work and possible improvements going forward", OECD Health Working Papers, No. 115, OECD Publishing, Paris.

[22] Toumi, M., & Jarosławski, S. (2022). Managed Entry Agreements and Funding for Expensive Therapies. CRC Press.

[23] Managed Access: Our Programmes. https://www.nice.org.uk/about/what-we-do/our-programmes/managed-access

England's National Health Service (NHS) is involved in confidential rebate negotiations with manufacturers leading to further cost savings.

An example of an outcomes-based agreement implemented by NICE was for Hepatitis C drugs (Glecaprevir/Pibrentasvir Maviret® and Sofosbuvir Sovaldi®).[24] Due to their high cost, the NHS England was required to limit access to direct-acting antiviral drugs only to selected patients, despite a positive recommendation from NICE. To manage public pressure and improve patient access, in 2017 the NHS England signed a clinical-outcomes based agreement with manufacturers. Under this agreement, the NHS would be reimbursed by manufacturers for the cost of treatment for those patients who completed their treatment but did not achieve a cure (sustained virologic response). Patients were followed in a hepatitis C registry to monitor treatment uptake and outcomes so reimbursement could be calculated.

Another example from NICE relates to Spinraza® (Nusinersen) for spinal muscular atrophy (SMA) where a coverage with evidence development (CED) agreement was used. In 2019, NICE raised several concerns in the assessment of Spinraza related to the collection of clinical data and resource utilization.[25] A five-year CED agreement was signed with the manufacturer that included a minimum of three years of data collection. The final reimbursement was agreed to be done in the fifth year of the CED scheme. Various endpoints for the CED agreement were collected from different sources: ongoing studies, some registries such as SMA REACH UK, the NHS Blueteq system used in the UK for high-cost medicines, and ongoing patient-reported outcomes. Data was analyzed twice a year according to a plan developed by the manufacturer, with the data collection and analysis costs borne by the manufacturer. This scheme is still ongoing.

## *3.4 Evaluation of potential utility*

MEA can improve access to therapies by increasing the likelihood of reimbursement when there is uncertainty related to efficacy or cost-effectiveness. They can also increase the time to make a final funding decision if they are very complex or expensive.

In 2022, Efthymiadou et al.[26] published a study where they examined the role of MEAs in improving the availability and timely access to a sample of cancer drugs that had received at least one reimbursement rejection. They studied funding decisions for all cancer drugs approved between 2009 and 2018 in Australia, England, Scotland, and Sweden. Of the 59 previously rejected technology-indication combinations studied, 88.2% (n=45) received a favorable decision after resubmission where a MEA was proposed, versus 11.8% (n=6) where no such agreement was proposed. The average time from the original submission to the final coverage decision was

[24] 25,000 Hepatitis C patients receive new treatment. https://www.england.nhs.uk/blog/25000-hepatitis-c-patients-receive-new-treatments/

[25] Facey KM, Espin J, Kent E, Link A, Nicod E, O'Leary A, Xoxi E, van de Vijver I, Zaremba A, Benisheva T, Vagoras A, Upadhyaya S. Implementing Outcomes-Based Managed Entry Agreements for Rare Disease Treatments: Nusinersen and Tisagenlecleucel. Pharmacoeconomics. 2021 Sep;39(9):1021-1044

[26] Efthymiadou, O., Kanavos, P. Impact of Managed Entry Agreements on availability of and timely access to medicines: an ex-post evaluation of agreements implemented for oncology therapies in four countries. BMC Health Serv Res 22, 1066 (2022).

404 (±254) and 452 (±364) days for submissions without and with MEAs, respectively. New submissions that included a MEA were more likely to receive a favorable funding decision compared to those without. The time to the final funding decision was greater for those agreements based on clinical outcomes than when hard outcomes were used instead of surrogates.

**Barriers and Facilitators**

In general, MEA are more likely to be successful if they are simple, supported by robust clinical data, and easily monitored. Other factors that seem to facilitate successful implementation and effective program design include the existence of a legal framework to support patient enrollment and clear contracts with precise definitions. Adoption of MEA is further facilitated where the performance assessment of the therapy is linked to clear, measurable, realistic, and objective metrics.

Culture seems to play a role in the degree of acceptance of certain types of agreements. For example, PBAs (schemes frequently adopted in the United States) are often used for innovative and expensive drugs to treat conditions with high unmet clinical need such as orphan diseases. In countries where price controls for new drugs do not apply, such as the United States, agreements based on performance or coverage with evidence development may be more feasible than financial discounts. The level of trust and willingness to negotiate between payers and pharmaceutical companies were also found to be factors that could facilitate or hinder the implementation of this type of agreement.

Despite the potential advantages of MEAs, there are authors who suggest their implementation is often labor and resource intensive, which is more pertinent to clinical outcomes-based agreements or those requiring evidence development.[27] [28] For agreements to be implemented well, they require services that can meet their operational, administrative, and financial requirements with availability of adequate and reliable data systems capable of monitoring them.

Another potential barrier reported in the literature pertains to the quality of data and evidence. The need for good quality data on prices and real-world evidence on clinical outcomes must be considered in the implementation of this type of agreement.

In addition, important contextual factors were identified in the literature review as potential challenges that can hinder implementation, for instance: price transparency, confidentiality of agreements, competition regulation, and information on discounts and refunds. Other studies note the challenges related to the confidentiality of the agreements, which can inhibit the ability to analyze the trends and impacts of the MEA programs and using this knowledge to inform future decisions.

[27] Ferrario, A. et al. (2017), "The Implementation of Managed Entry Agreements in Central and Eastern Europe: Findings and Implications", PharmacoEconomics, Vol. 35/12, pp. 1271-1285.

[28] Health Care Financing and Affordability in the Emerging Global Markets. Jakovljevic; Souliotis; Groot. Frontiers Media SA. 2016

## 3.5 Possible Future Uses

In Garrison et al work they identified and mention good practices and recommendations for the implementation of managed entry agreements and risk sharing agreements.[29]

Presented below are some of the potential uses of MEA in the region:

- Expanding coverage: Expanding coverage of high-cost and innovative treatments not currently available to all patients. By sharing financial risks, payers may be more willing to cover these treatments, allowing greater access for those who need it.
- Adaptation to local contexts: MEA could be adapted to the specific needs and conditions of each country or region. This would require consideration of factors such as disease prevalence, available resources, and public health priorities. By customizing agreements, a more equitable distribution of resources and fairer access to treatment could be ensured.
- Multi-stakeholder engagement: In the future, MEA could increasingly involve more stakeholders, such as patient organizations, public health experts, and medical societies. This would allow for greater transparency, representation, and participation in decision-making, which could lead to more equitable and efficient agreements.
- Implementation of monitoring and assessment strategies: It is crucial to have strong monitoring and assessment mechanisms to ensure the success of MEA. In the future, more robust strategies could be implemented to measure agreement outcomes, and to assess their impact on treatment access, and to make adjustments based on the lessons learned.

It should be recognized that clinical outcome-based agreements are resource intensive and they make reimbursement funding mechanisms more complex and dependent on health outcomes, which can divert attention from price negotiations and the ultimate budget impact of health technology delivery. It is therefore helpful for payers to establish an overall strategy or clear policy and guidelines for determining when to use an outcomes-based agreement. Such a strategy can situate these agreements and their role within the overall coverage decision-making process and they include a defined governance framework and transparency requirements.

The commitments established in the framework of a MEA, with its confidentiality clauses and the need for prospective data collection during a certain period of time, can hinder the participation of products that enter the market later, which reduces competition. For this reason, where there is data to suggest that competition from upcoming products is imminent, this should be taken into account when deciding whether an RSA is appropriate. If an agreement is pursued in such a situation, it should be designed so that the agreement commitments do not inhibit the competition value of new products.

[29] Garrison, L. et al. (2013), "Performance-Based Risk-Sharing Arrangements—Good Practices for Design, Implementation, and Evaluation: Report of the ISPOR Good Practices for Performance-Based Risk-Sharing Arrangements Task Force", Value in Health, Vol. 16/5, pp. 703-719, http://dx.doi.org/10.1016/j.jval.2013.04.011.

A value framework is a tool to support transparent decision making that payers can use in their decisions about whether or not to use a clinical outcomes-based agreement. Such a framework should compare the value of the incremental information about product performance generated in an MEA against the incremental cost of its negotiation and execution. One possible framework has been suggested, for example, by NICE's Decision Support Unit. Earlier work by Hutton, Trueman, and Henshall (2007) and Garrison et al. (2013) also suggested approaches to determine when agreements based on clinical outcomes are appropriate.[30] [31]

## 4. Regional Experiences

**Gene Therapy Access Strategy (onasemnogene abeparvovec (ZOLGENSMA®) Spinal Muscular Atrophy (SMA): Argentina Experience**

Natalia Soledad Messina - Directorate of Special and High-Cost Drugs, Ministry of Health, Argentina

***Background***

Spinal muscular atrophy (SMA) is an inherited neuromuscular condition that affects nerve cells (motor neurons) in an area of the spinal cord called the anterior horn. Without treatment it is a disease that leads to severe disability and death. Four subtypes have been defined based on the age of onset and the severity of the disease. The SMA Type I form is the most common and severe (58%) with symptoms appearing in children, with an estimated prevalence of approximately 1/30,000. Given this prevalence, the pathology is framed in the National Law of Rare Diseases No. 26,689.

In 2019, the National Administration on Drugs, Foods, and Medical Devices (ANMAT) in Argentina approved for 1-year term the drug nusinersen under special conditions for this pathology (Spinraza®), this approval was renewed for the same term but excluding SMA type 3 from such approval.

In the situation of increasing judicialization and no response from the State to patients without health coverage, in January 2021, the Ministry of Health added Spinraza®[32] to the Supervised Program (Programa de Tutelaje), thus providing coverage to this group of people. They defined inclusion and exclusion criteria to access it, which must be determined by the National Commission on Spinal Muscular Atrophy known as CONAME.

[30] Hutton J, Trueman P, Henshall C. Coverage with evidence development: an examination of conceptual and policy issues. Int J Technol Assess Health Care. 2007 Fall;23(4):425-32.

[31] Garrison, L. et al. (2013), "Performance-Based Risk-Sharing Arrangements—Good Practices for Design, Implementation, and Evaluation: Report of the ISPOR Good Practices for Performance-Based Risk-Sharing Arrangements Task Force", Value in Health, Vol. 16/5, pp. 703-719, http://dx.doi.org/10.1016/j.jval.2013.04.011.

[32] Disposición 2/2021 incorporando nusinersen como tecnología tutelada publicada en el B.O. https://www.argentina.gob.ar/normativa/nacional/disposici%C3%B3n-2-2021-346519/texto

While Argentina was in the process of covering the drug nusinersen as described, the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) regulatory agencies approved the first gene therapy to treat SMA, causing a significant impact on health systems around the globe since its launch came with a price of USD 2.1 million. Consequently, in February 2021, the ANMAT through Provision No. 484/2021 approved and granted 5-year registration to the first recombinant gene therapy onasemnogene abeparvovec (Zolgensma®) that uses a non-replicating adeno-associated virus (AAV9) to deliver a copy of the SMN1 gene that encodes the human SMN protein. Single intravenous administration of Zolgensma® results in cell transduction and expression of SMN protein in humans under another mechanism of action.

In May 2018, the therapy was approved by the U.S. Food and Drug Administration (FDA) for the treatment of pediatric patients under 2 years of age with SMA, with biallelic mutations in the survival motor neuron 1 (SMN 1) gene.[33]

On 18 May 2020, in Europe it received conditional marketing authorization valid throughout the European Union. This became a full marketing authorization on 17 May 2022.[34]

From the moment prior to its approval by ANMAT, the technical teams of the National Ministry of Health began to analyze the available evidence, providing the producing laboratory with information about the published clinical trials.

At the same time, a technology assessment report was jointly conducted by CONAME[35] and the National Commission for the Assessment of Health Technologies (CONETEC), which was published in January 2021 and updated in August of the same year.[36] This report allowed the health authority to lay the foundations to start talking about a possible RSA.

It is important to point out that during this time there was a significant increase in legal proceedings for access to this treatment, even in patients who were not candidates for this technology, which created serious repercussions in the media and social networks. In 2021, there were nine injunctions initiated to obtain the gene therapy, and 12 actions were initiated in 2022. In many of these cases, the drug had to be acquired by court order at the international retail price for this drug, which for Argentina was USD 2,057,000.

***Towards a comprehensive access strategy: key aspects of shared risk agreements***

In order to address this extremely high-priced innovative technology in a comprehensive and centralized way, it was necessary to design a strategy with a new purchasing model. In this model

[33] FDA Zolgensma https://www.fda.gov/vaccines-blood-biologics/zolgensma acceso 25/06/2023.

[34] EMA Zolgensma http://www.ema.europa.eu/medicines/human/EPAR/zolgensma acceso 25/6/2023

[35] Conformación CONAME. Resolución MSAL 1860/2020 publicada en el B.O: https://www.boletinoficial.gob.ar/detalleAviso/primera/237295/20201113#:~:text=RESOL%2D2020%2D1860%2DAPN%2DMS&text=CONSIDERANDO%3A,de%20ellas%20y%20sus%20familias.

[36] CONETEC. informe rápido N° 1 https://www.argentina.gob.ar/sites/default/files/2021/01/informe_1-zolgensma.pdf

payment becomes conditional on the therapeutic outcome; and this, in turn, can be framed within the contracting laws of Argentina. This required a succession of administrative acts which, in combination with the analysis of evidence by the technical teams of both the producing laboratory and the Ministry of Health, laid the foundations to arrive at a definition of the patient profile, criteria of inclusion and exclusion for treatment access, and the different clinical milestones expected to be reached according to age for those eligible to receive treatment.

It is important to highlight that since 2020, the Directorate of Special and High-Cost Drugs has successfully developed the access strategy to the drug nusinersen (Spinraza®), with a SMA registry that currently contains 229 patients[37] (Unified Supervised Registry of Technologies for patients with SMA: RUTT-AME) along with the National SMA Commission's fundamental role to assess cases for initiation and continuity of treatment according to the information presented. This creates greater certainty regarding the potential number of patients for inclusion, age of diagnosis, place of treatment, center of reference, type of coverage, etc.

Finally, although obtaining a lower price for Argentina was a fundamental issue, the primary intent was price transparency, that is, the non-confidentiality of the agreed price per vial. Such confidentiality conditions are generally required by industry as seen in international experiences with this type of agreement.

After a long process, the advancement of this strategy began to occur after the National Ministry of Health received a letter of intent from the Novartis laboratory.

This motivated the formal incorporation of the technology in January 2023[38] into the National Program for Supervised Health Technologies, and after this a process for the purchase of onasemnogene abeparvovec (Zolgensma®) was commenced. It was issued through a document that incorporated the following aspects:

- An open purchase for exclusivity, which uses a reference price per vial of USD 1,300,000 + VAT with logistics to the infusion center included, scheduled for 12 treatments and for a period of 12 months over the validity of the contract.

- Payment will be subject to the patient outcomes produced by the therapy, as expressed in the same document and will be made through an advance of 20% with the infusion, and, as long as it reaches the variables by the age indicated in the document, the remaining balance disbursed as follows:
    - 20% at 12 months post-infusion
    - 20% at 24 months post-infusion
    - 20% at 36 months post-infusion
    - 20% at 48 months post-infusion

[37] Datos relevados del RUTT-AME del día 22/6/2023

[38] Disposición 2/2023 incorporando onasemnogene abeparvovec como tecnología tutelada publicada en el B.O. https://www.argentina.gob.ar/normativa/nacional/disposici%C3%B3n-2-2023-378405

Given the particular characteristics of gene therapy treatment, patients will have to be assessed at the time of therapy administration and for a minimum period of 6 years after this. The assessment of motor scales must be completed in a detailed manner for each component. The professionals in charge of these assessments must prove their training in said techniques in accordance with the parameters defined by CONAME.

This strategy is completed through the creation of a new CONAME[39], that will continue to determine if the patients added by their treating physicians in the RUTT-AME meet the inclusion criteria for the different available treatments. The CONAME will have expanded powers to assess the evolution of these patients regarding their compliance with the established milestones, and this information will be necessary to proceed with the agreed payment by the contracting parties as specified in the RSA.

These criteria have been prepared by the technical teams and CONAME, based on the best available evidence and are presented in Annexes II and III of the recent Resolution 1234/2023.

Both the Specifications and Particular Conditions of the purchase as well as Annex III of the recent resolution stipulate monitoring guidelines for the patient assessment that are to be followed before the payment to the laboratory can be made. These guidelines are established in the following way:

If one or more of the following HINE scale (Hammersmith Infant Neurological Examination) criteria are met, this will be considered as response to treatment:

- Increase ≥ 2 points in the motor milestones category of kicking ability
- Achievement of the maximum score in that category (touching the toes)
- Increase of 1 point in the motor milestone category of head control, rolling, sitting, crawling, standing or walking

Additional response to treatment will be recognized if one or more of the following CHOP INTEND (The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders) is met: improvement ≥ 4 points or stabilization of the situation since treatment initiation.

In relation to effects on respiratory function, a reduction in the requirement of respiratory support will be considered as a response to treatment for patients <9 months of age.

The following criteria are considered as a lack of response to treatment:

- For motor milestones, worsening is defined as the loss of a previously acquired motor milestone. The loss must be confirmed with two separate assessments, separated by a period of not less than three weeks.

- For respiratory mechanics, worsening is considered if any of the following situations occurs (outside of an acute event): 1) requirement of invasive ventilation, 2) requirement

[39] CONAME, criterios de inclusión y pautas de seguimiento. Resolución MSAL 1234/2023 publicada en el B.O. https://www.boletinoficial.gob.ar/detalleAviso/primera/288590/20230621

of non-invasive ventilation in a patient who previously did not require it, 3) requirement of non-invasive ventilation for more than 6 hours a day in a patient who previously required non-invasive ventilation for less than 6 hours.

Furthermore, certain milestones were determined that are expected to be reached by age, as described below:

- For 12 months: 1) maintenance of baseline respiratory status and mechanics; 2) maintenance of previously acquired motor milestones.
- For 18 months: 1) CHOP INTEND > 40; 2) maintenance of baseline respiratory status and mechanics; 3) maintenance of previously acquired motor milestones.
- For 24 months: 1) maintenance of baseline respiratory status and mechanics; 2) maintenance of previously acquired motor milestones; 3) sit independently for at least 30 seconds or roll over.
- For 36-48 months: 1) maintenance of baseline respiratory status and mechanics; 2) maintenance of previously acquired motor milestones; 3) sit independently for 30 seconds or more and roll over.

To achieve this, in each instance the laboratory must submit a note to the Directorate of Special and High-Cost Drugs requesting an assessment of the patient to determine if they meet the milestones required by age and that the criteria for suspension of payment are not met. CONAME then intervenes for this purpose as their role is necessary to be able to continue with the payment to the laboratory.

The process established by the Argentinian Ministry of Health for funding Zolgensma® is a "risk sharing agreement" where payment is subject to the realization of the anticipated clinical benefits, with predetermined objectives upon which the continuation (or not) of funding of the medicine will depend.

***Managed entry agreements: Brazil's Approach***

*Luciene Fontes Schluckebier Bonan – Director, CONITEC*

Risk Sharing Agreements (RSAs) present a way to incorporate technologies into the Brazilian public health system. However, this approach is under development and not yet fully implemented. Political interest in this topic began in 2019 with a RSA pilot project proposal for the drug nusinersen in patients with spinal muscular atrophy (SMA) types II and III. The National Committee for Technology Incorporation (Conitec) had already assessed this product months before and recommended coverage only for type I of the disease. A RSA was proposed in this case, initiated by the Ministry of Health as an access alternative for patients not included in coverage (Denizar et al., 2022). However, based on a legal evaluation of the process the pilot project could not be implemented because it was not preceded by an assessment by Conitec, which is required according to Brazilian law.

From this point, the Executive Secretariat of Conitec began work to understand the theoretical and practical aspects of the RSA, which included the organization of workshops with health

authorities from various countries, as well as technical visits to countries such as England, Spain, and Italy. The Ministry of Health also began experimenting with other forms of managed access agreements based on volume discounts, rebates after reaching a limit on the number of treatments, as well as conditional requirements to reassess after 3 years of monitoring technology effectiveness.

In 2021, due to the interest expressed by a pharmaceutical company to build an agreement prior to the submission of the reimbursement dossier to Conitec, a case study was carried out for an RSA proposal for Zolgensma® in the Brazilian context. The case study was developed over five meetings between August and December 2021. The result of this exercise would not necessarily be used as a proposal for coverage by the company nor be tied to a health system decision about reimbursement. During these meetings, innovative access models in Latin America presented by the Latin American Federation of the Pharmaceutical Industry (FIFARMA) were discussed. Additionally, the challenges and alternatives present in the new Brazilian legislation on public procurement and contracts were explored, as this would permit the legal use of alternative contracting models for product procurement by public entities in Brazil. The pharmaceutical industry also presented possibilities of payment models for Zolgensma®, with consideration to different formats and implementation complexities based on ongoing experiences in other countries.

In the development of the case study, the Conitec Executive Secretariat constructed an example RSA for the therapy. The RSA was a performance-based agreement indicated only for patients up to the age of six months with SMA type I of the 5q gene, with deferred payment installments. This proposal considered the studies of Zolgensma® published to that point along with the uncertainties related to long-term therapy performance. Since this was an exploratory exercise, it included a highly complex model to anticipate and discuss all the negotiation and implementation challenges that a RSA might encounter in a real situation. At the time, the therapy did not have a defined price for commercialization in Brazil and, according to the company, the decision to actually propose an agreement would depend on the price determined by the Brazilian Medicines Market Regulation Chamber (CMED).

In 2022, with the price of the therapy set at a much lower level than expected by the company (R$ 6.5 million compared to R$ 12 million), the coverage proposal presented to Conitec included a proposal for a RSA but with a much more modest design. The price proposed for reimbursement was R$ 5.7 million and the intended target population was children up to two years of age. Payment would be made in three installments (50% at the time of infusion; 30% after 12 months; and, 20% after 24 months), provided only in the absence of mortality or the need for permanent invasive ventilation due to disease progression.

The Conitec Plenary assessed the proposal presented by the company and considered it insufficient. During public consultation, which is done for all technology reimbursement processes in the single healthcare system (SUS), the company presented a new proposal. This revised proposal included payment in five equal installments (20%) over 5 years and the inclusion of maintenance outcomes or motor improvement milestones, assessed by means of a score on a

specific scale (CHOP-INTEND) along with a limit on annual treatments above which point treatments would be provided free of charge to the Ministry of Health. Ultimately, Conitec recommended coverage of Zolgensma® for patients up to 6 months of age with type I SMA who are off invasive mechanical ventilation for more than 16 hours a day in accordance with the RSA.

The first coverage decision in Brazil with an explicit provision for an RSA was published in December 2022. In the same month, a publication was released about the new organization of technology reimbursement processes in the SUS. This new regulation included provisions for conditional coverage and managed access to reimbursed technologies. It also created a Technical Subcommittee on Managed Access within Conitec, which has powers related to monitoring and reassessment of reimbursed technologies, as well as the definition of guidelines, criteria, methods, and workflows for the execution of MEAs and their implementation in the SUS.

Through this experience some challenges and lessons learned can be identified. First, similar to the institutionalization of HTA in Brazil, the use of RSAs as a mechanism for technology reimbursement depends on certain prerequisites. The first of these refers to awareness of and commitment to the subject, both at a political and a technical-bureaucratic level, since RSAs require a significant transformation in the organizational culture. The implementation of the agreements entails an intense administrative burden, with corresponding changes in workflows and work processes.

Second, there is the need for a explicit regulatory framework specific for RSAs, with a simultaneous strengthening of HTA, so as to avoid parallel reimbursement pathways. In Brazil, the health system arrangement is complex, with both the centralized procurement of technologies by the Ministry of Health, as well as the possibility of purchase and funding by federal entities (states and municipalities) and the private supplementary health insurance sector.

In addition, health system priorities need to be clearly defined to be able to identify situations where the interests of manufacturers, individuals, and payers are aligned. In this context, the key lies in the proximity and mutual recognition among these stakeholders, which makes it easier to find appropriate solutions to the various challenges that may arise along the way.

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**Managed entry agreements: Experience of Uruguay**

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The National Resources Fund (FNR) in Uruguay is a non-state public body that, since 1981, has administered universal insurance coverage for harms caused by high healthcare costs, covering high-cost diagnostic and therapeutic procedures and high-priced medicines. This insurance has as beneficiaries all people living in the country.

The Ministry of Health has the responsibility to select technologies that have coverage guaranteed by the National Integrated Health System, including those that are covered by the FNR.

The technologies that have coverage guaranteed by the National Integrated Health System are all included in either the Comprehensive Health Care Plan (PIAS) (for diagnostic and therapeutic procedures and techniques), or in the Therapeutic Formular of Medicines (FTM) (for drugs).

Once a technology is covered by the FNR, it becomes the responsibility of the FNR regarding price negotiation of medicines, as well as the identification of commercial brands and indications for coverage.

Specifically with regard to drugs, the FNR is empowered with certain advantages when negotiating with industry:

- The FNR is the only buyer of high-priced medicines in the country, with payment ensured within 60 days of receiving the invoice.
- Due to its non-state legal form, it is governed by private law when negotiating prices with industry, and it maintains transparency and participation of the management team and representatives of the Administrative Honorary Commission in purchasing decisions.
- Most purchase agreements are made in Uruguayan pesos without clauses or adjustment parameters. Some signed agreements have been implemented for a two year term.
- Purchases are made through the PAHO Strategic Fund and jointly with MERCOSUR and UNASUR countries.
- Different negotiation models are used with the industry. Risk sharing agreements have been made with some manufacturers.

Different agreement formats have been implanted at different times:

- Total volume: the higher the volume, the lower the price.
- Units consumed-outcomes: here payment is made based on units consumed, for example only up to the expected survival rate. If patients live longer than the expected survival rate, the drug is provided free of charge by the manufacturer.
- Adherence (average dose): bonuses for patients with good adherence assessed at one year. The FNR pays for the medication according to consumption, but only up to the expected monthly average of adherence; if patients consume a product amount greater than this average, the manufacturer provides the drug free of charge.
- Fixed monthly payment: Flat rate:
    - Adjusting the price for a group of drugs for the same pathology, e.g., breast cancer if the minimum quota of patients is not met or if the maximum is exceeded. There is increased coverage but with the same expense.
    - For a group of drugs for several different treatments, e.g., rheumatoid arthritis, lymphomas, and chronic lymphoid leukemia there is a global price reduction of 8%.

***A recent example: Treatment of hemophilia A in the pediatric population with Emicizumab without inhibitors***

Emicizumab entered the FTM under the remit of the FNR by Ministerial Order 1938/2021 according to coverage criteria that includes patients aged ≥1 year with Factor VIII inhibitors and patients aged ≥12 and <18 without Factor VIII inhibitors VIII.

A special outcomes-based program was implemented for pediatric patients from 1 to 11 years of age inclusive with hemophilia "A" without inhibitors who were not eligible for coverage (03/04/2022). These patients must meet the same inclusion requirements as stated in the coverage regulations for patients of the same age group with inhibitors.

The program was one-year in duration and the implementation site was the main pediatric hospital in the country. This site was chosen given the high number of patients with this pathology that are managed there and the attending professionals with relevant expertise.

It was agreed that the manufacturer would provide a set number of milligrams of the drug (50,000) free of charge to be used exclusively in these patients during the duration of the program.

After one year of the program, an assessment was conducted by the FNR. This group of patients would receive coverage as long as at least one of the following conditions was met:

- At least 85% of the patients do not present spontaneous bleeding that requires additional actions for resolution.
- The annualized rate of spontaneous bleeding is less than 1 bleed/patient/year.

The operational definitions used were as follows:

- Any bleeding appearing in the same topography up to 72 hours after treatment is considered as the same bleeding.
- Any bleeding in a different topography will be considered a new bleeding regardless of the treatment time.
- Bleeding will be recorded from the second month of treatment (full load) and patients with at least 6 months of treatment who have received all the corresponding doses will be considered.

The FNR aims to send the collected and anonymized data every 4 months.

In accordance with the agreement, in December 2022 the scheduled assessment was carried out, which showed that of the 26 patients included in the program there were no cases of spontaneous bleeding that required the additional actions for resolution.

In conclusion, and in accordance with the agreement, the FNR Honorary Administrative Commission approved the coverage of Emicizumab for patients with the characteristics defined in the program. Currently, the necessary administrative processes are being implemented to make this resolution effective (i.e., inclusion in the FTM).

Some structural elements of the FNR that facilitate this type of agreement:

- Political and economic stability of the country
- National epidemiological information
- FNR information system with complete and validated records
- Coverage regulations establishing explicit criteria for inclusion, exclusion, and suspension of coverage
- Availability of control instruments
- Statistical data and assessment of outcomes
- Budget impacts – stochastic simulation software

In summary, models of different negotiation with industry have enabled efficient medicines procurement, as well as improved access and reduced risks and uncertainty. Furthermore, they allow the possibility of more realistic spending estimates with reduced uncertainty about the budget impact while providing transparency in decision-making.

These models are particularly important when they are based on real-world data and, most importantly, where there is a country-wide scope and support from a powerful information system that integrates clinical data about authorizations with monitoring and administrative data.

Resources and control mechanisms are required to strictly monitor the evolution of the agreements, which contribute, in some cases, to improving the quality of care through personalized monitoring of patients.

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