PharmacoEconomics (2019) 37:1469–1483
https://doi.org/10.1007/s40273-019-00838-w

SYSTEMATIC REVIEW

The Use of Risk-Sharing Contracts in Healthcare: Theoretical and Empirical Assessments

Fernando Antonanzas[1] · Carmelo Juárez-Castelló[1] · Reyes Lorente[1] · Roberto Rodríguez-Ibeas[1]

Published online: 18 September 2019

Abstract

Objective The aim of this review is to provide a summary of the literature on risk-sharing agreements, including conceptual, theoretical and empirical (number of agreements and their achievements) perspectives, and stakeholders' perceptions.

Methods We conducted a systematic literature search in MEDLINE from 2000 to April 2019, following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) methodology, and completed it with a manual search of other publications (mainly grey literature). The search was restricted to publications with English abstracts; the initial identification of articles was restricted to the title, abstract and key words fields. The geographical scope was not restricted.

Results Over 20 studies proposed different taxonomies of risk-sharing contracts, which can be summarised as financial and paying-for-performance agreements. Theoretical studies modelling the incentives to implement risk-sharing agreements are scarce; they addressed different types of contracts and regulatory contexts, characterizing the drug prices and the optimal strategies of the involved agents. Empirical studies describing specific agreements are abundant and referred to different geographical contexts; however, few articles showed the economic results and assessed the value of such contracts. Stakeholders' perceptions of risk-sharing contracting were favourable, but little is known about the economic and clinical advantages of specific agreements. Whether risk-sharing contracts have yielded the desired results for healthcare systems remains uncertain.

Conclusion Risk-sharing contracts are increasingly used, although the lack of transparency and aggregated registries makes it difficult to learn from these experiences and assess their impact on healthcare systems.

1 Introduction

Health authorities face several uncertainties when they add a new drug to the list of those subject to price regulation and public reimbursement [1]. There is uncertainty about the size of the patient population, the duration of treatments, and the strength and number of doses, and these aspects affect healthcare budgets. There may also be uncertainty about the actual clinical efficacy of the drug, which may imply having to pay for ineffective treatments. Over the last two decades, several proposals to introduce management tools to deal with these uncertainties have been made. The tools have been given different names in the literature (access with evidence development, pay for performance, price–volume agreements, etc.), but risk-sharing agreements is the generic term and the one we have adopted in this text [2]. In essence, these agreements aim to spread the financial and clinical risks deriving from administration of a drug between the pharmaceutical company and the health authorities. This approach differs from traditional management in which health authorities assumed almost all risks. Furthermore, in some healthcare systems, these agreements may facilitate patient access to new technologies that otherwise would not have been authorized or that would be subject to major prescribing restrictions because of their high prices and the uncertainty around key variables such as efficacy and safety.

The recent literature on risk-sharing agreements is abundant and focuses on conceptual elements (mostly definitions and terminology used in the agreements), empirical issues (reviews of the temporal and geographical implementation of the agreements, and evaluations of their results) and subjective assessments by stakeholders. To date, there have been some reviews of the literature on risk-sharing agreements [1–4], mainly describing the agreements implemented, in which the authors propose different taxonomies to classify them. Stakeholders' perceptions have also received some attention in the literature [5, 6]. As the results of most risk-sharing agreements are not disclosed, stakeholders' perceptions are used indirectly to assess the potential value of the

✉ Fernando Antonanzas
fernando.antonanzas@unirioja.es

[1] Department of Economics, University of La Rioja, Logroño, Spain

Key Points for Decision Makers

Taxonomies of risk-sharing agreements have evolved between 2010 and 2017, from rather simple classifications to those that are more sophisticated where agreements are classified depending on the level of decision. These agreements are increasing in number and can be framed as either financial or pay-for-performance agreements, with price–volume contracts the most frequent.

Few agreements have been assessed, and little information is available on the health outcomes and financial results achieved by the contracting activity. Better knowledge of the effects of these agreements would help improve the design of future agreements.

To facilitate the use of risk-sharing contracts, national and international registries and databases that hold information about the terms of the contracts as well as their financial and clinical outcomes would be desirable.

agreements and to foresee their future utilization. However, a systematic review of these perceptions is lacking in the literature. Risk-sharing contracts have also been analysed from a theoretical viewpoint [7, 8] using formal economic models to integrate key variables and parameters as well as stakeholders' strategic behaviours.

This article aims to provide comprehensive insight into risk-sharing agreements, summarizing the different research approaches that, using our knowledge of the subject, can be classified into four major areas: conceptual articles describing the contracts, economic theoretical models, empirical analysis of the contracts and descriptions of stakeholders' perceptions. Thus, we present a holistic approach to risk-sharing agreements from the different perspectives in the literature, assess the current situation and highlight potential improvements and ways to move forward.

2 Methods

We conducted a systematic literature review for the period 2000–2019. Following Yu et al. [1], who recently performed a vast systematic review, we used a search strategy in MEDLINE–PubMed. This database has been widely used in many systematic reviews, and its contents—although focused on developed countries and English literature—overlaps substantially with that of other databases, which optimised the selection of articles in the field. We also used the keywords that Yu et al. [1] identified in a previous review as the most adequate to maximise the sensitivity of the search:

value-based pricing[Title/abstract] OR value-based contract*[Title/abstract] OR value-based agreement*[Title/abstract] OR performance-based agreement*[Title/abstract] OR performance-based scheme*[Title/abstract] OR price–volume agreement*[Title/abstract] OR price–volume arrangement*[Title/abstract] OR outcomes-based contract*[Title/abstract] OR outcomes-based agreement*[Title/abstract] OR coverage with evidence[Title/abstract] OR conditional coverage[Title/abstract] OR conditional reimbursement[Title/abstract] OR risk-sharing agreement*[Title/abstract] OR risk-sharing arrangement*[Title/abstract] OR outcome guarantee*[Title/abstract] OR ("health impact"[Title/abstract] AND guarantee*[Title/abstract]) OR ("pay back"[Title/abstract] AND scheme*[Title/abstract]) OR ("paying"[Title/abstract] AND for outcomes[Title/abstract]) OR no cure no pay[Title/Abstract]

The search was restricted to publications with English abstracts; initial identification of articles was restricted to the title, abstract and key words fields. Among these publications, we only considered articles with full texts in English and Spanish. The geographical scope was not restricted. We completed the search with an ad hoc procedure consisting of double-checking the references relating to risk-sharing agreements quoted in some reviews. We excluded documents without abstracts. Two authors (CJC and RL) initially reviewed all articles to ensure no relevant publications were rejected or omitted. Uncertainty about relevance was resolved by the other co-authors (RRI and FA). To be included in the review, articles had to have dealt with the four major categories of research on risk-sharing agreements mentioned in Sect. 1 (i.e. conceptual and theoretical models, empirical results and stakeholders' perceptions). Then, we read the selected articles in full and manually extracted the precise information that contributed to knowledge on the subject and constructed tables to summarise their main findings. We used the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) methodology to describe the literature review process (Fig. 1).

3 Results

The MEDLINE–PubMed search identified 3057 references that included the key words. Researcher CJC initially screened these results to exclude those without an English abstract or those for which the full text was not freely accessible in English or Spanish. The abstracts were then read by RRI and FA to eliminate those that had no economics content or that, in the opinion of the reviewers, were not relevant to the objectives of this research, that is, the paper did not

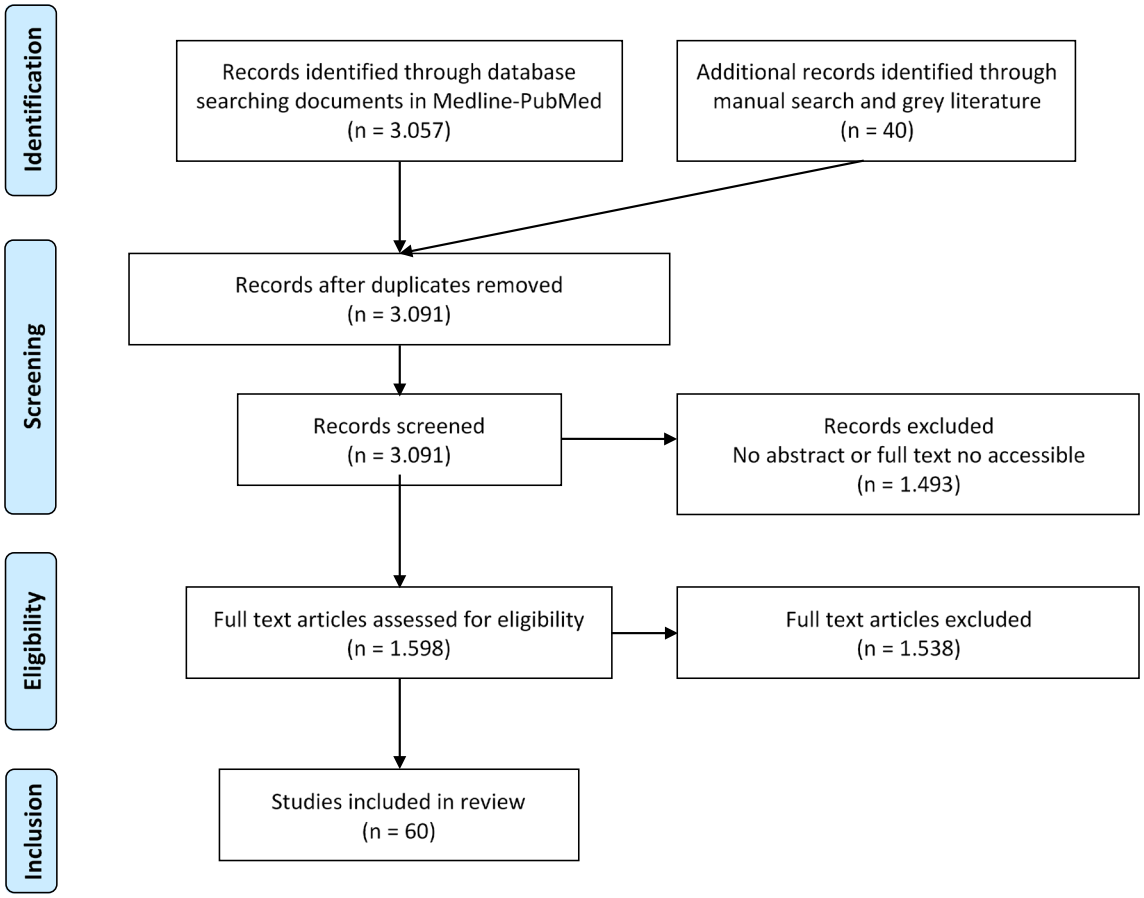

Fig. 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram of literature review process

clarify the concept, provide empirical results, develop analytical models or describe stakeholders' perceptions about risk-sharing contracts.

Applying the PRISMA methodology to the literature review produced the following results: 3057 articles were initially selected, and 40 additional records were found in the manual search. After excluding duplicates and records with no abstracts or full text available, 1598 articles were eligible.

After preliminary review of these documents, 1538 were excluded because their contents were out of scope for this review. Finally, 60 texts were analysed in depth.

3.1 Concept and Typology of Risk-Sharing Agreements

Risk-sharing contracts have been given a plethora of different names in the literature over the past two decades. As mentioned, the new paradigm of risk sharing emerges in this period as a response to uncertainty about key variables that affect decisions related to authorisation, price and reimbursement and prescribing of new technologies (mainly drugs). In this sense, terms such as access with evidence development, pay for performance, price–volume agreements, performance-based risk-sharing agreements or managed entry agreements (MEAs) are frequently used.

Towse and Garrison [9] were the first authors to systematically define the different categories of risk-sharing agreements; they observed that agreements could have objectives based not only on efficiency criteria (i.e. cost effectiveness) but also on financial criteria such as budget management and drug discounts. Furthermore, they characterised the uncertainty sources the agreements could cope with and suggested an initial taxonomy for the agreements. They primarily classified contracts as based on budget thresholds, effective price discounts and uncertainties related to clinical outcomes for all patients or a specific subgroup. These authors have been extensively quoted, and their initial classification is widely accepted, with minor variations.

Stafinski et al. [10] conducted a literature review and focused on coverage with evidence development (CED) agreements. They found 32 schemes funding technologies used in clinical studies, aiming to reduce uncertainties related to their use. They also found 26 studies of agreements classified as coverage with outcomes guarantee agreements,

wherein pharmaceutical firms were required to refund the drug costs to payers when health outcomes were below pre-agreed levels. This structure was also used by McCabe et al. [11] to evaluate current schemes and to speculate about the utility of future schemes.

The literature review of risk-sharing agreements for the period 1998–2009 performed by Carlson et al. [2] characterised pay-for-performance agreements. They found 34 CED agreements, ten conditional treatment continuation agreements and 14 pay-for-performance agreements. Most of the agreements were for Europe and Australia, but they pointed out that the number of agreements was growing in Canada and the USA. They differentiated agreements according to whether they were based on performance. They also distinguished between conditional coverage agreements (based on evidence development, applied only to patients included in the research or to all patients with that indication) and agreements whose payments were based on health outcomes (with outcome guarantee related to an endpoint or based on a treatment process such as an intermediate endpoint). This taxonomy has been widely used by other authors to analyse the evolution and geographical distribution of these contracts.

Similarly, Adamski et al. [12], after a literature review of real-world experiences, classified agreements as either financial or outcome based, and Jaroslawski et al. [13] suggested distinguishing between commercial (financial), pay for outcome and pay for evidence generation agreements. In the same sense, Walker et al. [14] proposed that agreements could promote changes in the effective price through paybacks if patients did not achieve a pre-agreed health outcome, conditional treatment continuation or linking price to health outcomes. Other authors have also considered these agreements as tools to facilitate access to new and costly drugs with uncertain health outcomes, making budget control feasible. These authors frequently followed the classification of financial and pay-for-performance agreements [3, 15–23].

Coulton et al. [24] reviewed the literature on risk-sharing agreements to analyse the possibilities of applying them in the Asia–Pacific region. They observed that some agreements in that region differed from those based on paying for performance (such as agreements for innovative and expensive drugs, agreements to treat small groups of patients, agreements targeting areas of high medical need or agreements related to drugs with uncertain efficacy). Subsequent investigations have barely used this classification.

Launois and Ethgen [25], based on Carlson et al. [2], proposed a taxonomy that noted the possibility of doing research within the framework of the agreements to confirm the results of the clinical trials in medical practice as well as to measure the real consequences of new drugs. This text has had little application in subsequent studies, although it noted the importance of linking agreements to clinical research.

Kanavos et al. [4] suggested classifying the agreements according to four criteria: the objectives (financial or performance based), the monitoring process (of costs and usage of the technology), the instruments (discounts, outcome guarantees, etc.) and impact. Again, this taxonomy, although appealing, has had few followers.

To summarise, different authors have proposed several taxonomies detailing the subtleties of the risk-sharing agreements over the last 10 years. However, it is common to classify them into two major categories related to the uncertainty problem they address: (1) financial agreements, usually called price–volume agreements, and (2) pay-for-performance agreements, which take into account the outcomes yielded by the use of the health technology. Within the latter, payments may be linked to a specific clinical metric or even require the development of additional evidence when the technologies have been authorised with existing uncertainties.

3.2 Theoretical Models

Risk-sharing agreements have also been formally studied from a theoretical perspective. A theoretical model allows the analysis of the strategic interactions between the involved agents and characterisation of the conditions under which risk-sharing agreements are financially and clinically desirable. The theoretical contributions in this area have been scarce, although they have helped improve understanding of the design of these agreements, the incentives for their implementation and the development of policies to encourage their use.

Zaric et al. [26] reviewed the theoretical papers on risk-sharing agreements and classified them into three groups: (1) articles focusing on how pharmaceutical firms react optimally to such agreements, (2) articles analysing the impact of risk-sharing agreements on social welfare and (3) articles modelling their features from a principal-agent perspective. We follow instead the taxonomy previously stated and present an alternative and updated review of the theoretical papers on financial agreements (price–volume agreements) and those based on health outcomes (pay-for-performance agreements). We first provide a short description of each paper to show the conceptual evolution of the topic and their main features. Tables 1 and 2 summarise their most relevant elements and results.

In general, a price–volume agreement fixes a sales threshold above which the pharmaceutical firms agree to apply a price discount. Theoretical models of price–volume agreements analyse the characteristics of the agreements and the behaviour of the pharmaceutical firms regarding strategic variables such as drug prices and marketing effort. Models

Table 1 Theoretical models of price–volume agreements

Study	Source of uncertainty	Type of model	Features of the model	Results
Zaric and O'Brien [7]	Market size (number of patients)	The firm decides the number of patients to maximise expected profit	The details of the agreement and the price of the drug are exogenous	The optimal decision for the firm does not coincide with the mean or the median of the distribution of patients
Zaric and Xie [29]	Efficacy	Given two types of agreements, the firm decides the price and the marketing effort	Two-period model. With the first agreement, the firm sells the drug in the second period if the net monetary benefit for the health authority in the first period is non-negative. With the second agreement, the firm pays a discount in each period if the net monetary benefit is negative	There are cases in which the health authority and the firm prefer the same agreement. In other cases, preferences differ. The model suggests that the specific circumstances of each particular situation should be taken into account to choose the best agreement
Zhang et al. [27]	Market size unknown by the health authority and the firm. The firm has private information about the average demand	Principal–agent model	The principal (the health authority) offers the risk-sharing contract (discount) to the informed agent (the firm) to minimise the expected costs subject to non-negative net monetary benefits	The first-best contract does not include discounts if the social cost of capital is positive. If this cost is negative, the optimal contract includes discounts. The second-best contract generally includes discounts
Mahjoub et al. [30]	Efficacy	Markov probabilistic model for progression of the disease	The risk-sharing contract discounts a proportion of sales to the health authority if the real efficacy is below a threshold	The model characterises the conditions under which the firm makes a profit
Gavious et al. [28]	Number of patients	Simultaneous move game of complete information. Nash equilibrium	The government designs the discount policy based on a real patient population. The pharmaceutical firm and the healthcare provider simultaneously decide the number of patients to treat. The price of the drug is exogenous	As the discount increases, the difference between the estimates decreases. The model suggests that a discount to the firm should be set to reduce such a difference
Zhang and Zaric [31]	Size of the market	In the first model, the sales threshold is exogenous, and the firm chooses the marketing effort. In the second model, the firm chooses the sales threshold before signing the agreement and then determines the marketing effort. In the third model, health authorities set the sales threshold and then, after signing the contract, the firm chooses the marketing effort	The price of the drug is exogenous and similar in all markets. The model analyses how a risk-sharing agreement affects the marketing effort of pharmaceutical firms to promote off-label sales	When the sales threshold is exogenous, the agreement controls the promotional effort. This is not necessarily true when the firm or the health authorities fix the threshold. From a social welfare perspective, it is better to use the agreement to control off-label sales than to ban them

Table 2 Theoretical models of pay-for-performance agreements

Study	Source of uncertainty	Type of model	Characteristics of the model	Results
Gandjour [32]	Efficacy, ICER	The health authority decides the price contingent on the observed efficacy	The health authority is risk averse	The price is lower if the observed efficacy is lower than expected
Barros [8]	Efficacy	Health authorities only pay if the treatment does not fail. Full penalisation is exogenous to the model. Patients differ in the probability of cure	The pharmaceutical firm determines the price of the drug to maximise its expected profits. Prescribers, once the probability of cure is observed, decide which patients to treat	Health authorities must use pay-for-performance agreements carefully as they may have undesirable results, specifically if the firm sets the price of the drug
Antonansas et al. [33]	Efficacy	The pharmaceutical firm and the health authority negotiate á la Nash the price of the drug. Social welfare is compared for both schemes (no risk-sharing; risk-sharing)	Extension of Barros [8]. Full exogenous penalisation for treatment failure	The result is ambiguous and depends on the social welfare of the untreated patients if there is a payment by results policy. If this welfare is negative, a risk-sharing contract may be preferred. If the health authority can define the clinical protocols when payments are not contingent on results, the ambiguity disappears, and such a policy is always preferred. It is advisable to be careful with risk-sharing contracts, as social welfare can be lower than when payments are not contingent on health outcomes
Levaggi et al. [34]	Cost-effectiveness thresholds	Dynamic model	The model analyses the influence of pay-for-performance agreements in the R&D decisions	Risk-sharing agreements allow more flexibility for market access and increase the value of R&D decisions
Mahjoub et al. [35]	Efficacy	Complete information game with simultaneous moves	Extension of Barros [8]. The firm chooses the price and the health authority the penalisation for treatment failure	The model identifies the threshold for the penalisation that equalises the net benefits for responders and non-responders. For extensive use drugs, there is a single solution for both decision variables
Antonanzas et al. [36]	Efficacy	They analyse the behaviour of a pharmaceutical firm with marketing authorisation for a new therapy believed to be a candidate for personalised use in a subset of patients, and a health authority that wants the firm to undertake R&D activities to know about potential responders	The health authority uses a reimbursement policy based on clinical outcomes to incentivise R&D to personalise treatments. The model characterises the optimal outcome-based reimbursement policy and the penalisation	The penalisation is maximal if the firm does not undertake the investment and the treatment fails. By contrast, the penalisation is not the maximal if the firm undertakes the investment. When the efficacy of the drug is high and the size of the target population small, there is no penalisation for treatment failure

ICER incremental cost-effectiveness ratio, *R&D* research and development

consider either the market size or the efficacy of the drug as uncertain. The first paper to analyse a price–volume agreement was that by Zaric and O'Brien [7]. In their model, the pharmaceutical firm announced the estimated budget impact of the drug, and the risk-sharing agreement set the reimbursement by the firm to the health authority as a proportion of the difference between the budget estimate and the real cost. Zhang et al. [27] built on Zaric and O'Brien [7] and analysed, within the framework of the agency theory, the determination of the optimal price–volume agreement under asymmetric information about market size. However, this line of research based on the agency theory has not been pursued further in the health economics literature. Gavious et al. [28] extended the model by Zaric and O'Brien [7] to analyse how a price–volume agreement designed by the government influenced interactions between the pharmaceutical industry and a healthcare provider. Following a game theory approach, the firm and the healthcare provider simultaneously chose the estimated number of patients to treat, knowing that the government fixed the threshold of patients used to design the discount policy as a linear combination of both estimates. Zaric and Xie [29] focused on analysing how pharmaceutical firms make decisions on drug price and marketing effort when facing a risk-sharing agreement. Unlike the model in Zaric and O'Brien [7], in which the market size was uncertain, they considered the existence of efficacy uncertainty in a two-period model to compare the performance of two risk-sharing contracts. A distinctive feature of this model was that, for the first time, it included how decisions on marketing efforts affected demand for the drug. Mahjoub et al. [30] also modelled a risk-sharing contract in which a proportion of sales revenues was discounted by the health authority when drug efficacy was below a given threshold. Finally, Zhang and Zaric [31] analysed whether a price–volume agreement influenced pharmaceutical firms' decisions about marketing efforts to promote unauthorised off-label or unlisted indications of the drug.

In summary, theoretical models of price–volume agreements analyse the best response to the agreement by the pharmaceutical firms but differ in their structures and results, making it difficult draw general conclusions. Most of the models assume that the price of the drug is exogenous. Given the importance of this variable for the firm when it makes its decision (the estimated budget or the number of patients to treat), we believe that the price should be endogenously determined because, in the real world, the budget impact of a drug depends on price and patient population. Some formulations modelled the interaction between the health authority and the pharmaceutical firm as a complete information simultaneous moves game, whereas others assumed asymmetric information within the framework of the agency theory to characterise the optimal price–volume agreement. Regardless, all models emphasised the behaviour of the firm given a generic financial contract, although they did not characterise the optimal price–volume agreement (the level of the discount) for the health authority.

Pay-for-performance agreements involve payments to firms contingent on ex-post observable clinical measures. The first reference of this type of agreements was by Gandjour [32], who characterised the price that a risk-averse health authority would pay if the observed efficacy of the drug was lower than expected. However, the first article to provide an economic analysis of risk-sharing contracts based on pay for performance, evaluating whether they were desirable for health systems, was Barros [8]. The main conclusion of the article was that health authorities should use risk-sharing contracts carefully as they might produce undesirable results, for example, a reduction in social welfare, especially if the pharmaceutical firm endogenously determined the price of the drug. Antonanzas et al. [33] built on Barros [8] and developed a model where the health authority and the pharmaceutical firm negotiate *à la* Nash the price of the drug to compare the effects on social welfare when payment to the firm was independent of health outcomes and when such payments were contingent on clinical results. The result was ambiguous and depended on the social welfare of the untreated patients if there was a payment-by-results policy. Levaggi et al. [34] presented a dynamic model to analyse the properties of two reimbursement policies based on cost-effectiveness thresholds and on pay for performance. They found that a payment policy based on results incentivises research and development (R&D) activities more than a policy based on cost effectiveness, as the former allows faster market access and increases the value of the R&D activities. Mahjoub et al. [35] modelled the determination of a risk-sharing agreement as a game between a health authority and a pharmaceutical firm. They extended the Barros model to allow the firm and the health authority to determine, respectively, the price and the penalisation when the treatment failed. Finally, unlike the other models reviewed, Antonanzas et al. [36] studied the use of risk-sharing contracts in the context of personalised medicine, emphasising that this type of agreement could be used to incentivise decisions to improve health outcomes.

In summary, models that analyse risk-sharing agreements based on pay for performance describe the interactions between the health authority and a pharmaceutical firm as a sequential or simultaneous decision-making process. The health authority chooses the characteristics of the agreement (the proportion of the price the firm must pay back in case of treatment failure), and the firm chooses the price of the drug (except for Antonanzas et al. [33], wherein the stakeholders negotiated the price). The main lesson learned from the reviewed articles is the ambiguity about the desirability of this type of agreement. The same ambiguity appeared in the models dealing with price–volume agreements. Although

the risk-sharing agreements may generate gains in social welfare and be preferred by stakeholders, a careful analysis considering the specific values of the parameters involved (efficacy, prevalence, price, monitoring costs, etc.) in each case is needed to determine their desirability.

3.3 Review of Risk-Sharing Agreements

This section reviews the studies that analysed the implementation of risk-sharing agreements from a temporal and geographical perspective. We focused on surveys that summarised the situation of a country or set of countries. We review the reviews published between 2010 and 2019. Furthermore, as a by-product of the review, we assess the consequences of some of the agreements. So as not to duplicate these published works, we summarise their major findings and complete the reviews with the latest publications. Showing this information this way provides an up-to-date state of the art and a broad view of the evolution of the contracting activity.

3.3.1 Agreements by Category and Country

Table 3 summarises 13 surveys [1, 2, 10, 37–45] that reviewed agreements published in the period 2010–2019. The information in this table refers to the number of agreements, their types, the countries of their implementation and the study period. Most of the reviews focus on countries with more experience in the use of these risk-sharing contracts (USA, the EU, Australia and Canada), and fewer than 150 agreements are quoted in each study. One of the summaries addresses Asian-Pacific countries; another refers to central-eastern European countries. Two studies (not shown in Table 3) reported data on North Africa, Israel and South Africa. In this respect, Maskineh and Nasser [46] described the activities related to the implementation of risk sharing in Middle East and North African countries; without identifying specific countries, they noted that the majority of the agreements were financial (71%) and that a few linked payments to health outcomes (29%).

It is difficult to say, based on Table 3, which type of agreement is more frequently used in each country, as some of the reviews only aimed to summarise a particular type, for instance, pay for performance [44] or coverage with evidence and financial agreements [22]. The technologies subject to these agreements were mostly drugs, although there was also some experience with medical devices [47]. In the area of drugs, oncology and neurological treatments were the most frequent targets for the agreements.

The reviews dealt with previous publications that referred to individual cases of agreements implemented in several countries, regions or medical centres. The information for the reviews mainly came from scientific research articles and the websites of health systems where those agreements were registered and detailed (e.g. the Italian Medicines Agency [Agenzia Italiana del Farmaco; AIFA] and the UK National Institute for Care and Excellence [NICE]). In Italy, AIFA [48] reported 30 financial, 38 pay-for-performance and one hybrid agreement up to March 2019. No detailed list of the agreements with NICE [49] was found; NICE only provides an appraisal of the technologies and recommends potential risk-sharing agreements and discounts to match the efficiency criteria, as discounts are confidential [44]. In the absence of generalised registries for agreements with health systems and of grey literature data (excluded from our search of reviewed documents), we conclude that the current lists of agreements per country in this study likely underestimate their number. This underestimate is believed to be greater for price–volume agreements because they are signed locally (at the hospital level) and there is no transparency about the terms of the contracts and the discounts applied. However, the CED and pay-for-performance agreements are more publicly available, as they usually include clinical research, patient registries and monitoring that requires official approval by ethics committees.

3.3.2 Assessment of the Results of the Agreements

As mentioned, the objectives of risk-sharing agreements are clear. A substantial number of agreements have been completed, and some agreements are currently in use, in a group of about 15–20 countries worldwide. It is interesting to analyse whether the results of the agreements and their achievements align with the objectives and expectations that prompted them to be signed. First, it is surprising how few of the agreements have been assessed for financial and clinical results. Some authors have detected this issue and recommended ways to overcome it. Carlson et al. [2, 40, 50] remarked that the confidentiality of the agreements and lack of transparency made it difficult to obtain data to assess whether objectives were achieved.

The first risk-sharing agreement to be assessed was that for the use of β-interferon and glatiramer acetate in the treatment of multiple sclerosis. Pickin et al. [51] published the results of that agreement in England, noting that disease progression was similar to that in the pivotal studies of this treatment. The authors did not perform an economic analysis but rather a clinical one.

Fagnani et al. [52] elaborated on a model to understand and estimate the efficiency of certolizumab pegol in the treatment of rheumatoid arthritis within a context of pay for performance with a treat-to-target strategy. The authors remarked that, in the absence of both a model to conceptualise the elements of the contract and an alternative scenario, measuring the health gains for patients and payers was unfeasible. This drug was also the subject of two other agreements: in Finland, Soini et al. [53] estimated an anticipated

Table 3 Main reviews of risk-sharing agreements

Study	Dates and countries Countries	Number of agreements
Carlson et al. [2]	Jul 1998 to Oct 2009	
	UK	CED (10), CTC (3), PLR (6)
	USA	CED (7), CTC (1), PLR (4)
	Canada	CTC (1)
	Italy	CTC (3)
	Netherlands	CED, CTC, PLR
	Sweden	CED (14)
	France	CED (1), CTC, PLR
	Germany	PLR (1)
	Australia	CED (1), CTC (3), PLR (1)
Stafinski et al. [10]	Up to May 2009	
	UK	PBRSA (10), price–volume (1)
	USA	(9)[a], PBRSA (5)
	Canada	(18)[a], PBRSA (1)
	Italy	(3)[a], PBRSA (7)
	Netherlands	(1)[a], PBRSA
	Australia	(3)[a], PBRSA (1)
Garattini et al. [37]	Up to Oct 2010	18 as of October 2010. Two medicines for age-related macular degeneration and 15 for cancer drugs (sorafenib has two contracts)
	Italy	Cost sharing (6), payment by results (12), manufacturer pays back half (cost sharing) or the full price (payment by results) for each non-responder
Ferrario and Kanavos [38]	Survey Oct 2011 to Jan 2012	345 (240 PBA), (20 financial)
	UK	20 financial
	Netherlands	35 PBA
	Belgium	20 financial
	Sweden	25 PBA
	Lithuania	40 financial
	Czech Rep	25 PBA
	Portugal	80 financial, 10 PBA
Morel et al. [22]	2006–2012 orphan drugs	42 MEA. If France and Germany are combined, the number is 45
	UK	8 MEA financial
	Italy	15 MEA (8 PBRSA, 7 financial)
	Netherlands	10 MEA (CED "only with research")
	Belgium	4 MEA financial
	Sweden	5 CED
	France	2 MEA financial (2008)
	Germany	1 MEA financial
Ferrario and Kanavos [42]	Up to Dec 2012	133 agreements in the four countries
	UK	Introduced in 2007. Active: 30 (mostly price discounts), 7 MEA for orphan drugs
	Netherlands	Introduced in 2006. 53 active in 2012. Declined in 2008–2011. 13 MEA for orphan drugs. Mostly CED
	Belgium	Introduced in 2010. 5 MEA for orphan drugs, 20 (combination of discounts and CED)
	Sweden	Introduced in 2003. Peak years 2007 and 2010 then sharp decline. 25 (mostly CED)

Table 3 (continued)

Study	Dates and countries Countries	Number of agreements
Garattini et al. [39]	Up to Oct 2012	29 MEAs for 25 drugs
	Italy	Cost sharing or price discounts (11), risk sharing (2), payment by results (16)
Lu et al. [43]	Up to July 2012	106 for Asia–Pacific regions (103 for pharmaceuticals). Little evidence on whether agreements achieved goals (details confidential)
	Australia	95 agreements (21 outcomes based, 3 evidence generation, 33 financial, 41 hybrid, combining pricing and conditional treatment)
	South Korea	3 financial based
	New Zealand	5 financial based
Carlson et al. [40]	Up to 15 Dec 2016	437 PBRSAs: 157 active, 154 expired, 26 presumed active (< 5 years since signing) and 100 presumed expired (> 5 years since signing)
	UK	52 PBRSAs (2000–2016), 11 active, 21 financial, 13 CED, 12 performance-linked, 8 CTC. Top areas: oncology (24), rheumatology (12), neurology (6)
	USA	62 PBRSAs (1997–2016), 42 active. 29 for pharmaceuticals, 21 for devices and 12 for diagnostics. Among 33 agreements (2012–16), 16 performance linked, 16 CED. Top areas: cardiology (19), oncology (13)
	Italy	85 PBRSAs (2007–16) 58 active. 61 performance linked, 23 financial, 17 CTC, 4 CED. Top area: oncology (65)
	Sweden	68 PBRSAs (2008–16). Only 5 active. 65 CED. Oncology and endocrinology (12 each)
	Australia	100 PBRSAs in 2001–15. 64 CTC, 25 financial, 9 performance linked, 6 CED. Top areas: oncology (34), rheumatology (20), neurology (8), pulmonary diseases (8)
Ferrario et al. [41]	Up to Feb 2017	Bulgaria, Croatia, Czech Republic, Estonia (237), Hungary (159), Latvia (42), Poland and Romania (6)
	Eight countries in central and eastern Europe	Most agreements based on discounts (Estonia 230, Hungary 84 discounts and 72 payback, Latvia 29 price–volume). In general, most are financial; very few outcome-based agreements
	UK	Patient access schemes. As of March 2013, 28 (15 simple discounts), 4 were PBRSA
	USA	PBRSA. 20 (mostly for devices and surgical procedures), 4 for drugs. Mainly CED
	Italy	12 (cost-sharing scheme), 2 risk-sharing scheme, 14 payment by results
	Netherlands	By 2011, 26 expensive drugs and 10 orphan drugs were on the positive list (for a 3- to 4-year follow-up to assess their outcomes that condition reimbursement)
	France	140 post-launch studies, among them 3 were PBRSA; little is known about the rest
Yu et al. [1]	Up to Apr 2017	26 PBRSAs
	USA	Top area: cardiology
Piatkiewicz et al. [44]	Up to Jan 2016. No financial schemes	Up to 2013, 148 PBRSA (most implemented in 2007–11) (CED ~ 60, the rest PBRSA and financial). Financial agreements show growth
	UK	207 NICE drug appraisals (2001–14). More than 40% after 2010 included a confidential discount from the company to the NHS
	Italy	82 therapies for 2006–15 (59% PBRSA, 33% financial, 1% both types)

Table 3 (continued)

Study	Dates and countries Countries	Number of agreements
Darbà and Ascanio [45]	2013–2018	7 MEAs
	Catalonia (Spain)	Top area: oncology

CED coverage with evidence development, *CTC* conditional treatment continuation, *MEA* managed entry agreement, *NHS* National Health Service, *NICE* National Institute for Care and Excellence, *PBA* performance-based agreements, *PBRSA* performance-based risk-sharing agreement, *PLR* performance-linked agreements

[a]Payer provided provisional funding for the technology for use as part of a clinical study

savings of €7800 per patient (which would imply 1.7% savings in 2015 and 5.6% in 2019), and in Spain, Calleja et al. [54] found savings of €871 for a cohort of 81 patients.

Clopes et al. [55] analysed the pay-for-performance agreement for gefitinib signed by the Catalan Health Service and the drug manufacturer for the period 2011–2013. They found savings of €800 per patient, which yielded total savings within the period of approximately €36,000. The authors remarked on the crucial need for integrated data systems to facilitate the measurement of both health outcomes and resources. Also in Spain, Campillo-Artero and Kovacs [47] assessed the results of a risk-sharing contract applied to neuroreflexotherapy (a technology to alleviate neck and thorax pain) in the Balearic Islands. They reported gains > 50% in the selected clinical indicators, but financial results were missing.

Garattini et al. [39] estimated the payments made by firms resulting from 29 MEAs in Italy up to October 2012. They amounted to €31.3 million, representing 5% of pharmaceutical expenditure for all agreements. They estimated management costs of €1 million but did not report health outcomes.

Makady et al. [56] assessed the CED reimbursement framework in the Netherlands for the period 2006–2012, focusing on the procedures and evaluations used by the health technology assessment agencies to recommend such schemes. They found 49 drugs were included in this conditional reimbursement system. The generated evidence was insufficient for reimbursement for five drugs. The paper highlighted that conditional reimbursement might be a good strategy to promote faster market access for an innovative drug, although health authorities should improve the design and implementation of the programme to generate value in clinical practice.

Han et al. [57] analysed the evolution of pharmaceutical spending to treat diabetes in South Korea in the period 2003–2012 and assessed whether the price–volume agreement implemented in 2007 had been successful. They found that the rate of growth of pharmaceutical spending decreased and concluded that this type of agreement could be an adequate tool to control long-term pharmaceutical spending. Also in South Korea, from a more general perspective, Park et al. [58] analysed which factors increased sales volumes above the thresholds set in a price–volume agreement that set price reductions if sales were 30% above a threshold value. They found that sales of 35% of the drugs considered (186) were above such threshold; most were drugs produced by multinationals and of clinical utility to treat patients.

To summarise, publications assessing the financial and health results of these contracting policies are limited. Few present clear data relating to these aspects. Furthermore, articles that did present data on savings under a particular agreement addressing a specific technology indicated they were rather small compared with the administrative burden imposed by the contract. Analysis of these articles indicates that assessment of this management tool requires not only more published data but also models to understand and estimate the advantages of such agreements and to enable the consequences of these agreements to be compared with those in situations without them.

3.4 Stakeholders' Perceptions

Risk-sharing contracts include confidentiality clauses that preclude the release of financial and clinical outcomes, making it difficult for stakeholders (mainly health authorities) to assess the usefulness of adopting them. Given this lack of information, some authors have used semi-structured interviews and structured questionnaires to survey stakeholders' perceptions about the pros and cons of adopting these types of contracts.

Regarding methodology, the most frequently employed method was a semi-structured interview based on a previous questionnaire. One study [24] interviewed a panel of experts attending a scientific meeting and obtained further information via a follow-up questionnaire. The stakeholders most frequently interviewed were industry and health administration representatives, together with clinical personnel [5, 6, 46, 55, 59–61]. These studies focussed on the interviewed stakeholders' real-word experiences with a particular drug or risk-sharing contract. The main therapeutic areas involved were oncology, immunology, central nervous system and

cardiovascular diseases, rheumatoid arthritis and multiple sclerosis.

Most studies emphasised the importance of financial issues in these types of agreements and remarked that they improved the management and control of health budgets and health outcomes because they eased market access and reduced clinical uncertainty. Likewise, the pharmaceutical firms also saw benefits, with early market access and improved relationships with payers. Nazareth et al. [62] used a structured questionnaire to interview 27 experts (19 health authorities, eight pharmaceutical industry representatives) from the USA and five European countries (France, Germany, Italy, Spain and the UK). All stakeholders perceived that public information underestimates the number of agreements signed because of the confidentiality and scant publicity about agreements. They also believed the number of agreements, especially financial agreements, would increase over the next 5 years, as several factors favoured this trend (creation of regulatory frameworks in several countries, new drugs that need to prove their benefits in real-world studies, new high-cost drugs, etc.). The pharmaceutical industry representatives considered early market access an advantage. Among the drawbacks of these agreements, all stakeholders emphasised that data management infrastructure needed to be improved and administrative barriers relaxed. Likewise, they mentioned difficulties in obtaining evaluations of the results of agreements because of their confidentiality clauses.

Most studies mentioned stakeholders' perceptions about the actual difficulties in developing these types of agreements. Lu et al. [5] highlighted concerns about bureaucracy, a burden mainly for clinical personnel. Clopes et al. [55] and Coulton et al. [24] mentioned the need for improved information systems to manage agreements and for follow-up of patient and clinical results. They also highlighted that better trained personnel are needed in the preliminary negotiation phases and in the pharmacy and clinical analysis areas of hospitals, as corroborated by other authors [5, 6, 55, 60]. Finally, Rojas and Antonanzas [60] stated that health professionals believe risk-sharing contracts might favour the introduction of personalised medicine, meaning that both paradigms could have positive synergies in their future evolution.

4 Discussion

In the last 20 years, risk-sharing agreements have become a useful management tool to cope with uncertainty around the financial and clinical implications of health technologies. As Piatkiewicz et al. [44] mentioned, the fluctuations in the evolution of risk-sharing agreements are related to the push for value-based-pricing in each healthcare system. Value-based pricing, coverage with evidence and risk-sharing contracts have become three related concepts. The latter facilitate market access for expensive drugs, the efficacy of which has yet to be fully demonstrated when the development of the drug is rather immature. Moreover, although the efficacy may be known in some cases, uncertainties remain regarding the administration of the drug in real-world settings, and the effectiveness is not well-known. Again, risk-sharing contracts ease market access for these drugs. However, as drawbacks, some stakeholders suspect this tool may help pharmaceutical firms finance with public funds further research that they would otherwise have to fund themselves [12] and may disincentivise the development of new drugs because of uncertainties for laboratories about their future income stream [4].

Taxonomies of risk-sharing agreements have evolved in the 2010–2017 period, from rather simple classifications to more sophisticated agreements that are classified according to the level of decision. Our systematic review of the literature revealed that, nowadays, there is a concise and widely accepted taxonomy for these contracts, that distinguishes between financial and pay-for-performance agreements. These agreements have been most widely used in the USA, UK, Italy and Australia.

Stakeholders perceive that financial agreements are widely used, although the reviewed articles also reported finding many pay-for-performance agreements, especially articles focused only on this kind of agreement. They considered that these contracts favour faster market access and help protect public health budgets [62]. It may be that typical price–volume agreements do not need to be publicised as they do not require the approval of committees or central authorities, whereas pay-for-performance agreements require active involvement by stakeholders and have more visible health consequences. However, we found no study that showed the relative proportion of each class of agreement in a given jurisdiction. Furthermore, there is no public registry for either type of agreement in most countries. The exception is Italy and England, where AIFA and NICE list the agreements signed each year [48, 49]. Although those registries do not include all the terms of the contracts, they do at least provide knowledge about the drugs under such arrangements. More countries could mirror this initiative and incorporate more details of the contracts to learn from the experience.

Regarding the evaluation of results from either the financial or the health perspective, few agreements have been assessed. To do this, we need comprehensive databases with information on clinical outcomes, health resource utilisation and expenditures. Better knowledge of the effects of these agreements would help improve the design of future agreements. Garrison et al. [3], leading an International Society for Pharmacoeconomics and Outcomes Research (ISPOR) task force, reviewed some of the existing agreements and

proposed a good practice guide; they highlighted the need to assess the agreements and publish their outcomes on the evidence of drug effectiveness as well as their final results. In this regard, in addition to data, we need to develop specific models, as Fagnani et al. [52] and Kanavos et al. [4] pointed out, because estimating the gains derived from the agreement requires comparison with results in a counterfactual scenario without such an agreement. So far, no guidelines exist for how to proceed with this type of modelling, and the few papers reviewed that showed any financial results had no clear comparator to validate their findings.

Theoretical economic modelling of risk-sharing agreements has been rare. We believe that theoretical economic models applied to risk-sharing contracts should be developed, as these models could provide insights that could be useful for the implementation of contracts. If there is a lesson to be learned from the theoretical literature, it would be that each situation should be carefully examined to determine the suitability of using a risk-sharing contract and, if deemed desirable, its details. Likewise, their application will depend on whether it is possible to observe and verify the ex-post values of the variables and parameters (number of patients treated, real efficacy of the drug, prevalence, price, monitoring costs, patients cured, etc.) on which the payments are contingent, as well as on the existence of private information available to the stakeholders. For future research, it could be interesting to integrate both types of uncertainty (financial and clinical) in one model and analyse when it would be better to use a price–volume or a pay-for-performance agreement. None of the reviewed articles focused on CED agreements. Thus, it could also be interesting to study when a firm would prefer this type of market access or another type of entry agreement.

Regarding the evolution of these agreements over time, we observed that they are growing in number, and more countries are adopting them. However, the pace of their introduction varies across modalities (i.e. faster for price–volume agreements and slower for pay-for-performance agreements). Furthermore, these agreements are more common in oncology, an area in which the new paradigm of personalised medicine is being applied. Hence, we anticipate that the growing tendency to use risk-sharing agreements will be reinforced by the personalisation of treatments, as this requires tests and follow-up registries, both relevant elements for terms of the agreements [60].

4.1 Limitations

We performed our literature search in the MEDLINE-PubMed database, following criteria by Yu et al. [1]. However, the search could also have been performed in other existing databases (e.g. Embase, Scopus and Web of Science). We acknowledge that MEDLINE-PubMed has been commonly used by many other authors for similar purposes to identify papers in this area. Embase contains publications from both developed and other countries, where these risk-sharing contracts are less likely to be implemented. Hence, we estimated that the potential papers not captured by MEDLINE-PubMed would be very few given the objectives of our research. (See, for instance, Lam et al. [63] for a discussion on these databases.) Scopus and Web of Science are general databases that also cover other scientific areas and therefore, may exclude some biomedical publications, the targets of our review. Publications in languages other than English and Spanish were not considered, what might have excluded some useful articles.

5 Conclusions

Given our research, we acknowledge that risk-sharing contracts have been increasingly used over the last 15 years. More countries are using this managerial tool, and some countries are witnessing an increase in the number of signed contracts. Furthermore, several factors will favour their future use: wider application of precision medicine and value-based pricing, swiftly increasing drug prices and budgetary constraints. To facilitate their future use, national and international registries and databases with information about the terms of the contracts as well as their financial and clinical outcomes would be desirable. Thus, we conclude that these types of agreements have a promising future.

Acknowledgements The authors thank the editor and three anonymous referees for their comments and suggestions.

Author Contributions RRI acted as a health economist on this article, summarised the articles, developed the tables and was responsible of the final writing of the text, together with FA. CJC acted as a health economist on this article, collaborated in the search of the final texts, reviewed them and developed the PRISMA summary. RL acted as a health economist on this article and collaborated in the search of the articles and in the literature review. FA acted as a health economist on this article, conceptualised the design of the text, contributed to its writing, and acts as the overall guarantor for the overall content of this article. All authors contributed to the conception and planning of the work and critically revised and approved the final submitted version of the manuscript.

Data Availability No underlying data exist for this article as it is based on a review of other published studies.

Compliance with Ethical Standards

Conflict of interest F. Antonanzas, C. Juárez-Castelló, R. Lorente and R. Rodríguez-Ibeas have no conflicts of interest directly relevant to the content of this article.

Funding This study was funded by MINECO Grant (Project ECO2016-78685-R).

References

1. Yu JS, Chin L, Oh J, Farias J. Performance-based risk-sharing arrangements for pharmaceutical products in the United States: a systematic review. J Manag Care Spec Pharm. 2017;23(10):1028–40.
2. Carlson JJ, Sullivan SD, Garrison LP, Neumann PJ, Veenstra DL. Linking payment to health outcomes: a taxonomy and examination of performance-based reimbursement schemes between healthcare payers and manufacturers. Health Policy. 2010;96(3):179–90.
3. Garrison LJ, Towse A, Briggs A, de Pouvourville G, Grueger J, Mohr P, et al. 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 Health. 2013;16:703–19.
4. Kanavos P, Ferrario A, Tafuri G, Siviero P. Managing risk and uncertainty in health technology introduction: the role of managed entry agreements. Glob Policy. 2017;8(S2):84–92.
5. Lu CY, Ritchie J, Williams K, Day R. The views of stakeholders on controlled access schemes for high-cost antirheumatic biological medicines in Australia. Aust N Z Health Policy. 2007;4:26.
6. Morgan SG, Thomson PA, Daw JR, Friesen M. Canadian policy makers' views on pharmaceutical reimbursement contracts involving confidential discounts from drug manufacturers. Health Policy. 2013;112:248–54.
7. Zaric GS, O'Brien BJ. Analysis of a pharmaceutical risk sharing agreement based on the purchaser's total budget. Health Econ. 2005;14:793–803.
8. Barros PP. The simple economics of risk-sharing agreements between the NHS and the pharmaceutical industry. Health Econ. 2011;20(4):461–70.
9. Towse A, Garrison LP. Can't get no satisfaction? Will pay for performance help? Toward an economic framework for understanding performance-based risk-sharing agreements for innovative medical products. Pharmacoeconomics. 2010;28:93–102.
10. Stafinski T, McCabe C, Menon D. Funding the unfundable: mechanisms for managing uncertainty in decisions on the introduction of new and innovative technologies into healthcare systems. Pharmacoeconomics. 2010;28:113–42.
11. McCabe CJ, Stafinski T, Edlin R, Menon D, Behalf Banff AEDS. Access with evidence development schemes a framework for description and evaluation. Pharmacoeconomics. 2010;28:143–52.
12. Adamski J, Godman B, Ofierska-Sujkowska G, Osinska B, Herholz H, Wendykowska K, et al. Risk sharing arrangements for pharmaceuticals: potential considerations and recommendations for European payers. BMC Health Serv Res. 2010;10:153.
13. Jaroslawski S, Toumi M. Market access agreements for pharmaceuticals in Europe: diversity of approaches and underlying concepts. BMC Health Serv Res. 2011;11:259.
14. Walker S, Sculpher M, Claxton K, Palmer S. Coverage with evidence development, only in research, risk sharing, or patient access scheme? A framework for coverage decisions. Value Health. 2012;15(3):570–9.
15. Cook JP, Vernon JA, Manning R. Pharmaceutical risk-sharing agreements. Pharmacoeconomics. 2008;26(7):551–6.
16. Breckenridge A, Walley T. Risk sharing and payment by results. Clin Pharmacol Ther. 2008;83(5):666–7.
17. Carapinha JL. Setting the stage for risk-sharing agreements: international experiences and outcomes-based reimbursement. S Afr Fam Pract. 2008;50(4):62–5.
18. Espín J, Oliva J, Rodríguez-Barrios JM. Esquemas innovadores de mejora del acceso al mercado de nuevas tecnologías: Los acuerdos de riesgo compartido. Gac Sanit. 2010;24(6):491–7.
19. Barros PP. Pharmaceutical policies in European countries. Adv Health Econ Health Serv Res. 2010;22:3–27.
20. Klemp M, Frønsdal K, Facey K, on behalf of the HTAi Policy Forum. What principles should govern the use of managed entry agreements? Int J Technol Assess Health Care. 2011;2011(27):77–83.
21. Campillo-Artero C, Del Llano J, Poveda JL. Contratos de riesgo compartido, ¿con medicamentos huérfanos? Farm Hosp. 2012;36(6):455–63.
22. Morel T, Arickx F, Befrits G, Siviero P, van der Meijden C, Xoxi E, et al. 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 J Rare Dis. 2013;8:198.
23. Paredes Fernández DM, Lenz Alcayaga RC. Acuerdos de Riesgo Compartido: Lecciones Para su Diseño e Implementación a la Luz de la Experiencia Internacional. Value Health Reg Issues. 2019;20:51–9.
24. Coulton L, Annemans L, Carter R, Herrera MB, Thabrany H, Lim J, et al. Outcomes-based risk-sharing schemes: is there a potential role in the Asia-Pacific markets? Health Outcomes Res Med. 2012;3(4):e205–19.
25. Launois R, Ethgen O. Risk-sharing agreements: Choice of study design and assessment criteria [Contrats de risk-sharing: Choix des schémas d'étude et des critères de jugement. Ann Pharm Fr. 2013;71(5):346–57.
26. Zaric GS, Zhang H, Mahjoub R. Modeling risk sharing agreements and patient access schemes. In: Zaric G, editor. Operations research and health care policy. International series in operations research and management science, vol. 190. New York: Springer; 2013. p. 295–310.
27. Zhang H, Zaric GS, Huang T. Optimal design of a pharmaceutical price-volume agreement under asymmetric information about expected market size. Prod Oper Manag. 2011;20(3):334–46.
28. Gavious A, Greenberg D, Hammerman A, Segev E. Impact of a financial risk-sharing scheme on budget-impact estimations: a game-theoretic approach. Eur J Heal Econ. 2014;15(5):553–61.
29. Zaric GS, Xie B. The impact of two pharmaceutical risk-sharing agreements on pricing, promotion, and net health benefits. Value Health. 2009;12:838–45.
30. Mahjoub R, Odegaard F, Zaric GS. Health-based pharmaceutical pay-for-performance risk-sharing agreements. J Oper Res Soc. 2014;65(4):588–604.
31. Zhang H, Zaric GS. Using price–volume agreements to manage pharmaceutical leakage and off-label promotion. Eur J Health Econ. 2015;16(7):747–61.
32. Gandjour A. Pharmaceutical risk-sharing agreements. Pharmacoeconomics. 2009;27:431–2.
33. Antonanzas F, Juarez-Castello C, Rodriguez-Ibeas R. Should health authorities offer risk-sharing contracts to pharmaceutical firms? A theoretical approach. Health Econ Policy Law. 2011;6(3):391–403.
34. Levaggi R, Moretto M, Pertile P. The dynamics of pharmaceutical regulation and R&D investments. J Public Econ Theory. 2017;19(1):121–41.
35. Mahjoub R, Ødegaard F, Zaric GS. Evaluation of a pharmaceutical risk-sharing agreement when patients are screened for the probability of success. Health Econ. 2018;27(1):e15–25.
36. Antonanzas F, Rodríguez-Ibeas R, Juárez-Castelló C. Personalized medicine and pay-for-performance: should pharmaceutical firms be fully penalized when treatment fails? Pharmacoeconomics. 2018;36(7):733–43.
37. Garattini L, Casadei G. Risk sharing agreements: what lessons from Italy? Int J Technol Assess Health Care. 2011;27(2):169–72.
38. Ferrario A, Kanavos P. Managed entry agreements for pharmaceuticals: the European experience. Brussels: EMiNet; 2013.

39. Garattini L, Curto A, Van de Vooren K. Italian risk sharing agreements on drugs: are they worthwhile? Eur J Health Econ. 2015;16:1–3.
40. Carlson JJ, Chen S, Garrison LP. Performance-based risk-sharing arrangements: an updated international review. Pharmacoeconomics. 2017;35(10):1063–72.
41. Ferrario A, Araja D, Bochenek T, Čatic T, Dannkó D, Dimitrova M, et al. The implementation of managed entry agreements in Central and Eastern Europe: findings and implications. Pharmacoeconomics. 2017;35(12):1271–85.
42. Ferrario A, Kanavos P. Dealing with uncertainty and high prices of new medicines: a comparative analysis of the use of managed entry agreements in Belgium, England, the Netherlands and Sweden. Soc Sci Med. 2015;124:39–47.
43. Lu CY, Lupton C, Rakowsky S, Babar ZUD, Ross-Degnan D, Wagner AK. Patient access schemes in Asia-pacific markets: current experience and future potential. J Pharm Policy Pract. 2015;8(1):6.
44. Piatkiewicz TJ, Traulsen JM, Holm-Larsen T. Risk-sharing agreements in the EU: a systematic review of major trends. Pharmacoecon Open. 2018;2(2):109–23.
45. Darbà J, Ascanio M. The current performance-linked and risk sharing agreement scene in the Spanish region of Catalonia. Expert Rev Pharmacoecon Outcomes Res. 2019. https://doi.org/10.1080/14737167.2019.1587296.
46. Maskineh C, Nasser SC. Managed entry agreements for pharmaceutical products in middle East and North African countries: payer and manufacturer experience and outlook. Value Health Reg Issues. 2018;16:33–8.
47. Campillo-Artero C, Kovacs F. The use of risk sharing tools for post adoption surveillance of a non-pharmacological technology in routine practice: results after one year. BMC Health Serv Res. 2013;13:181. https://doi.org/10.1186/1472-6963-13-181.
48. AIFA Agenzia Italiana del Farmaco. http://www.aifa.gov.it/content/comunicazioni-managed-entry-agreements-mea. Accessed 4 Mar 2019.
49. NICE Patient access schemes liaison unit. https://www.nice.org.uk/about/what-we-do/patient-access-schemes-liaison-unit. Accessed 5 Mar 2019.
50. Carlson JJ, Gries KS, Yeung K, Sullivan SD, Garrison LP Jr. Current status and trends in performance-based risk-sharing arrangements between healthcare payers and medical product manufacturers. Appl Health Econ Health Policy. 2014;12(3):231–8.
51. Pickin M, Cooper CL, Chater T, O'Hagan A, Abrams KR, Cooper NJ, et al. The multiple sclerosis risk-sharing scheme monitoring study-early results and lessons for the future. BMC Neurol. 2009;9:1.
52. Fagnani F, Pham T, Claudepierre P, et al. Modeling of the clinical and economic impact of a risk-sharing agreement supporting a treat-to-target strategy in the management of patients with rheumatoid arthritis in France. J Med Econ. 2016;19(8):812–21.
53. Soini E, Asseburg C, Taiha M, Puolakka K, Purcaru O, Luosujärvi R. Modeled health economic impact of a hypothetical certolizumab pegol risk-sharing scheme for patients with moderate-to-severe rheumatoid arthritis in Finland. Adv Ther. 2017;34(10):2316–32.
54. Calleja MA, Martín M, García C, Rubio-Terrés C, Rubio-Rodríguez D. Análisis del impacto económico del acuerdo de riesgo compartido clínico (ARCC) con certolizumab pegol (Cimzia®) para el tratamiento de la artritis reumatoide. Rev Esp Econ Salud. 2016;11(2):178–91.
55. Clopes A, Gasol M, Cajal R, Segú L, Crespo R, Mora R, et al. Financial consequences of a payment-by-results scheme in Catalonia: gefitinib in advanced EGFR-mutation positive non-small-cell lung cancer. J Med Econ. 2017;20(1):1–7.
56. Makady A, van Veelen A, de Boer A, Hillege H, Klungel OH, Goettsch W. Implementing managed entry agreements in practice: the Dutch reality check. Health Policy. 2019;123(3):267–74.
57. Han E, Park SY, Lee EK. Assessment of the price-volume agreement program in South Korea. Health Policy. 2016;120(10):1209–15.
58. Park SY, Han E, Kim J, Lee EK. Factors influencing the difference between forecasted and actual drug sales volumes under the price–volume agreement in South Korea. Health Policy. 2016;120(8):678–774.
59. Dunlop WCN, Staufer A, Levy P, Edwards GJ. Innovative pharmaceutical pricing agreements in five European markets: a survey of stakeholder attitudes and experience. Health Policy. 2018;122(5):528–32.
60. Rojas P, Antonanzas F. Los contratos de riesgo compartido en el Sistema Nacional de Salud: percepciones de los profesionales sanitarios. Rev Esp Salud Pública. 2018;92(1):1–20.
61. Kolasa K, Kalo Z, Hornby E. Research Pricing and reimbursement frameworks in Central Eastern Europe: a decision tool to support choices. Expert Rev Pharmacoecon Outcomes Res. 2015;15(1):145–55.
62. Nazareth T, Ko JJ, Sasane R, Frois C, Carpenter S, Demean S, et al. Outcomes-based contracting experience: research findings from US and European stakeholders. J Manag Care Spec Pharm. 2017;23(10):1018–26.
63. Lam MT, De Longhi C, Turnbull J, Lam HR, et al. Has Embase replaced Medline since coverage expansion? J Med Libr Assess. 2018;106(2):227–33.