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REVIEW ARTICLE

Implementation of risk sharing models in access to treatment of rare diseases: an integrative review

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Abstract *The objective of this integrative review was to identify the implementation of risk-sharing models in access to treatment for rare diseases in Brazil and the world. The chosen databases were: BVS – Biblioteca Virtual em Saúde, Embase, PubMed, and Scopus. After exclusions, 18 studies were included. The high cost of treatment and uncertainty regarding clinical evidence were observed as the primary barriers to access. Risk-sharing models are generally divided into financially-based models and performance-based models. It was noted that the implementation of these mechanisms widens access to technology that would probably not be available otherwise and highlights significant insights, such as the lack of transparency and standardization in implementation, resulting in inequity of access to orphan drugs. It is concluded that the implementation of these models minimizes financial and performance barriers, potentially expanding access to treatment for rare diseases. Transparency and the exchange of experiences between countries are crucial for the creation of policies and guidelines that make the process more effective in expanding access.*
Key words *Financial risk sharing, Rare diseases, Orphan drug, Access to treatment, Integrative review*

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Introduction

According to the criteria established by Ordinance No. 199, of January 30, 2014, the National Policy for Comprehensive Care for People with Rare Diseases, a rare disease is a pathology that affects up to 65 for every 100 thousand individuals[1]. These pathologies are characterized by several symptoms, which vary from disease to disease, as well as from individual to individual affected by the same condition[2].

It is currently estimated that there are approximately six thousand rare diseases in the world[3,4]. About 80% are of genetic origin, but there are also those that are triggered by viral or bacterial infections and/or allergies. In Brazil, rare diseases affect 13 million people, 75% of whom are children, 30% of whom lose their lives before the age of five[5]. They are also often called "orphan" diseases, since the causes are not fully understood, and effective therapies, in many cases, are still limited[6].

Much has been discussed and discovered about rare diseases. With the support of patient organizations and associations, important advances have been made related to the implementation of public policies and expansion of access to treatment in Brazil[6]. However, the scenario is complex and challenging in Brazil and throughout the world. Many patients affected by these rare diseases – which are often chronic, progressive and disabling – do not have adequate access to healthcare and treatment[6,7].

Added to the complexity of the disease, the monetary factor of the treatment makes the scenario even more challenging. In recent decades, technological development has resulted in the possibility of treating many rare diseases, with the development and approval of new drugs[8]. Often, these drugs are unique for the treatment of a certain pathology, considered as orphan drugs, and command exorbitant prices on the market.

In addition to the costs involved and the budgetary impact on the system, the adoption of a new technology can lead to a number of uncertainties, especially when evidence in the scientific literature is scarce, as in the case of rare diseases, or when there are gaps in the effectiveness of the drug confirmed in scientific research[8]. In conventional health technology assessment (HTA) processes, which consider available clinical evidence and economic analysis, orphan drugs often do not prove to be cost-effective and have a significant budgetary impact on health systems. In this context, patient funding and access to rare disease medicines are normally limited[9].

These difficulties and gaps can be addressed through alternative methods that aim to: (1) generate additional evidence on the therapeutic value of the technology; or (2) limit the financial impact, allowing treatment funding to be divided between the health system and the manufacturer. Risk sharing is one of the most commonly used measures for the managed or conditional entry of a drug, especially in countries with universal healthcare systems[10].

According to HTAi (Health Technology Assessment International), risk sharing is defined as "an agreement between the producer/manufacturer and the payer/provider that allows access (coverage/co-participation) to a health technology under certain conditions. These agreements may use a variety of mechanisms to address uncertainty about the performance of technologies or to manage the adoption of technologies in order to maximize their effective use or limit their budgetary impact"[10].

In this highly complex world of rare diseases, it is necessary to broaden discussions and understanding in relation to risk-sharing models, both to fill gaps regarding treatment effectiveness and to minimize costs and expand access to innovations. Therefore, this review addresses, in a comprehensive and systematic manner, the barriers to access to treatment for rare diseases, a topic little explored in medical literature. Through the analysis of different risk-sharing models, the study presents an in-depth insight into how these strategies can reduce the access gaps and financial challenges involved in implementing treatment of rare diseases. By mapping the different types of models already applied and discussing their implications, the article contributes to the advancement of knowledge in health technology assessment, offering practical insights for managers and policymakers.

The present study aims to identify the implementation of risk-sharing models in access to treatment of rare diseases in Brazil and worldwide.

Methodology

This study is an integrative review of the literature relating to the research question that aims to discuss the implementation of risk-sharing models as a strategy to expand access to treatment for rare diseases in Brazil and worldwide.

To guide and establish the specific inclusion criteria for this review, the following guiding question was formulated: "What does scientific literature have to say about the implementation of risk-sharing models in access to treatment for rare diseases in Brazil and worldwide?". To ensure the quality of this article, the "technical procedure for research methodology – quality indicators for integrative review articles"[11] was used as a support tool.

For the literature review, four databases were chosen: BVS – Biblioteca Virtual em Saúde (https://bvsalud.org/); Embase (http://embase.com/); PubMed (https://pubmed.ncbi.nlm.nih.gov/); and Scopus (https://www.scopus.com/).

Based on the research question and the objective of the study, guiding poles were identified and descriptors were selected, through the Health Science Descriptors (http://decs.bvs.br/) platform, as keywords for the systematized search in the literature. The poles were defined as: 1) phenomenon: risk-sharing models; 2) population: rare diseases; 3) context: access to treatment. The poles and the respective descriptors used are shown in Chart 1.

Using the descriptors in English, the research syntaxes for each of the databases were constructed in a broad and systematized manner. For each base, the descriptors were tested individually and then, using the Boolean operator 'OR', they were joined based on each pole. Finally, the poles were joined together for the final syntax using the Boolean operator 'AND'. The final syntax used and the results of each database are detailed in Chart 2. The searches were carried out in October 2024.

The choice to use four databases and the descriptors in a comprehensive and unrestricted manner was due to the complexity of the topic and in order to ensure the necessary scope.

The review included complete articles published from 2013 onwards in Portuguese, English or Spanish; scientific articles that address the topic and contribute to the question under investigation. The authors chose to include peer-reviewed publications due to the methodological rigor to which they are submitted, thereby ensuring greater reliability and quality of the data. Thus, the following items were excluded: books, documents, theses, conference proceedings, articles that did not refer to the proposed topic of analysis or that did not address rare diseases and/or orphan drugs; preclinical or clinical trials in phases 1, 2 or 3; patient preference studies or multicriteria analysis, such as Multiple-Criteria Decision Analysis (MCDA); and articles containing comments, opinions, or reports.

Results

A total of 1,572 publications were identified and imported into the Zotero program (https://www.zotero.org/). Through the program, 153 duplicates were deleted electronically and then one manually. Of the 1,418 remaining publications, 1,017 were excluded by reading the title. 401 publications were selected for reading of the abstracts and 278 were removed at this stage. The main reasons were: articles that did not refer to the topic (N = 246); comment or opinion articles (N = 20); and articles with study designs that do not meet the inclusion/exclusion criteria (N = 12). A total of 123 publications were selected for reading in full, of which 105 were removed for reasons such as: articles that did not refer to the topic (N = 82); articles in a language other than Portuguese, English, or Spanish (N = 12); and articles that did not have full texts, only published in abstract form (N = 11). The result was the inclusion of 18 publications that contributed to the topic of the review.

The process from identification to inclusion of the articles can be verified in the PRISMA Flowchart, shown in Figure 1.

The articles included were categorized and synthesized for analysis using the following attributes: authors and year of publication; main barriers to access the treatments in question; and the risk-sharing models used. The research data were made available in an open data repository, which can be accessed through the website: https://drive.google.com/drive/folders/1rPUEp68KWeKCYSv96DJe7lD4L4jEKzpG?usp=sharing.

Based on the inclusion and exclusion criteria, 18 articles were selected for inclusion in this review. Chart 3 shows the complete list by author, year, title and journal published.

Subsequently, all the articles selected to constitute the result of the study were categorized and synthesized for analysis, as shown in Chart 4.

To search for information about risk-sharing models, the studies used several types of databases for collection. Of the 18 included, only two articles did not describe the database used, both descriptive studies. The six reviews used a systematic literature search; two qualitative studies used primary research data and interviews with experts; one of the retrospective studies used central patient registries and expense data from

Chart 1. Description of the poles and descriptors.

Phenomenon: risk-sharing models		
Participação no risco financeiro	Financial risk-sharing	Prorrateo de riesgo financiero
Financiamento da saúde	Healthcare financing	Financiación de la atención de la salud
Custos de medicamentos	Drug costs	Costos de los medicamentos
Reembolso de incentivo	Reimbursement, incentive/ incentive reimbursement	Reembolso de incentivo
Pagamento baseado em performance	Pay for performance	Pago por rendimento
Avaliação de resultados em cuidado de saúde	Outcome assessment, health care	Evaluación de resultado en la atención de salud
Avaliação de resultados da assistência ao paciente	Patient outcome assessment	Evaluación del resultado de la atención al paciente
Population: rare diseases		
Doenças raras	Rare diseases / rare disease	Enfermedades raras
Medicamentos para doenças raras	Drugs for rare diseases	Medicamentos para enfermedades raras
Tecnologia de alto custo	High-cost technology / technology, high-cost	Tecnología de alto costo
Medicamento órfão	Orphan drug	Medicamento para enfermedades huérfanas
Medicamento do componente especializado da assistência farmacêutica	Drugs from the specialized component of pharmaceutical care	Medicamentos del componente especializado de los servicios farmacéuticos
Doenças órfãs	Orphan diseases / orphan disease	Enfermedades huérfanas
Context: access to treatment		
Acesso aos serviços de saúde	Health services accessibility	Accesibilidad a los servicios de salud
Acesso a medicamentos	Access to medicines	Acceso a medicamentos
Acesso a novas tecnologias	Access to new technologies	Acceso a nuevas tecnologías
Acesso a medicamentos essenciais e tecnologias em saúde	Access to essential medicines and health technologies	Acceso a medicamentos esenciales y tecnologías sanitarias
Acesso ao tratamento	Access to treatment	Acceso al tratamiento

Source: Authors.

Catalonia; and the others used public sources such as national payers' websites and repositories of national documents and reports.

Most of the articles addressed rare diseases and orphan drugs in a broad and generalized manner, only one being described at the drug level, namely the drug nusinersen for Spinal Muscular Atrophy. Regarding access barriers, the 18 articles cited mainly the high cost of treatment, generating a high budgetary impact for the system; and uncertainty regarding the clinical evidence of the drugs.

The articles discussed the risk-sharing models differently, with six broadly defining them as "managed entry/access agreements", two focused only on performance-based risk-sharing; and the other ten differentiated between finance-based and performance-based agreements. Among these, four also defined subtypes of agreements.

Discussion

Risk-sharing models are variously described in the literature as managed entry agreements, managed access agreements, alternative access agreements, conditional entry schemes, and others. In general, these models are alternative measures that aim to divide the uncertainties of incorporating a new treatment between the manufacturer and the healthcare system. In other words, they are designed to tackle the current barriers to accessing treatment.

The two main barriers to accessing treatment, on which all the authors agree, are the cost of the treatment, in a scenario of budget constraints; and the uncertainties in relation to the scientific evidence applied in the real world, that is to say, the uncertainty regarding the equivalence between the price of the drug and its therapeutic value in clinical practice[30].

Chart 2. Final syntax of search in databases.

Database	Final syntax	Findings
BVS - Biblioteca Virtual em Saúde	("financial risk sharing" OR "healthcare financing" OR "pay for performance" OR "outcome assessment, health care" OR "drug cost" OR "patient outcome assessment" OR "reimbursement, incentive") AND ("Health Services Accessibility" OR "Access to Essential Medicines and Health Technologies" OR "Access to Treatment" OR "Access to New Technologies" OR "Access to Medicines") AND ("Rare disease" OR "Drugs for rare diseases" OR "High-cost technology" OR "Orphan drug" OR "Orphan disease" OR "Drugs from the Specialized Component of Pharmaceutical Care")	36 publications
Embase	('financial risk sharing' OR 'healthcare financing'/exp OR 'healthcare financing' OR 'pay for performance'/exp OR 'pay for performance' OR 'outcome assessment'/exp OR 'outcome assessment' OR 'drug cost'/exp OR 'drug cost' OR 'reimbursement'/exp OR 'reimbursement') AND ('health services accessibility'/exp OR 'health services accessibility' OR 'access to essential medicines and health technologies' OR 'access to treatment' OR 'access to new technologies' OR 'access to medicines') AND ('rare disease'/exp OR 'rare disease' OR 'drugs for rare diseases' OR 'high-cost technology'/exp OR 'high-cost technology' OR 'orphan drug'/exp OR 'orphan drug' OR 'orphan disease'/exp OR 'orphan disease' OR 'drugs from the specialized component of pharmaceutical care')	317 publications
PubMed	((financial risk sharing) OR (healthcare financing) OR (pay for performance) OR (Outcome Assessment, Health Care) OR (drug cost) OR (Patient Outcome Assessment) OR (Reimbursement, Incentive)) AND ((Health Services Accessibility) OR (Access to Essential Medicines and Health Technologies) OR (Access to Treatment) OR (Access to New Technologies) OR (Access to Medicines)) AND ((rare disease) OR (drugs for rare diseases) OR (High-cost technology) OR (Orphan drug) OR (Orphan disease) OR (drugs from the Specialized Component of Pharmaceutical Care))	1,146 publications
Scopus	("financial risk sharing" OR "healthcare financing" OR "pay for performance" OR "outcome assessment, health care" OR "drug cost" OR "patient outcome assessment" OR "reimbursement, incentive") AND ("Health Services Accessibility" OR "Access to Essential Medicines and Health Technologies" OR "Access to Treatment" OR "Access to New Technologies" OR "Access to Medicines") AND ("Rare disease" OR "Drugs for rare diseases" OR "High-cost technology" OR "Orphan drug" OR "Orphan disease" OR "Drugs from the Specialized Component of Pharmaceutical Care")	73 publications
Total		**1,572**

Source: Authors.

Treatment for highly complex diseases, such as rare diseases, usually have a substantial budgetary impact on the healthcare system. Drugs for rare diseases are often unique for the treatment of a certain pathology, considered as orphan drugs, and command exorbitant prices on the market. In addition to this scenario, because these are diseases with low prevalence, there is usually scarce and often immature evidence on the clinical results of the technology[30], due to the difficulty of recruiting an adequate number of patients, clinical trials with surrogate outcomes, without randomization and control arm, due to ethical issues, and which end up leaving gaps in terms of the effectiveness of the drug proven in the real world and in the long term[8,12].

In a standard HTA process, which uses the search for available clinical evidence combined with an economic analysis, orphan drugs are generally not cost-effective and have a significant budgetary impact on healthcare systems[9]. In an exploratory analysis of requests for the incorporation of drugs for rare diseases to Conitec (National Commission for the Incorporation of Technologies in the Unified Health System in Brazil), 46.7% of the technology not incorpo-

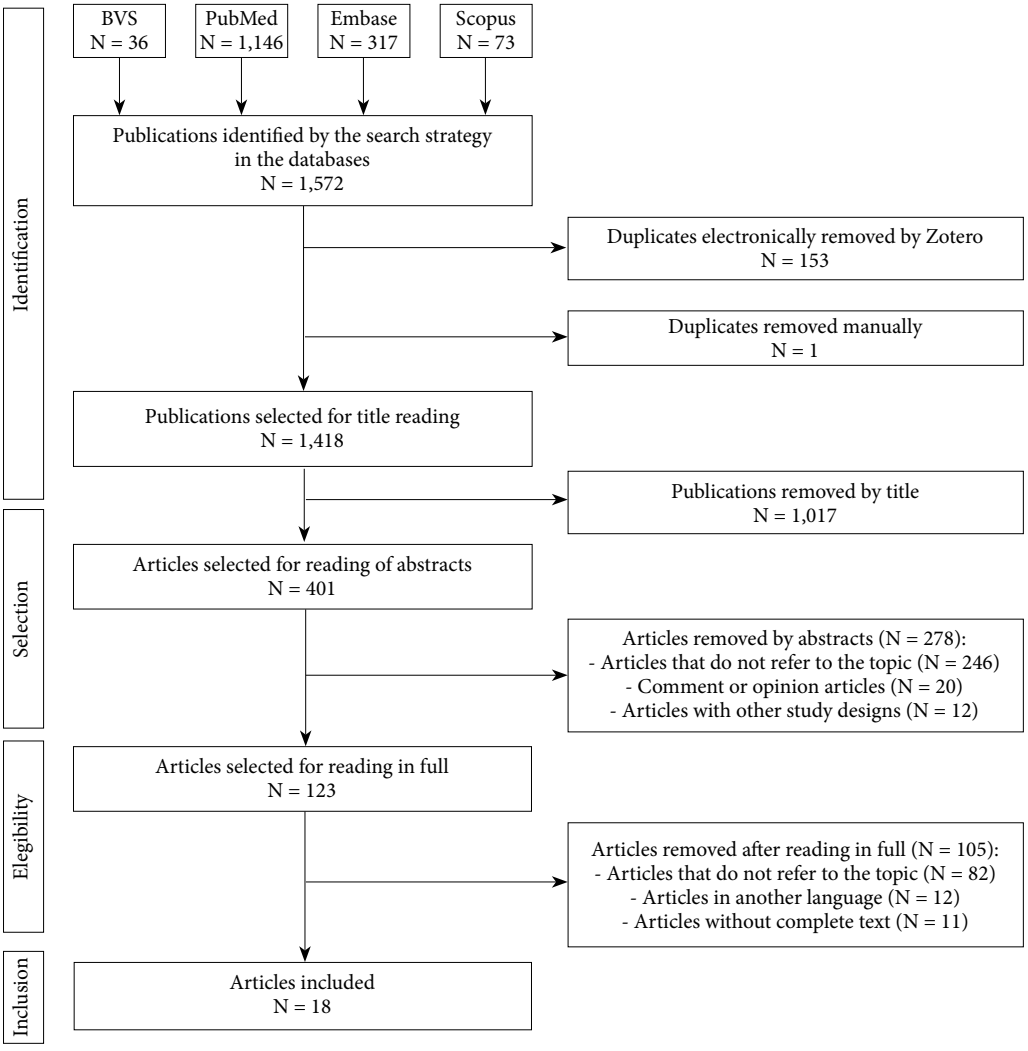

Figure 1. PRISMA flowchart.

Source: Authors.

rated was justified by: lack of clinical evidence, non-cost-effective technology, and modest benefits that did not justify the price[19].

In this context, patient funding and access to rare disease drugs are normally limited[9]. Due to the complexity of the scenario, treatments for rare diseases are often the main targets of risk-sharing agreements.

This partnership between the pharmaceutical industry (manufacturer) and the healthcare system can be found in various countries. In the present review, articles were found discussing risk-sharing models in countries in Europe, the Americas, Asia and Oceania. Even considering the huge economic differences between the countries, the challenge of providing access to technology and the management of financial resources for healthcare is the same for many.[29,31] In this scenario, it is observed that the pharmaceutical industry finds in these models a way to facilitate the entry of drugs into the market, since they substantially increase the chances of incorporation, even in the face of a scenario of budgetary and scientific uncertainties[16,17,21,28,29,32].

The adoption of risk-sharing models by countries appears increasingly in literature, but in a heterogeneous manner, both in the procedures adopted and in the classification or no-

Chart 3. Description of articles included for analysis.

Author(s)	Year	Title	Magazine
Morel T *et al.*[12]	2013	Reconciling uncertainty of costs and outcomes with the need for access to orphan medicinal products: a comparative study of managed entry agreements across seven European countries	*Orphanet Journal of Rare Diseases*
Gibson SG, Lemmens T. [13]	2014	Niche markets and evidence assessment in transition: a critical review of proposed drug reforms	*Medical Law Review*
Gammie T, Lu CY, Babar ZUD[14]	2015	Access to orphan drugs: a comprehensive review of legislations, regulations and policies in 35 countries	*PLOS ONE*
Degtiar I[15]	2017	A review of international coverage and pricing strategies for personalized medicine and orphan drugs	*Health Policy*
Bae EY [16]	2019	Role of health technology assessment in drug policies: Korea	*Value in Health*
Van Wilder P, Pirson M, Dupont A[17]	2019	Impact of health technology assessment and managed entry schemes on reimbursement decisions of centrally authorised medicinal products in Belgium	*European Journal of Clinical Pharmacology*
Atikeler EK, Leufkens HGM, Goettsch W[18]	2020	Access to medicines in Turkey: evaluation of the process of medicines brought from abroad	*International Journal of Technology Assessment in Health Care*
Biglia LV *et al.*[19]	2021	Incorporation of drugs for rare diseases in Brazil: is it possible to have full access to these patients?	*Ciência & Saúde Coletiva*
Blonda A *et al.*[20]	2022	Assessing the value of nusinersen for spinal muscular atrophy: a comparative analysis of reimbursement submission and appraisal in European countries	*Frontiers in Pharmacology*
Blonda A *et al.*[21]	2022	How can we optimize the value assessment and appraisal of orphan drugs for reimbursement purposes? A qualitative interview study across European countries	*Frontiers in Pharmacology*
Guarga L *et al.*[22]	2022	Implementing risk-sharing arrangements for innovative medicines: the experience in Catalonia (Spain)	*Value in Health*
Shengnan D *et al.*[23]	2022	Using 5 consecutive years of NICE guidance to describe the characteristics and influencing factors on the economic evaluation of orphan oncology drugs	*Frontiers in Public Health*
Simoens S *et al.*[24]	2022	How to balance valuable innovation with affordable access to medicines in Belgium?	*Frontiers in Pharmacology*
Iglesias-López C *et al.*[25]	2023	Financing and reimbursement of approved advanced therapies in several European countries	*Value in Health*
Kim H *et al.*[26]	2023	Introduction of managed entry agreements in Korea: problem, policy, and politics	*Frontiers in pharmacology*
Ng QX *et al.*[27]	2024	Comparative policy analysis of national rare disease funding policies in Australia, Singapore, South Korea, the United Kingdom and the United States: a scoping review	*Health Economics Review*
Douglas CMW, Grunebaum S[28]	2024	Lessons learned from the Canadian Fabry Disease Initiative for future risk-sharing and managed access agreements for pharmaceutical and advanced therapies in Canada	*Health Policy*
Nieto-Gómez P, Castaño-Amores C[29]	2024	Factors influencing the reimbursement of cancer drugs in Europe: a scoping review	*Journal of Evaluation in Clinical Practice*

Source: Authors.

menclature used. It is therefore considered an international trend in constant expansion and still pending further analysis[30].

Risk-sharing models are generally divided into two broad groups according to their purpose: (i) financial-based models, which aim to limit budgetary impact; and (ii) performance-based models, which aim to analyze real-world evidence regarding the therapeutic value of the technology.[33] The mapping of existing model types and discussion of the examples of implementation are described below:

Chart 4. Summary of articles included.

Author(s)/ year	Access barriers	Risk-sharing model
Morel T *et al.*, 2013[12]	Uncertainty about the clinical and economic performance of new orphan drugs in the real world (difficulty in recruiting a sufficient number of patients, generally heterogeneous population, clinical trials based on substitute outcomes, without randomization, and inclusion of control arms); little knowledge about the natural history of the disease; relatively high treatment costs, generating great budgetary uncertainty and/or financial risk if treatment does not work as expected	Managed entry agreements: (1) performance-based risk-sharing schemes, which may be: a) 'performance-linked reimbursement' schemes; or (b) 'coverage with evidence development'; (2) finance-based arrangements, which may adopt: a) patient-level perspective; or b) population-level perspective
Gibson SG, Lemmens T, 2014[13]	Uncertainties regarding clinical evidence (effectiveness/safety) due to limitations of clinical studies; and a high cost per therapy	Performance-based risk-sharing arrangements, where product performance will be tracked in a defined population over a specific period and the continuation or level of reimbursement is based on the health and economic outcomes that have been achieved. Can manage utilization by linking reimbursement to various performance measures: reimbursement may depend on the clinical decision-making process (e.g., only patients who test positive for a particular biomarker will be covered); other schemes may focus on final or intermediate clinical points to determine reimbursement or involve outcome guarantees where the manufacturer receives a lower payment for patients who do not respond to therapy.
Gammie T, Lu CY, Babar ZUD, 2015[14]	High costs and insufficient evidence limit orphan drugs from meeting traditional health technology assessment criteria, especially cost-effectiveness	Two types of Managed Entry Agreements: (1) Performance-based schemes (2) Finance-based arrangements (different models, including cost cap, utilization cap, and free and/or discounted initiation)
Degtiar I., 2017[15]	Uncertainties regarding efficacy and safety and often high prices	Managed entry agreements with national results registries
Bae EY, 2019[16]	High treatment cost and uncertainties of treatment effect	There are four types of risk sharing in Korea: reimbursement of the difference between the listed price and the contracted price; mixing of conditional treatments based on response and reimbursement; global spending limit; and spending limit per patient.
Van Wilder P, Pirson M, Dupont A, 2019[17]	Increasing expenditure on health plans (annual increase of around 25 million euros); drugs with high prices; relative effectiveness and/or cost-effectiveness uncertainties; low willingness to pay for health plans	Managed entry schemes
Atikeler EK, Leufkens HGM, Goettsch W, 2020[18]	Very high prices for orphan drugs	Alternative access agreements
Biglia LV *et al.*, 2021[19]	Scarcity of adequate scientific evidence and high cost of treatments	Risk sharing agreements
Blonda A *et al.*, 2022[20]	High cost of treatment	Financial-based Managed Entry Agreements, when related to a discounted price, and/or performance-based, where additional data on the efficacy of the drug in the real world will be collected

it continues

Chart 4. Summary of articles included.

Author(s)/ year	Access barriers	Risk-sharing model
Blonda A *et al.*, 2022[21]	Drugs at rising prices and uncertainties regarding cost-effectiveness	Managed entry agreements that allow for a temporary refund upon providing a price reduction (on a financial basis) or on the condition that additional data about real-world effectiveness is collected in a record (based on results or performance)
Guarga L *et al.*, 2022[22]	Uncertainties about effectiveness, cost-effectiveness or budgetary impact	Performance-linked reimbursements and cost-sharing agreements
Shengnan D *et al.*, 2022[23]	High cost of treatment; small population in studies; and uncertainty regarding the clinical evidence of orphan oncology drugs	Managed access agreements
Simoens S *et al.*, 2022[24]	Failure to identify unmet medical needs in all therapeutic areas; limitations of available clinical evidence (long-term efficacy and safety); high budgetary impact	Managed entry agreements
Iglesias-López C *et al.*, 2023[25]	Uncertainty in the cost-effectiveness of drugs (high costs and uncertainties regarding clinical evidence)	Managed entry agreements and results-based payment
Kim H *et al.*, 2023[26]	High cost of drugs; uncertainty about the effectiveness of drugs	Financial-based and outcome-based agreements
Ng QX *et al.*, 2024[27]	High cost of treatment; difficulties in financing and reimbursing medicines	Agreements between governments or health systems and pharmaceutical companies to manage uncertainty regarding the cost and effectiveness of high-cost medicines
Douglas CMW, Grunebaum S, 2024[28]	Uncertainty about the effectiveness of therapies; High costs	Agreements between payers and pharmaceutical companies to address uncertainty about the effectiveness of treatments and contain costs. Performance-based, to reduce the uncertainty of effectiveness, or financial-based, to limit expenses
Nieto-Gómez P, Castaño-Amores C., 2024[29]	High cost of medicines; lack of transparency regarding the criteria used for the price and reimbursement of medicines; uncertainty regarding the clinical benefits and cost-effectiveness of medicines	Performance-based agreements and country-specific adaptations that allow flexible reimbursement strategies while ensuring patient access to necessary treatments

Source: Authors.

I – Financial-based models

The main objective of financial-based risk-sharing models is to limit the budgetary impact when incorporating a new technology.

Morel T and colleagues analyzed 42 risk-sharing arrangements in seven European countries, 19 of which were classified as financial-based agreements. Countries such as Belgium (with four agreements) and England/ Wales (with eight agreements) presented only financial agreements, from different perspectives. Italy, being the country that presented the highest number, with 15, used different agreements based on finance and performance. Financial-based agreements, according to the authors, may adopt a patient or population-level perspective. At the patient level, it may be: cost limitation (maximum cost per treatment); usage limitation (total number of doses or cycles); or free or reduced-cost initial treatment. At the population level, it can be a simple reduced cost for all eligible patients; "limitless" price-volume agreements, i.e. a price is stipulated based on the expected volume, decreasing if the volume is exceeded; or "with a limit", when there is a limit on the volume purchased. If the volume is exceeded, the manufacturer must bear the excess[12].

In agreement, Gammie T and collaborators report the presence of a variety of forms to these schemes in some countries, including cost limits, usage limits, and free and/or reduced-cost initial treatment[14].

In South Korea, according to Bae EY, the government has implemented measures to expand access to treatments, including risk

sharing, in order to reduce the effective price. Among the possibilities, the model in which the pharmaceutical industry refunds the difference between the list price and the price considered cost-effective, or that pays the cost of the drug from non-responders, stands out. According to the article, until 2017, most drugs were reimbursed corresponding to the difference in prices[16].

Most management agreements in South Korea are financial contracts, in which the discounts granted limit the impact on the budget. The implementation of these agreements helps to overcome the resistance of pharmaceutical companies to launch medicines at lower prices and expands access to treatment for serious diseases[26,27].

In Turkey, agreements are generally focused on price, but they can also focus on generating evidence. Among the financial-based models, these can be through additional discounts, confidential discounts, return, or volume-based pricing. However, the country does not have an HTA agency or specific legislation for rare diseases[18].

Some articles reported, in addition to theoretical mechanisms, some practical examples of the implementation of financial-based risk sharing models.

Guarga and colleagues analyzed 15 agreements in the Catalan health system, of which three were for rare diseases (gastroenterology, nephrology and respiratory) and based on cost-sharing. The uncertainty to be addressed for gastroenterology and nephrology was related to the number of patients and budgetary impact, and the agreement was based on a budget limit per year. For respiratory disease, the budgetary impact was related to the number of patients outside the recommendations of the clinical criteria, and the agreement was based on the selection of the patient subgroup and a volume-price agreement per year[22].

The only article that specifically addressed a drug gave details of Belgium's agreement for the inclusion of nusinersen for Spinal Muscular Atrophy. The financial part of the agreement was based on a price reduction and an "absolute limit" in order to manage the uncertainties concerning the total number of eligible patients. In addition, it was defined that the healthcare system would not reimburse the costs of non-responders or any extra costs during the first year of the patients starting treatment[20].

II – Performance-based models

Performance-based risk-sharing models aim to overcome uncertainties regarding the scientific evidence of the drug and/or its real-world outcomes. To this end, mechanisms are established to generate additional evidence on the therapeutic value of the technology, in order to understand whether the technology should be reimbursed.

In the study by Morel and collaborators, of the 42 agreements analyzed, 23 correspond to performance-based risk-sharing agreements. Countries such as the Netherlands and Sweden applied only performance-based agreements, ten and five agreements respectively, with the coverage conditional on the development of additional evidence. According to the authors, this aspect can be divided into two categories: (a) reimbursement linked to performance: the performance of the drug at the patient level is linked to the payment of the technology; or (b) reimbursement with evidence development: the decision to reimburse is made after additional evidence has been collected at the population level[12].

In the "performance-linked reimbursement" category, payment may be linked to certain eligibility criteria for a treatment, such as that directed to patients who have a certain result of a genetic test; or by measuring intermediate or clinical outcomes, i.e., payment will only be made to responders, or the manufacturer returns the payment to non-responders, or even a conditional continuation, for those who reach an intermediate treatment milestone[12].

In the "reimbursement with evidence development" category, there are models that reimburse the drug only for those patients who are already in research, or reimburse for all new patients who can participate in the research[12].

The study by Gibson SG and Lemmens T discusses performance-based risk sharing in the United Kingdom. Over 100 schemes have already been or are being performed in various jurisdictions and are linked to different performance measures, such as through a clinical decision for subgroups; other schemes may focus on "clinical outcomes" or intermediaries to determine reimbursement and/or involve outcome guarantees where the manufacturer receives a lower payment for patients who have not responded to therapy[13].

Still from the perspective of the United Kingdom, the study by Shengnan D and col-

leagues analyzed 30 guidelines for orphan oncological drugs carried out by the National Institute for Health and Care Excellence (NICE) and all drugs had at least one type of agreement, with 70% using a "patient access scheme", which is defined as a simple discount; 6.7% using a commercial access agreement; and 23.3% using a managed access agreement, which include a data collection contract plus a simple discount. The drugs were funded for a limited time of up to two years, during which they were maintained according to: (a) the results that need to be collected to address uncertainty in key clinical areas; and (b) the cost of the drug in the agreement. Then, the drugs undergo a rapid reconsideration to decide whether they are recommended for use in the health system[30].

Degtiar I states in his article that orphan drugs generally receive special care, even if often with insufficient evidence. Globally, there is a significant increase in managed entry agreements to mitigate the risk of the absence of robust evidence. In Australia, for example, companies are paying to establish national registries to validate the uncertainties of the outcomes, and the price of the drug is reduced when outcomes do not meet expectations[15].

In countries such as the Netherlands, Spain, and Italy, payment based on results is more frequent, being linked to the achievement of predetermined clinical outcomes. Despite being widely used, it is observed that the strategies are applied heterogeneously among countries, even for the same treatment[25].

The study on nusinersen for the treatment of Spinal Muscular Atrophy also explores examples of countries that have carried out performance-based reimbursement. In the Netherlands and Belgium, the agreements were based on finance and results. In the results part of Belgium, it was defined that they would not reimburse the costs of non-responders. In England and Wales, a discount agreement was made combined with coverage conditioned on the development of evidence. After the agreement was finalized, NICE recommended the drug under the same conditions and specificities established in the agreement[20].

Although discussed in separate categories, many of the articles discussed risk-sharing models, both financial and performance-based, jointly, and many countries apply both mechanisms in the same agreement. In the study by Blonda A and collaborators, the authors state the importance of using this mechanism as something more than a simple form of short-term cost containment, but suggest that the agreement focus on outcome-based schemes or one that combines the two alternatives[21].

In addition, there is a lack of available data on the models already implemented in many countries, such as France and Germany[12], and an absence of policies for orphan drugs and rare diseases, such as in China and India[14]. The study carried out from the perspective of the Brazilian scenario also reports that only England and Brazil state their willingness to enter into innovative risk-sharing contracts with manufacturers. France, Australia and Canada did not openly report the possibility[19].

As regards the Brazilian healthcare system, in 2019 the Ministry of Health announced the first risk-sharing agreement for the incorporation of the drug nusinersen for Spinal Muscular Atrophy types II and III[34]. In accordance with Ordinance No. 1,297 of June 2019, the agreement aimed to promote a balance between the availability of the technology, the cost, and the collection of additional evidence of the technology in the real world, in order to enable the reassessment of the incorporation. The agreement included price reduction, subgroup eligibility criteria, definition of expected health outcomes and clinical effectiveness parameters, evaluation frequency, interruption criteria if the expected outcomes are not reached, and the maximum number of patients per year (if exceeded, the manufacturer would bear the costs)[35].

However, at the end of 2020, it was revealed that the risk-sharing agreement had failed to reach adequate terms and was terminated even before implementation. After a further submission to Conitec, it was determined that the drug be incorporated for type II of the disease, but not type III. In addition to the absence of specific contractual rules for this type of acquisition, the Ordinance did not present performance clauses, such as the specific obligations of the parties, the minimum and maximum value of the drug, and the maintenance of risk sharing in the event of judicial proceedings. This demonstrated the absence of specific regulations for this type of acquisition in Brazil[36].

At the end of 2022, the Ministry of Health announced a commitment to develop a new risk-sharing agreement for the treatment of Spinal Muscular Atrophy, now for onasemnogene abeparvovec, a gene therapy priced at R$ 6.5 million. Due to the uncertainty of the long-term clinical and safety benefits, as well as the budgetary impact on the healthcare system, Conitec approved the incorporation under a managed

access agreement. The agreement provides payments in installments and linked to the performance of the drug. The 180-day deadline for availability in the healthcare system has already expired and the therapy is not yet available to patients. Brazil still faces important challenges for new agreements to come into force in the public healthcare system[37].

In general, the implementation of risk-sharing models has as its main objective the expansion of access to the treatment of rare diseases and, at the same time, mitigation of the possible risks involved in this reimbursement process. The articles included in the analysis, in consensus with each other, point out that many rare disease drugs would not be available to patients without a managed entry mechanism[16,17,21].

Van Wilder and colleagues emphasize in their study that the implementation of a managed entry model substantially increased the chances of a positive reimbursement decision in Belgium. Among orphan drugs that did not submit a proposal for a risk-sharing model, 53.8% received a positive recommendation, while among those that used a mechanism, approvals reached 80%[17]. In Belgium, at the present time, more than 75% of orphan drugs are reimbursed through innovative contracts based on risk sharing. These models generated substantial savings for the healthcare system, around 38.5% or €1.6 billion of gross revenue in 2019[24].

Although it is still a recent topic, the authors demonstrate important lessons learned about the challenges of this implementation. The lack of experience and negotiating power, the difficulty in establishing realistic outcomes, withdrawal criteria if the medication does not reach the agreed outcomes, and the extra workload for reassessment at the end of the study are some of the main challenges pointed out by the authors[17,21,24].

Another issue widely discussed in the articles was the lack of transparency, due to confidentiality terms, and the lack of standardization in implementation. Strategies tend to be heterogeneous between countries and even internally, even for the same drug. This can lead to inefficiency in the sharing of data and good practices, a lack of robust evidence between countries, and especially a lack of fair access to treatment for rare diseases[14,15,17,20,21,24,25].

It should be noted that the present study has some limitations. The first relates to the lack of standardization of the descriptors used for publications on risk sharing in the scientific literature, which may lead to the loss of relevant studies for the review. There are working groups that aim to contribute to such standardization, such as the one created by ISPOR (International Society for Pharmacoeconomics and Outcomes Research), but which exclude the concept of risk sharing based on finance.[10] In addition, because this is a recent topic, there are still few studies published. When published, many do not provide the outcomes of the models implemented, as a result of the confidentiality terms, which makes the discussion about learning even more challenging.

Final considerations

In this highly complex universe of rare diseases, it is necessary to broaden discussions and understanding in relation to risk-sharing models, whether to fill gaps in treatment effectiveness, through performance-based models; or to minimize costs, through financial-based models. It is suggested that the use of these mechanisms should be more than a simple form of short-term cost containment, but should rather focus on combined schemes that include an analysis of the effects of the drug.

It is concluded that the implementation of risk-sharing models is a way to minimize the barriers of financial impact and uncertainties regarding the effectiveness of the drug, thus expanding access to treatments for rare diseases worldwide.

Due to the importance and complexity of the topic, it is necessary to increase transparency and the exchange of experiences between countries, since these factors are fundamental for the creation of policies and guidelines that make the process more effective in the expansion of access in Brazil and throughout the world.

Collaborations

G Puopolo: responsible for the study's conception, methodological design, data collection and organization, analysis and interpretation of results, initial manuscript drafting, and critical review of the content. She coordinated all stages of the research and writing. MLA Rodrigues: collaborated in the interpretation of the findings, participated in the analysis of the results, and contributed with conceptual suggestions. She assisted in the drafting and revision of the introduction and discussion sections. JV Bulgareli: Supervising author. Responsible for guiding the study's conception, methodological design, general supervision of the work, critical analysis of all stages, in-depth revision of the manuscript, and approval of the final version.

Data availability statement

The data sources adopted in the research are indicated in the article's body.

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