Title: **The use of risk-sharing contracts in health care: theoretical and empirical assessments.**

Running title: **The State of the Art in Risk-sharing Contracts**

Authors

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Abstract

Introduction: The aim of this review article is to provide a summary of the state of the art of the literature on risk-sharing agreements from different perspectives: conceptual, theoretical, empirical (number of agreements and their achievements) and stakeholder perceptions.

Methods: A systematic literature search was carried out in Medline, following PRISMA methodology completed with a manual search of other publications (mainly, grey literature), from the year 2000 until April 2019. The search was restricted to publications whose abstracts were in English; the first identification of the articles was restricted to the title and abstract fields (including the key words selected by their authors). The geographical scope was not restricted.

Results: Over 20 studies proposed different taxonomies of risk-sharing contracts, which can be reduced in summary to 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' perception showed a favourable attitude towards this risk-sharing contracting; however, little is known about the economic and clinical advantages of specific agreements. It remains uncertain whether risk-sharing contracts have yielded the desired results for the health care systems.

Conclusion: Risk-sharing contracts are increasingly used although the lack of transparency and aggregated registries still make it difficult to learn from the experience and assess their impact on health care systems.

Keywords: Risk-sharing contracts, managed entry agreements, performance-based agreements, stakeholders' perceptions

JEL Classification: I11, I18

Keypoints:

1- Taxonomies of risk-sharing agreements have evolved in the 2010-17 period from rather simple classifications to ones that are more sophisticated where the

agreements are classified depending on the level of decision; these agreements have a growing trend and can be framed as either financial or pay-for-performance agreements, being the price-volume type the most frequent ones.

2- Few agreements are assessed and little information is available on the results (health outcomes and financial) achieved by the contracting activity. Better knowledge of the effects of these agreements would help improve the design of new ones in the future.

3- To facilitate the future use of risk-sharing contracts, 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.

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]. On one hand, there is uncertainty about the size of the patient population, the duration of treatments, and the strength and number of their doses, and these aspects affect healthcare budgets. On the other hand, there may also be uncertainty about the actual clinical efficacy of the drug, which may imply to pay for ineffective treatments. Over the last two decades, there have been several proposals to introduce management tools to deal with these uncertainties. 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 used to denominate them, the one that is also 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 health care systems these agreements may facilitate patient access to new technologies that otherwise would have not been authorized or that would be subject to major prescribing restrictions because of their high prices and uncertainties in key variables such as efficacy and safety.

The recent literature on risk sharing agreement is abundant, and has focused 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. Until now 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. Stakeholder' 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 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 point of view [7-8], using formal economic models to integrate key variables and parameters as well as stakeholders' strategic behaviours.

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

2. Material and Methods

A systematic literature review for the period 2000-2019 was carried out. Following Yu *et al.* [1], who performed a recently published vast and systematic review, we used a search strategy in Medline-PubMed. This database has been widely used in many systematic reviews and its contents, although more focused to developed countries and English literature, overlap to great extent with the contents of other databases, what

guaranties the potential selection of the articles in the field. We also used the keywords, that Yu *et al.* [1] had identified in a previous review as the most adequate to maximize 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 whose abstracts were in English; the first identification of the articles was restricted to the title and abstract fields (including the key words selected by their authors). Among these publications, we have only considered articles whose full texts were 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 quoted in some reviews relating to risk-sharing agreements. We excluded documents without abstracts. Two of the authors of this study (CJC and RL) initially reviewed all the articles to avoid rejecting irrelevant hits, and to ensure that no relevant publication was omitted. Doubtful cases were solved by the other co-authors (RRI and FA). The inclusion/exclusion criteria were that the articles really dealt with the four major categories of research on risk-sharing agreements, mentioned at the introduction section (i.e. conceptual, theoretical models, empirical results and stakeholders' perceptions). Then, we read the selected articles, manually extracting the precise information that contributed to a knowledge of the subject. Finally, we constructed some tables summarising their main findings. We have used the PRISMA methodology to describe the literature review process.

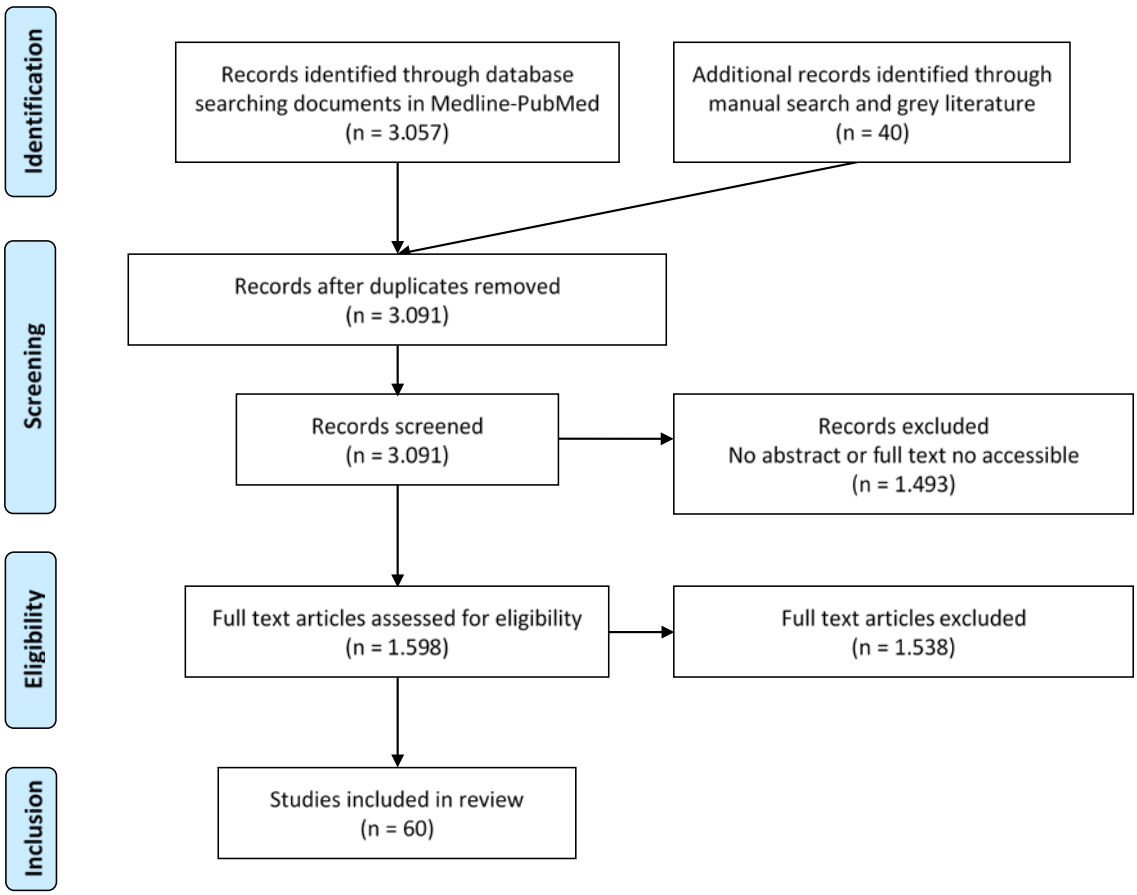
3. Results

The Medline-PubMed search identified 3057 references that met the keywords. Researcher CJC did an initial screening of these results excluding those that were inaccessible because they had no abstract in English or because the full text was not freely accessible in these languages. The abstracts were read by researchers 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. In other words, the paper had no information to clarify the concept, to provide empirical results, to develop analytical models and to describe stakeholders' perceptions about risk-sharing contracts.

Applying the PRISMA methodology to the literature review gave the following results: 3057 articles were initially selected, and 40 additional records were included after

finding them by manual search. After excluding records with no abstracts or full text available, and duplicates, 1598 articles were eligible.

After a preliminary review of these documents performed by two authors, 1538 were excluded because their contents were deemed to be 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 above, the new paradigm of risk sharing emerges in this period as a response to uncertainty about key variables that affects decisions related to authorization, 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 (PBRSA), or managed entry agreements (MEA) are frequently used.

Towse and Garrison [9] were the first authors to define systematically the different categories of risk-sharing agreements; they observed that agreements could not only have objectives based on efficiency criteria (i.e. cost-effectiveness) but also financial ones, such as budget management and drug discounts. Furthermore, they characterized the uncertainty sources the agreements could cope with and suggested an initial taxonomy for the agreements. Mainly, they classified the contracts into those based on budget

thresholds, on effective price discounts, and on uncertainties related to clinical outcomes for all patients or a specific subgroup. These authors have been extensively quoted, and their initial classification widely accepted with minor variations.

Other authors such as Stafinski *et al.* [10], following a literature review, focused on coverage with evidence development agreements (CED). They found 32 schemes funding technologies used in clinical studies, aiming to reduce uncertainties related to their use. They also found 26 studies, classified as coverage with outcomes guarantee agreements, as they stated that pharmaceutical firms should refund the costs of the drugs back to the 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 ones.

The literature review of risk-sharing agreements for the period 1998-2009 performed by Carlson *et al.* [2] allowed characterizing pay-for-performance agreements. They found 34 CED agreements, 10 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 or not 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 referred to an endpoint, or with guarantee 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 experiences, classified the agreements as either financial or outcome-based ones, and Jaroslawski *et al.* [13] suggested to distinguish between commercial (financial), pay for outcome and pay for evidence generation agreements. In the same sense, Walker *et al.* [14] proposed that the agreements could promote changes in the effective price, through paybacks if patients did not achieve a pre-agreed health outcome, condition treatment continuation, or link 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. In their articles, 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 for 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 were for innovative and expensive drugs, agreements to treat small groups of patients, agreements targeting areas of high medical need, or agreements related to drugs whose efficacy is uncertain). Subsequent investigations have barely used this classification.

Launois [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, we may say that different authors have proposed several taxonomies detailing the subtleties of the risk-sharing agreements over the last ten 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 developing additional evidence when the technologies have been authorized with outstanding uncertainties.

3.2. Theoretical models

Risk-sharing agreements have also been formally studied from a theoretical perspective. A theoretical model allows to analyse the strategic interactions between the involved agents and characterize 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 understand the design of these agreements, as well as 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: a) articles focusing on how pharmaceutical firms react optimally to such agreements, b) articles that analyse the impact of risk-sharing agreements on social welfare, and c) articles that model their features from a principal-agent perspective. We follow instead the taxonomy previously stated and we present an alternative and updated review of the theoretical papers on financial agreements (price-volume agreements) and agreements based on health outcomes ("pay-for-performance agreements). We first provide a short description of each paper to show the conceptual evolutions of this topic as well as their main features. Tables 1 and 2 summarize 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 on 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 consider uncertain either the market size or the efficacy of the drug. The first paper to analyse a price-volume agreement was 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 any 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 the interactions between the pharmaceutical industry and a health care provider. Following a game theory approach, the firm and the health care 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 size of the market 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 the decision on the marketing effort to affect the demand of 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 effort to promote unauthorized 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, as 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, while others assumed asymmetric information within the framework of the agency theory to characterize the optimal price-volume agreement. Anyways, all models emphasize the behaviour of the firm given a generic financial contract, although they do not characterize the optimal price-volume agreement (the level of the discount) for the health authority.

[INSERT TABLE 1]

The agreements based on pay-for-performance make payments to firms contingent on ex-post observable clinical measures. The first reference of this type of agreements is Gandjour [32], who characterized the price that a risk-averse health authority would pay if the observed efficacy of the drug were lower than expected. However, the first article that provided 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 bargain *à la* Nash the price of the drug to compare the social welfare when the payment to the firm was independent of the 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 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 allowing the firm and the health authority to determine respectively the price and the penalization 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 personalized medicine, emphasizing that this type of agreements could be used to incentivise decisions to improve health outcomes.

In summary, the 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, with the exception of Antonanzas *et al.* [33] where the stakeholders negotiate the price. The main lesson learned from the reviewed articles is the ambiguity about the desirability of this type of agreements. 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 the stakeholders, a careful analysis, taking into account the specific values of the parameters involved (efficacy, prevalence, price, monitoring costs, etc.) in each particular case, is needed to determine their desirability.

[INSERT TABLE 2]

3.3 Review of risk-sharing agreements

This section presents a review of the studies that have analysed the implementation of risk sharing agreements from a temporal and geographical perspective. The review focused on surveys that summarized the situation of a country or a set of countries. In other words, we present a review of the reviews published since 2010 until the most recent one of 2019. Furthermore, as a by-product of the review, we provide an assessment of the consequences of some of the agreements.In order not to duplicate these works already published, we summarize their major findings and complete the reviews with the latest publications. Showing this information this way provides an up-to-day state of the art as well as a broad view of the evolution of the contracting activity.

3.3.1 Agreements by category and country

Table 3 shows 13 surveys [1,2,10,24,37-45] with the reviews of the 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 the countries with more experience in the use of these risk-sharing contracts (USA, EU, Australia and Canada), and less than 150 agreements are quoted in each study. One of the summaries addresses Asian-Pacific countries and another one refers to Central-Eastern European countries. There are also two studies (not shown in table 3) reporting 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; they remarked that the majority of the

agreements were financial (71%), and a few linked payments to health outcomes (29%), without specifying specific countries.

[INSERT TABLE 3]

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 aim to summarize only a particular type, for instance, pay for performance (Piatkiewicz *et al.* [44]) or coverage with evidence and financial agreement (Morell *et al.* [24]). The technologies subject to these agreements were mostly drugs, although there is also some experience with medical devices (Campillo-Artero and Kovacs [47]). In the area of drugs, oncology and neurological treatments were the most frequent targets for the agreements.

The reviews dealt with previous publications 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 web sites of health systems where those agreements were registered and detailed(as it is the case of AIFA in Italy and NICE in England).For the case of Italy, AIFA [48] reports 30 financial, 38 pay-for-performance and one hybrid agreement up to March 2019. In the case of NICE [49], no detailed list of the agreements is found; NICE only provides an appraisal of the technologies and recommends potential risk sharing agreements as well as discounts to match the efficiency criteria, as discounts are confidential (Piatkiewicz *et al.* [44]). In absence of generalized registries for the agreements signed by health systems and of grey literature data (excluded from our search of reviewed documents), we can conclude that the current lists of agreements per country shown in this study likely underestimates their number. This underestimate is believed to be higher for price volume agreements, as 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 publicized, as they usually include clinical research, patient registries, and monitoring that require official approval by ethics committees.

3.3.2 Assessment of the results of the agreements

As mentioned in preceding sections, the objectives of risk-sharing agreements are clear. There is a significant number of signed and completed agreements together with some current ones in a group of about 15-20 countries worldwide. At this point, 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 how to overcome it. *Carlson et al.* [2,40,50] remarked that the confidentiality and lack of transparency of the agreements made it difficult to obtain data to assess the achievement of their objectives.

The first risk-sharing agreement assessed was the one dealing with the treatment of multiple sclerosis with beta interferon and glatiramer acetate. Pickin *et al.* [51] published the results of that agreement in England and remarked that patients showed a similar progression of their disease as found in the pivotal studies of this treatment. Authors did not perform an economic analysis but rather a clinical one.

Fagnani *et al.* [52] elaborated 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. This author remarked that in absence of a model to conceptualize the elements of the contract and of an alternative scenario, it was unfeasible to measure the health gains for patients and payers. This drug was also object of other two agreements: in Finland, Soini *et al.* [53] estimated anticipated savings of €7,800 per patient (which would imply 1.7% savings in 2015, and 5.6% in 2019), and Calleja *et al.* [54], in Spain, found savings of €871 for a cohort of 81 patients.

Clopes *et al.* [55] analysed the pay-for-performance agreement for gecitinib signed by the Catalan Health Service and the drug manufacturer for the period 2011-13.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 of above 50 % in the selected clinical indicators, but financial results were missing.

Garatini *et al.* [39] estimated the payments made by the firms resulting from 29 MEAs in Italy up to October 2012. They amounted up 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 2006-12, focusing on the procedures and evaluations made by the HTAs to recommend such schemes. They found 49 drugs included in this conditional reimbursement system. The generated evidence was insufficient for reimbursement for five drugs. The paper highlighted 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 2003-12 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 increase 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 of them being drugs produced by multinationals and of clinical utility to treat patients.

To summarise, there is a limited number of publications assessing the financial and health results of these contracting policies. Few of them present clear data relating to any of these two aspects. Furthermore, when some article shows data on savings under a particular agreement addressing a specific technology, they were rather small when compared to the administrative burden imposed by the contract. From the analysis of

these articles, it seems that the assessment of this management tool not only requires more published data but also requires design of models to understand and estimate the advantages of the agreement, and to compare them to the consequences in a situation without it.

3.4. On the stakeholders' perceptions

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

Regarding methodology, a semi-structured interview based on a previous questionnaire is the method most frequently employed. In one of the studies (Coulton *et al.* [24]), a panel of experts attending a scientific meeting is interviewed, and further information is obtained from a follow-up questionnaire. The stakeholders most frequently interviewed are the industry and health administration representatives and together with clinical personnel [5,6,46,55,59-61]. These studies focus on real experiences with a particular drug or risk-sharing contract by the stakeholders interviewed. The main therapeutic areas involved are oncology, immunology, central nervous system and cardiovascular diseases, rheumatoid arthritis and multiple sclerosis.

Most studies emphasize the importance of financial issues in this type of agreements and remark that they improve the management and control of health budgets, as well as the health outcomes, as they ease market access and reduce clinical uncertainty. Likewise, there are also benefits for the pharmaceutical firms derived from an early market access and a better relationship with the payers. Nazareth *et al.* [62] used a structured questionnaire to interview 27 experts from the US and five European countries (France, Germany, Italy, Spain and the UK), 19 health authorities, and eight representatives of the pharmaceutical industry. All stakeholders perceived that public information underestimates the number of agreements signed, due to the confidentiality and scant publicity about the agreements. They also perceived that the number of agreements would increase over the next five years, especially for financial agreements, 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 representatives of the pharmaceutical industry considered early market access an advantage. Among the drawbacks of these agreements, all stakeholders emphasized that there was needed to improve data management infrastructure and relax administrative barriers. Likewise, they mentioned the difficulties of obtaining evaluations of the results of the agreements due to their confidentiality clauses.

Most studies give stakeholders' perceptions about the actual difficulties for developing this type of agreement. Lu *et al.* [5] highlight concern about bureaucracy, a burden mainly for clinical personnel. Clopes *et al.* [55] and Coulton *et al.* [24] mention the need for an improved information system for managing the agreements and for follow-up of patients and clinical results. They also highlighted that better trained personnel are needed in the preliminary phases of the negotiation as well as in the pharmacy and clinical

analysis areas of the hospitals, as corroborated by other authors [5,6,55,60]. Finally, Rojas and Antonanzas [60] state that health professionals consider that risk-sharing contracts might favour the introduction of personalized 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 the uncertainty about 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 health care system. Value-based-pricing, coverage with evidence and risk-sharing contracts have become three related concepts.The latter facilitate market access for expensive drugs whose efficacy has yet to be fully demonstrated when the development of the drug is still rather immature. Moreover, although in other cases the efficacy may be known, uncertainties remain regarding the administration of the drug in real world settings, and the effectiveness is not well known. Again, risk-sharing contracts ease the market access for these drugs. However, as drawbacks, some stakeholders suspect that this tool may help pharmaceutical firms finance with public funds further research that they would otherwise have to bear themselves [12] and may disincentive the development of new drugs, as laboratories would have uncertainties about their future income stream [4].

Taxonomies of risk-sharing agreements have evolved in the 2010-17 period from rather simple classifications to ones that are more sophisticated where the agreements are classified depending on the level of decision. After the systematic review of the literature we have performed, we observe that nowadays there is a concise and widely accepted taxonomy for these contracts, distinguishing between financial and pay-for-performance agreements. The countries where these agreements have been most widely used are the USA, UK, Italy and Australia.

Stakeholders perceive that financial agreements are widely used, although the articles reviewed apparently report also having found many pay-for-performance agreements, especially the articles focused only on this kind of agreements. They consider that these contracts favour faster market access and help protect public health budgets [62]. Perhaps, typical price-volume agreements do not need to be publicized as they do not require the approval of committees or central authorities, while pay-for-performance requires active involvement by stakeholders and have more visible health consequences. We have not found, though, any study showing the relative proportion of each class of agreements 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 are not comprehensive of all the terms of the contracts, at least they provide a knowledge of the drugs under such arrangements. On this basis, more countries could mirror that initiative and incorporate more details of the contracts to learn from the experience.

Regarding the evaluation of the results (either from the financial or health perspective), we must say that few agreements were assessed. To carry out this activity, we need comprehensive databases with information on clinical outcomes, health resource utilization, and expenditures. Better knowledge of the effects of these agreements would

help improve the design of new ones in the future. Garrison *et al.*[3], leading an 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 the results in the counterfactual scenario in absence of the agreement. So far, there are no guidelines about how to proceed with this type of modelling, and the few papers reviewed that show any financial results have no clear comparator for validating their findings.

Theoretical economic modelling of risk-sharing agreements has been scarcely carried out. We believe that the development of theoretical economic models applied to risk-sharing contracts is a needed task as these models provide insights that can be useful for the implementation of the contracts. If there is a lesson to be learned from the theoretical literature, it would be that each particular 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.) the payments are contingent on, 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 focuses 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 have 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 and slower for paying-for-performance). Furthermore, these agreements are more common in oncology, an area where the new paradigm of personalized medicine is being applied. Hence, we anticipate that the growing tendency of risk-sharing agreements will be reinforced by the personalization of treatments, as it requires tests and follow-up registries, both relevant elements for the terms of the agreements [60].

4.1. Limitations

We have performed the literature search in Medline-Pubmed database, following Yu et al [1] criteria. However, the search could have also 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 the papers on this area. EMBASE contains publications from developed countries as well as from other ones, where likely these risk-sharing contracts are scarcely implemented. Hence, we estimate 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, they may leave out some biomedical publications, target of our review. Publications in languages other than English and Spanish were not considered, what might have left some articles out.

5. Conclusions

After the research we have carried out, 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, there are several factors that will favour their future use: wider application of precision medicine and value-based-pricing, drug prices rocketing and budgetary constraints. In order 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 may conclude that this type of agreements has a promising future.

Data Availability Statement: there are no underlying data for this article as it is based on a review of other published studies.

Compliance with Ethical Standards:

Confict 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.

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RRI acted as a health economist on this article, summarized the articles, elaborated 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 elaborated 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, conceptualized the design of the text, contributed to its writing, and acted 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.

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Table 1. Theoretical models of price-volume agreements

Article	Source of uncertainty	Type of model	Features of the model	Results
Zaric and O'Brien (2005) [7]	Market size (number of patients)	The firm decides the number of patients to maximize 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 (2009) [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 take into account to choose the best agreement.
Zhang *et al.* (2011) [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 minimize 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 includes, in general, discounts.
Mahjoub *et al.* (2014) [30]	Efficacy	Markov probabilistic model for the progression of the disease.	The risk-sharing contract states to discount a proportion of sales to the health authority if the real efficacy is below a threshold.	The model characterizes the conditions under which the firm makes a profit.
Gavious *et al.* (2014) [28]	Number of patients	Simultaneous move game of complete information. Nash equilibrium	The Government designs the discount policy based on real patient population. The pharmaceutical firm and the health care provider simultaneously decide the number of patients to treat. The price of the drug is exogenous.	As the discount grows, the difference between the estimates is lower. The model suggests that a discount to the firm should be set to reduce such a difference.
Zhang and Zaric (2015) [31]	Size of the market.	In the first model, the sales threshold is exogenous, and the firm chooses the marketing effort. In the second specification of the 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.

Source: Own elaboration

Table 2. Theoretical models of pay-for-performance agreements

Article	Source of uncertainty	Type of model	Characteristics of the model	Results
Gandjour (2009) [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 (2011) [8]	Efficacy	Health authorities only pay if the treatment does not fail. Full penalization is exogenous to the model. Patients differ in the probability of cure.	The pharmaceutical firm determines the price of the drug to maximize 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.
Antonanzas *et al.* (2011) [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 and risk-sharing)	Extension of Barros (2011) Full exogenous penalization 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 in the case in which the payments are not contingent on health outcomes.
Levaggi *et al.* (2017) [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.* (2018) [35]	Efficacy	Complete information game with simultaneous moves.	Extension of Barros (2011). The firm chooses the price and the health authority the penalization for treatment failure.	The model identifies the threshold for the penalization 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.* (2018) [36]	Efficacy	They analyse the behaviour of a pharmaceutical firm with marketing authorization for a new therapy believed to be a candidate for personalized 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 personalize treatments. The model characterizes the optimal outcome-based reimbursement policy and the penalization.	The penalization is maximal if the firm does not undertake the investment and the treatment fails. By contrast, the penalization 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 penalization for treatment failure.

Source: Own elaboration

Table 3. Main reviews of risk-sharing agreements

Issues / *Articles*	*Dates* / *Countries*	*Number of agreements*
Carlson *et al.* (2010) [2]	7-1998 to 10-2009	
	UK	CED (10). CTC (3). PLR (6).
	USA	CED (7), CTC (1), PLR (4).
	Canada	CTC (1)
	Italy	CTC (3)
	The 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.* (2010) [10]	Up to May 2009.	* Payer provided provisional funding for the technology for use as part of a clinical study.
	UK	PBRSA (10), Price-volume (1)
	USA	(9) * PBRSA (5)
	Canada	(18) * PBRSA (1)
	Italy	(3) * PBRSA (7)
	The Netherlands	(1) * PBRSA
	Australia	(3) * PBRSA (1)
Garattini *et al.* (2011) [37]	Up to October 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 backs half (cost sharing) or the full price (payment-by-results) for each non-responder.

Issues / *Articles*	*Dates* / *Countries*	*Number of agreements*
Ferrario and Kanavos (2013) [38]	Survey 10-2011 to 1-2012	345(240 PBA), (20 F)
	UK	20 Financial
	The Netherlands	35 PBA
	Belgium	20 Financial
	Sweden	25 PBA
	Lithuania	40 Financial
	Czech Rep	25 PBA
	Portugal	80 Financial, 10 PBA
Morel *et al.* (2013) [22]	2006-2012 Orphan drugs	42 MEA. If France and Germany are added up, the number is 45
	UK	8 MEA Financial
	Italy	15 MEA (8 PBRSA and 7 financial)
	The Netherlands	10 MEA (coverage with evidence "only with research")
	Belgium	4 MEA financial
	Sweden	5 covered with evidence development
	France	2 MEA Financial (2008)
	Germany	1 MEA Financial
Ferrario and Kanavos (2015) [42]	Up to December 2012	133 agreements in the four countries
	UK	Introduced in 2007. Active: 30 (mostly price discounts) 7 MEA for orphan drugs
	Italy	82 therapies from 2006-2015 (59 % PBRSA, 33 % financial, 1% both types)
	The Netherlands	Introduced in 2006. 53 active in 2012. Declined in 2008-2011. 13 MEA for orphan drugs. Mostly coverage with evidence
	Belgium	Introduced in 2010. 5 MEA for orphan drugs. 20 (combination of discounts and coverage with evidence)
	Sweden	Introduced in 2003. Peak years 2007 and 2010. Then, sharp decline. 25 (mostly coverage with evidence)

Issues / *Articles*	*Dates* / *Countries*	*Number of agreements*
Garattini *et al.* (2015) [39]	Up to October 2012	29 MEAs for 25 drugs
	Italy	Cost sharing or price discounts (11). Risk-sharing (2). Payment by results (16)
Lu *et al.* (2015) [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 outcome-based, 3 evidence generation, 33 financial and 41 hybrid, combining pricing and conditional treatment
	South Korea	3 financial based
	New Zealand	5 financial based
Carlson *et al.* (2017) [40]	Up to 15 December 2016	437 PBRSAs: 157 active, 154 expired, 26 presumed active (less than 5 years since signing and 100 presumed expired (more than 5 years since signing)
	UK	52 PBRSAs (2000-16) 11 active. 21 financial, 13 covered with evidence, 12 performance-linked and 8 conditional treatment continuation. Top areas: oncology (24), rheumatology (12) and 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 are performance-linked and 16 covered with evidence. Top areas: cardiology (19) and oncology (13)
	Italy	85 PBRSAs (2007-16) 58 active. 61 Performance-linked, 23 financial, 17 conditional treatment continuation and 4 covered with evidence development. Top area: oncology 65
	Sweden	68 PBRSAs (2008-16) Only 5 active. 65 covered with evidence. Oncology and endocrinology (12 each)
	Australia	100 PBRSAs in 2001-2015. 64 Conditional Treatment Continuation, 25 financial, 9 performance-linked and 6 coverage with evidence development. Top areas: oncology (34), rheumatology (20), neurology (8) and pulmonary diseases (8)

Issues / *Articles*	*Dates* / *Countries*	*Number of agreements*
Ferrario *et al.* (2017) [41]	Up to February 2017	Bulgaria, Croatia, Czech Republic, Estonia (237), Hungary (159), Latvia (42), Poland and Rumania (6)
	8 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, and 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 coverage with evidence type
	Italy	12 (cost sharing scheme), 2 risk sharing scheme, 14 payment by results.
	The Netherlands	By 2011, 26 expensive drugs and 10 orphan drugs were on the positive list (for a 3-4 years 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.* (2017) [1]	Up to April 2017	26 PBRSAs
	USA	Top area: cardiology
Piatkiewicz *et al.* (2018) [44]	Up to January 2016. No financial schemes	Up to 2013, 148 PBRSA (most implemented in 2007-2011) (Coverage with evidence about 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 from 2006-2015 (59 % PBRSA, 33 % financial, 1% both types)
Darbà and Ascanio (2019) [45]	2013-2018	7 MEAs
	Catalonia (Spain)	Top area: oncology

MEA: Managed Entry Access; PBRSA: Performance-based Risk-Sharing Agreements; CED: Coverage with Evidence Development; PLR: Performance Linked Agreements; CTC: Conditional Treatment Continuation; PBA: Performance based agreements
Source: Own elaboration.