

Review Article

Implementation of risk-sharing agreements in Saudi Arabia: Comparison and reflection on the NICE Model

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Sent for review: 16 June 2023

Revised accepted: 2 May 2023

Abstract

In recent years, healthcare spending has increased, due to factors such as aging population, lifestyle-based diseases, and high-cost health technologies. These factors have put enormous pressure on policymakers to curtail costs and shift towards value-based healthcare system. In this system, drug companies must demonstrate the value of their products in real-world settings. However, evidence may not be available at the time of product launch, leading to delays in reimbursement decisions and access of patients to products. To address this gap, risk-sharing agreements (RSA) have been introduced between manufacturers and payers. The most common type of RSA is the financial-based agreement which may take various forms such as annual sales caps, price-volume agreements, and comparator rebates. These agreements allow for rapid access to innovative medications. Another type of RSA is the outcome-based agreement which ties reimbursement to the real-world outcomes of products. These agreements are more complex, but they are expected to grow rapidly with the availability of real-world data. In the Middle East, the use of RSA is limited, although it is expected to increase with the ongoing shift towards a value-based healthcare system and introduction of health technology assessment. Saudi Arabia is leading these efforts in the region. This study was aimed at describing the current status of RSAs, trends in utilization of RSAs, and challenges of RSA implementation in Saudi Arabia (KSA). Real-world examples of RSAs in various healthcare sectors are also provided. Overall, the use of RSA facilitates access to innovative medications while ensuring value for money and efficient utilization of limited healthcare resources.

Keywords: Risk-sharing agreements, Managed-entry agreement, Value-based contracts, Outcome-based scheme, Financing, Reimbursement, Pricing, Saudi Arabia

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Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, Web of Science, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Recent years have witnessed a growing number of innovative technologies such as biological products, targeted therapies, and cell/gene

therapies which entered the market at high prices in order to provide manufacturers with realistic returns on investment. High prices are due to factors such as expensive research and development processes, as well as limited target

patient populations. However, with increasing regulatory control and pressure for cost containment, a balance must be made between incentivizing manufacturers to develop novel and innovative technologies, on one hand, and the ability of payers to fund healthcare costs, on the other hand [1].

Nowadays, payers tend to fund the technologies that demonstrate great value for money, relative to alternative technologies or standard of care. Additionally, payers are now more interested than ever in requesting local evidence of how medications will perform in real-world settings, as opposed to evidence from randomized clinical trials (RCT). Payers are also looking at outcomes beyond narrow clinical endpoints by emphasizing improvements in added value and impact on patient quality of life. However, cost-effectiveness studies and real-world data (RWD) are not available for some medications at the time of product launch. This may result in some uncertainty about the real value of the product, which may, in turn, delay patients' access to drugs and reduce manufacturers' return on investment. These problems may disincentivize the manufacturers from promoting and developing rare disease medications and orphan medications that have small markets. To overcome this issue and allow rapid access of patients to innovative technologies, manufacturers, and payers have adopted reimbursement approaches called risk-sharing agreements (RSA).

This type of agreement is being leveraged across different geographies, and it is expected to grow in the future in many countries, including Saudi Arabia. Currently, in Saudi Arabia, there is a limited but growing number of well-developed RSAs. However, there are no extant studies on assessment of the RSA status and its implementations in Saudi Arabia (KSA). This narrative review was carried out mainly to evaluate the current status and impacts of implementing RSAs in KSA, to discuss future applications and anticipated implementation challenges, and to provide examples of RSAs implemented in different sectors in KSA, as well as recommendations on how to implement such agreements in KSA.

Literature search and data collection

This review was aimed at studying and summarizing the experience of UK in implementing RSAs, and comparing the healthcare systems of UK and KSA so as to assess the potential applicability of National

Institute for Health and Clinical Excellence (NICE)-Like model in KSA. To achieve this, a comprehensive literature search was conducted in March 2022, utilizing three major databases i.e., PubMed, MEDLINE, and SCOPUS. The search was conducted using specific combinations of keywords such as *managed entry agreement*, *performance-based agreement*, and *risk-sharing agreement*. To ensure relevance of the sources, only articles published in English within the previous 10 years were included in the review.

In addition to the database search, a gray literature search was conducted, and NICE website was reviewed. Authors also reached out to NICE officials via email to inquire about the RSAs they implemented.

The inclusion criteria for the articles were limited to those with potentially relevant content. This review was aimed at providing a comprehensive overview of the RSA implementation in the UK, and its potential applicability in KSA. A narrative summary of all key types of RSAs was created and reviewed, based on the insights of this narrative review and opinion of the authors arising from their expertise in Saudi healthcare system. Data on some RSAs approved by different healthcare sectors in Saudi Arabia were collected and listed in this study. The authors provided key challenges and recommendations for developing an RSA model in Saudi Arabia.

Overview of risk sharing-agreements

Risk-sharing agreements (RSAs) are set between pharmaceutical companies and payers to enable rapid access of patients to new health technologies that have uncertain value. The RSAs allow for sharing of the risk of new technology between the two parties while addressing the issues surrounding the uncertainty of its value and cost-effectiveness. These agreements reduce the financial risk of unnecessary spending for reimbursing new products with limited data on values in a real-world setting. These arrangements may exist in a variety of forms such as financial-based agreements and outcome-based agreements. Several alternative names may be used. These are managed entry agreements (MEAs), RSAs, payment by results (PbRs), patient access schemes (PAS), and performance-based risk-sharing agreements (PBRsAs) [2]. In this study, RSA was used as a proxy for other forms of agreements.

The RSAs are defined by Health Technology Assessments Institutions (HTAi) as agreements

between a payer/provider and a manufacturer wherein the price level is related to the actual future performance of the product [3,4]. These agreements allow for faster reimbursement decisions under certain conditions [3,4]. It is a way for manufacturers to make high-cost medications more readily affordable [5]. An RSA is a specific form of conditional therapeutic coverage that requires a contractual agreement between the payer and manufacturer [6]. These arrangements are hinged on a 'guaranteed' outcome resulting from the treatment, based on clinical, financial, or cost-effectiveness evaluation. In effect, if the outcome is achieved, the payer pays; if not, the manufacturer reimburses the payer for the cost of medication or part thereof [7]. It is a useful tool, particularly when there are uncertainties about performance of a new medication in real-world settings.

Manufacturers are increasingly turning to RSAs as a means of increasing their chances of penetrating markets faster and achieving a larger market share before other "me-too" medications hit the market. Often, to provide faster patient access to expensive novel therapies, these companies depend on gaining positive guidance from the HTA agencies such as the National Institute for Health and Clinical Excellence (NICE) of UK, or uptake by health insurance agencies in the US. These agreements also encourage responsible prescription by healthcare professionals, thereby minimizing ineffective or sub-optimal treatments by addressing payer concerns regarding economic and clinical outcomes.

Types of risk-sharing agreements

The following are the common types of RSAs:

Performance-based RSAs

These involve risks associated with the therapeutic performance of a product which can be measured in terms of the clinical outcome or added value (cost-effectiveness). If the medication fails to meet a clinically defined outcome or specific cost-effectiveness threshold, the payer typically receives a reimbursement from the manufacturer.

Financial-based RSAs

These agreements specify the cost-containment process such as simple price discount/caps, utilization caps, and budget caps, or discounts based on data from real-world (clinical) effectiveness. Financial-based agreements offer great risk and reward potential to both the

manufacturer and the payer, as the basis of the agreement is price and/or expenditure [1]. The most-used RSA type is the financial discount-based RSA which may be in different forms such as annual sales caps, indication-wide caps, label caps, price-volume agreements, and comparator rebates.

Advantages and disadvantages of risk-sharing agreements

Risk-sharing agreements (RSAs) have the potential to change the reimbursement landscape of high-cost medications [1]. The use of these agreements has been on the increase, particularly in cancer therapeutics, due to their perceived low value for money, and the fact that these medications have multiple indications with limited data to support their value [3]. As shown in Table 1, these agreements have several advantages for the payer, manufacturer, and patient. The payers benefit from the agreements because of the more efficient reimbursement mechanisms that reduce the financial risk associated with high-cost medication, in addition to increased use of cost-effectiveness and value-based reimbursement which help in more efficient allocation of resources. The manufacturer benefits by having early access to the market while collecting and generating more RWE which is considered an incentive for continued investment in innovative medications. For patients, this agreement provides an opportunity for early use of the innovative medication.

All types of RSAs have a common goal of providing timely access to innovative medicines by reducing financial or clinical uncertainty. These agreements should be based on financial and/or health outcomes that are easily identifiable and measurable. The ultimate benefit of RSAs may not always be cost reduction but cost optimization. Countries have adopted different types of agreements in line with their objectives and type of health systems [3]. In 2010, the introduction of RSAs substantially improved access of Italian patients to cancer medicines. The median time for authorization of oncological medications with an RSA was 84 days, in contrast to 343 days in the absence of an RSA [8].

Besides the above-mentioned benefits, concern has been raised regarding transparency due to the confidentiality clause. While European countries have been implementing a set of policy options, there are no assessments of impacts of available pricing and reimbursement policies on affordable access. These challenges may be

addressed using opportunities such as increasing cooperation between authorities, sharing experiences, and improving transparency on price information, including disclosure of confidential discounts [9]. Furthermore, these agreements, especially the outcome-based agreement, require monitoring of the outcome and tracking of drug usage by patients to ensure that evidence in local clinical settings are comparable to the one in clinical trials. The data collection process is one of the most challenging barriers faced by both manufacturers and payers.

Table 1: Main advantages and disadvantages of RSA

Advantage	Disadvantage
Mitigates the risks associated with uncertainty	Difficult and complex to implement
Early access to the market	Requires large data
Promotes innovations that provide high value	High administration cost
Makes for efficient use of resources	Requires monitoring

Risk-sharing agreements in the United Kingdom

The UK has three national agencies that carry out cost-effectiveness evaluations: NICE, the Scottish Medicines Consortium (SMC), and All Wales Medicines Strategy Group (AWMSG). These agencies share a common goal of promoting cost-effective prescriptions. In particular, NICE assesses and produces advice on medications and other healthcare interventions that are referred by the Secretary of State. The goal of NICE is to provide guidelines for fairer and more efficient utilization of pharmaceuticals and medical devices by the National Health Service (NHS), principally through the use of pharmacoeconomic analysis for comparison of costs and benefits. It is worthy of note that NICE uses Patient Access Scheme (PAS) as a synonym for RSAs.

Due to the high development costs and small patient pool, many novel medications often exceed the country-specific threshold for cost-effectiveness. Therefore, NICE introduced RSAs to gain access without compromising the NHS budget. Such a system should stimulate the launch of innovative novel medications in the UK while fostering the pricing of medications based on their therapeutic values. In doing so, the new UK Pharmaceutical Price Regulation Scheme (PPRS) protects the NHS from medications that are not cost-effective, while accommodating the rise in prices of expensive novel medications such as biologicals [1].

In the UK, companies may submit a PAS proposal for any technology to go through the NICE appraisal processes. For example, the company may pay for the medications for an introductory period for each patient. Thereafter, NHS would take over the payments if the medication is shown to work for that patient. In the alternative, NHS might pay for the first course of medication, while the company takes over the payments if the patient needs treatment for a longer period than average. Each proposal is assessed by the PAS Liaison Unit at NICE. The first agreement that paved the way for RSAs began in 2002, after negative guidance by NICE on four medications for the treatment of multiple sclerosis: Avonex (interferon beta-1a), Betaferon (interferon beta-1b), Rebif (interferon beta-1a) and glatiramer acetate were not deemed sufficiently cost-effective and were therefore not eligible to be funded through NHS. This resulted in considerable opposition from patient and professional organizations, as well as manufacturers. Therefore, NICE recommended that the Department of Health and the four manufacturers should find a way to make their respective medications available on NHS in a cost-effective manner. This gave birth to the multiple sclerosis risk-sharing agreement whereby the manufacturers agreed to lower prices of their medications if they failed to meet a cost-effectiveness threshold of £36,000 (\$66,786) per quality-adjusted life year (QALY), with disease progression monitored in a minimum of 5,000 patients over a 10-year period [1,10].

The RSAs could potentially produce market equilibrium through adjustment of medication price to reflect outcomes, in combination with a post-launch evidence collection [11]. However, these agreements are usually complicated, and they require burdensome administration. For example, the management of patients' outcomes involves documentation, tracking, and monitoring large sets of data. It is also important to ensure that the agreement is not used to promote the medication involved. Patient adherence is another challenge, since outcomes are usually linked to adherence, and could result in unjustified reimbursement by the manufacturer. Furthermore, the decision on the type of RSA to implement and the associated outcome parameters require significant analysis in order to balance the risk between manufacturers and payers [1].

The multiple factors that affect the implementation of these agreements by HTA agencies could be summarized as shown below:

- (a) The cost-effectiveness threshold of NICE is too low to permit approval of certain costly and lifesaving medications.
- (b) Lack of coordination between HTA agencies may lead to disproportional access to novel medications.
- (c) Delays in issuing guidance by HTA agencies may be disadvantageous to both manufacturers and patients.
- (d) Lack of transparency which may make stakeholders question the value of QALYs.
- (e) Excessive cost-containment measures may hinder access to innovative life-saving medications [1].

Implementation of risk-sharing agreements in KSA

An important aspect of the healthcare transformation involves the establishment of HTA agency in KSA. However, the actual implementation may present a considerable challenge, given the expected level of complexity. Nonetheless, it would formalize the process for gathering information on comparative effectiveness [1]. The present review is focused on understanding how the implementation of RSAs at HTA organization NICE in UK may be adapted to KSA settings. Given the similarities between the healthcare systems in the UK and the KSA, it is likely that the adaptation of NICE model will be used as one of the main models to learn from, for HTA implementation in the KSA. Table 2 provides a comparison between the two healthcare systems. While the KSA has a national fund-based system, NICE is designed around the public National Health System (NHS) in the UK. The healthcare system in KSA is willing to accept explicit restrictions on access to services, and it has the same concerns about extensive government involvement in healthcare.

The importance of having innovative payments such as RSAs in Saudi Arabia has been promoted by the Saudi Health Council (SHC) which encourages HTA body to consider these types of payment for innovative and expensive health technologies [12]. Healthcare stakeholders in Saudi Arabia have also demonstrated the need for RSAs in the KSA so as to bridge the gap between high-cost medications and market access at the national level. In this respect, they have suggested a combination of payment models (financial-based and outcome-based) [13]. The use of RSAs speeds up accessibility of medication to the

market due to the dynamic nature of the negotiation process between manufacturers and HTA agencies or payers. This reduces the need for a second round of negotiations, as amendments to the agreement are settled directly. Although many stakeholders have a positive attitude toward RSA and its value, there are misgivings about the experiences of KSA agencies and their capabilities to implement such agreements. Moreover, there are confidentiality issues and a lack of legal framework. Currently, financial-based agreements are more commonly used in KSA, relative to outcome-based agreements. This is mainly due to their simplicity, ease of implementation, and non-requirement of data collection, with long follow-ups for capturing health outcomes. The establishment of a new HTA body could help facilitate and shape the use of RSAs in KSA [12,13].

Several advantages could be gained from implementing RSAs, including enhancement of access to high-priced medications following a negative approval. In addition, it has the potential to provide a form of formulary management strategy and appropriate prescription behavior. The RSA strategies share risks between manufacturers and payers, but ultimately, patients are enabled to gain access to innovative medications that would otherwise be rejected or delayed by negotiations. Therefore, RSA strategies improve health outcomes while reducing overall healthcare costs. Typically, the agreements involve a dynamic process consisting of negotiations over the cost-effectiveness of medications, which are often preferred to the long and expensive route of producing additional clinical trial data. The RSAs also allow manufacturers to maximize global sales of a given medication because lowering the price of medication in a key reference market such as the UK to make it cost-effective, would affect the price in all countries that reference UK price in their pricing structure.

However, despite the benefits of RSAs, the agreements must be managed correctly to ensure that healthcare systems are not burdened. The administration of RSAs is complicated further by the several types of funding arrangements possible. Given that it is already challenging to administer reimbursement and track outcomes, the greater the variety of RSAs available, the harder it is to manage them. Another drawback is that it may be difficult to conclude if such pricing programs work in real practice. However, the risk to manufacturers could reduce as confidence and utilization of the medication increase. There again, the cost on

manufacturers could increase if the medication fails to achieve more utilization [1].

Will a NICE-like model succeed in KSA?

Saudi Arabia is now targeting the delivery of more affordable and equitable healthcare through the adoption of value-based healthcare principles as part of the national health transformation plan. However, the country faces spiraling healthcare and social services costs which consumed 15.6 % (SAR 172 billion) out of the budget in 2019, representing an 8 % increase over SAR 159 billion in 2018 budget, and 10.5 % increase over SAR 133 billion in the 2018 budget [14,15]. This trend indicates potential for more increases in costs of healthcare and social services in the next few years. In addition, expensive novel medications and devices contributed significantly to the rise in healthcare costs over the past decade [14,15]. The Pharmaceutical Country Profile report published in 2012 by the Saudi Food and Drug Authority, in collaboration with the World Health Organization shows that KSA spends about 20 % of its healthcare budget on medications [16].

Currently, KSA is establishing a new HTA agency under the healthcare regulator umbrella to formalize the process of appraisal of medications and provision of recommendations to governmental payers. The HTA agency is aligned with Saudi 2030 vision of shifting to value-based healthcare, which is aimed at increasing the quality of care and quality of life of patients while utilizing resources more efficiently. An examination of a hypothetical NICE-like model and its implications for RSAs in the KSA resulted in the following observations:

Structure and composition

Although NICE in the UK is funded by the Department of Health, it has a distant relationship with the government. Indeed, it is seen as an independent body. In the KSA, decisions affecting governance, funding, and organization of any HTA body depend on whether it is a new independent governmental agency, part of an existing agency, or an agency outside the government. Consequently, if the agency is to report to the government alone, it would result in a relationship similar to that between NICE and the Department of Health in the UK. On the other hand, if an HTA body is to provide recommendations to a wider range of governmental and private payers, a broad spectrum of funding and organizational options would be available, such as a mixture of public and private funding.

Responsibility

Analysis of the clinical cost-effectiveness of medications forms the core responsibility of NICE. At the international level, NICE is one of the few HTAs that have clearly stated their responsibilities. Majority of institutions in KSA use 'comparative effectiveness' involving only clinical outcomes, to compare alternative technologies. On the other hand, other institutions believe that comparative effectiveness should also consider direct and indirect medical costs. In KSA, it is believed that comparative effectiveness should encompass a comprehensive review of the clinical merits, safety, and economic evaluation using different tools.

Assessments versus appraisals

NICE clearly distinguishes between assessments (where technology is assessed) and appraisals (where the evidence is evaluated and the decisions are made) and also relies on an external panel of experts during its decision-making process. The challenge in the Saudi market is deciding whether an HTA agency should have a decision-making role, whether it should merely make recommendations, and whether these decisions apply to all governmental and non-governmental healthcare sectors. This depends on whether the HTA agency is an independent body or whether it is under the umbrella of the MoH.

Cost-effectiveness threshold

Generally speaking, decisions by NICE are based on its £ 20,000 – £ 30,000 (\$ 37,104 – \$ 55,655) per quality-adjusted life-year (QALY) threshold. However, there is no official threshold in KSA, despite ongoing efforts to establish QALY value specific to KSA. There is an approved national project for establishing a country-specific QALY monetary valuation using the EQ-5D-5L tool. Nevertheless, an HTA agency is likely to limit its role to making assessments rather than appraisals until the QALY valuation is determined [5].

An HTA agency has the potential to create a more cost-effective use of healthcare resources in the KSA using RSA. However, it is important to note that this may increase the burden on manufacturers to produce local data. Based on recent successful experience of MoH in KSA regarding the development of these types of agreements, it is expected that manufacturers will take up and support RSAs in KSA.

Table 2: Comparison of population and healthcare systems of UK and KSA

Item	UK	KSA
Population	68 million	35 million
Healthcare system	Public, with one National reimbursement system	Public, with several providers (MoH (70 %), other institutions (20 %) and private (10 %))
Drug-approving body	EMA	SFDA
Pricing	NICE	Healthcare institutions
Reimbursement process	Single national payers through the NHS	Fragmented public and private payers
Availability of RSA framework and guideline	Available	No guideline
HTA	Well-established (NICE)	Newly-established (early stage)
Outcome data	Available	Difficult to get

However, it is not yet known if the newly-established HTA in KSA would be responsible for public pricing and reimbursement decisions. Currently, the SFDA is responsible for setting public prices of pharmaceuticals.

Example of current RSAs in KSA

Saudi Arabia did implement several RSAs between 2018 and 2020. The decision on these agreements was based on a thorough budget impact analysis which indicated that the prices proposed by manufacturers were not economically feasible. Table 3 lists few examples of RSAs from MoH and NHGA. For this review, light was shed on few examples of RSAs currently implemented in Saudi Arabia. An RSA for Ocrelizumab was recently approved for Relapsing-Remitting Multiple Sclerosis (RRMS) and Primary Progressive Multiple Sclerosis (PPMS). The consideration of this agreement was based on the new innovative therapy, the large number of MS patients covered by MoH, the high medication cost, the uncertainty in outcomes from RRMS (being the first medication in the market), and the long list of patients waiting to access the medication. The key measures in this agreement include initiation of free treatment for a defined number of patients, in addition to continuous assessment of clinical outcomes using magnetic resonance imaging (MRI) at defined time points. Payment for the maintenance regimen is linked to patient response. The benefits of this agreement are expedited formulary addition in MoH and faster patient access to the medication.

A new RSA has been approved for pro-protein convertase subtilisin kexin type 9 (PCSK9) inhibitor (Evolocumab) for the treatment of homozygous and heterozygous familial hypercholesterolemia. The main reasons for considering this agreement were the high cost of the medication and the uncertainty of the outcomes in the Saudi population due to the absence of local evidence. The main components of this agreement are free treatment initiation for a defined number of patients, price volume discount for the first 3 years, and continuous assessment of clinical outcomes evident in a 60 % reduction of LDL when the medication is added to a maximally-tolerated high-intensity statin in combination with ezetimibe, every 3 months. The manufacturer covers the cost of a certain number of units for a defined number of Major Adverse Cardiovascular Events (MACE). In KSA, the experience with RSAs is a recent phenomenon that is still in the early phase. Therefore, there is need for future assessment of RSAs with respect to success rate in achieving expected objectives. Other RSAs have been approved for Nusinersin, Lomitapide, Risankizumab, Atezolizumab, Daratumumab, Pertuzumab, Trastuzumab, Nivolumab, and Ipilimumab. Many of these RSAs are outcome-based agreements. Other financial-based agreements are implemented widely in KSA but are not included in this list, for confidentiality reasons (Table 3). This review indicates that the RSAs have been operating in KSA in the past few years. The effectiveness of such approach, and its impact on patient care and healthcare system, need to be assessed through further studies.

Table 3: List of RSAs in MOH and other institutions in KSA

Drug	Indication	Payer	Type of RSAs	Details
Nusinersin (Spinraza) [®]	SMA	MoH	Outcome-based	Risk sharing with FOC for the first 18 months of therapy, followed by assessment of response at 20 months and further rebates for patients who do not respond.
Ocrelizumab (Ocrevus) [®]	MS	MoH	Outcome-based	Risk sharing with FOC for new and switched patients, followed by assessment of response based on MRI results and clinical evaluation every 6 months, with free rebates if medication fails to perform as per set clinical response criteria.
PCSK9Is	Heterozygous FH	MoH	Outcome-based	Risk sharing with FOC for new and switched patients, followed by assessment of response based on LDL levels and clinical evaluation every 6 months for MACE, with free rebates if medication does not perform as per set clinical response criteria.
Lomitapide (Lojuxta) [®]	Homozygous FH	MoH	Outcome-based	Risk sharing with FOC for new and switched patients, followed by assessment of response based on LDL levels and clinical evaluation every 6 months for MACE, with free rebates if medication does not perform as per set clinical response criteria.
Risankizumab (Skyrizi) [®]	Psoriasis	MoH	Outcome-based	Patients are assessed at week 16 based on PASI 90 response. Partial and full rebates are offered by the company, depending on other endpoints such as PASI 75 and PASI 50.
Atezolizumab (Tecentriq) [®]	NSCLC	NHGA	Financial-based	One free vial for every 10 vials
Daratumumab (Darzalex) [®]	MM	NHGA	Financial-based	2 free cycles out of 8 cycles in the 1 st 2 months
Pertuzumab (Perjeta) [®] & Trastuzumab (Herceptin) [®]	mBC	NHGA	Outcome-based	Reimbursement of cycle no. 9 as FOC/patient after verifying administration of all consecutive cycles from 1 to 9 without missing any cycles -Reimbursement of cycle no. 18 as FOC/patient after verifying administration of all consecutive cycles from 9-18 without missing any cycles
Nivolumab (Opdivo) [®] & Ipilimumab (Yervoy) [®]	RCC	NHGA	Financial-based	Free Ipilimumab for 10 patients

Challenges of implementation of RSAs in KSA

The implementation of RSAs is associated with several challenges, especially for the outcome-based RSAs, despite their potential advantages. These challenges are related to high administration cost, lengthy negotiations, the uncertainty of success and benefit, and overly complex nature [17]. Other challenges include

lack of transparency of RSAs objectives, evaluations that limit the number of patients engaged, and transferability of RSAs to other institutions or countries. Another major concern in the implementation of RSAs is the limited awareness of the concept by different stakeholders, with respect to the requirements for data collection processes, registries, and patient response [18].

However, not much is known about the challenges with RSAs in KSA and the region. A cross-sectional survey was conducted in the Middle East and North African (MENA) countries (including KSA) to assess the challenges of implementation of RSAs from the perspectives of pharmaceutical manufacturers and public officials. The challenges identified in the survey were related to identifying/defining meaningful outcomes, measuring relevant real-world data/outcome, limited data infrastructure which is inadequate for measuring relevant outcomes, difficulty in reaching contractual agreements, lack of expertise, and significant cost of resources. Despite these challenges, the financial-based or volume-based agreement is more commonly used RSAs in MENA region [4].

The following factors could be considered by stakeholders in the determination of the efficiency of implementing RSAs in KSA: (i) the cost and practicality of real-world data collection by the payers; (ii) the cost of evidence collection with RSA, as it may reduce the incentive for the manufacturer to accept it; (iii) the difficulty of writing and monitoring RSAs; and (iv) the need for manufacturers to consider country-specific factors for implementation and key RSA considerations in these markets [2]. The appropriateness and availability of competent staff to fully evaluate proposed agreements, as well as access to IT support, are crucial [19,20]. The conditions governing RSAs should be clear, transparent, and balanced to address the expectations of various stakeholders [21].

The most common types of implemented financial RSAs are confidential discounts, followed by paybacks, price-volume agreements, free doses, bundles, and other agreements, and payment by the result [22]. All types of RSAs should be written, indicating clear rationale, aspects to be assessed, methods of data collection and review, and the criteria for ending the agreement [23]. In the future, RSAs will be used more often in KSA and the Gulf region mainly because of the shift to value-based healthcare system and the establishment of HTA agencies, along with the improvement in the availability of disease registry data and RWD.

Recommendations for optimizing RSAs in KSA

In KSA, RSA is still in its early phase, and it is being utilized to facilitate patients' access to costly medication. Based on the information collected in this review and the authors' opinion, the following recommendations are pertinent for optimizing RSAs in KSA:

- Deciding on which type of RSA to adopt: when creating an RSA, the manufacturers must measure health outcomes, medication costs, and type of reimbursement.
- The timing of RSA implementation is critical to its success at SFDA approval level or as part of formulary management at institutional level.
- Strong clinical and outcome data are required to support risk-sharing applications as these are very critical in the assessment of the value of medication.
- Setting identification criteria for a suitable medication: a medication should fulfill specific criteria to be suitable for an RSA.
- Improving training, development, and availability of expertise in health economics and health outcome: the implementation of RSAs requires an in-depth understanding of how to assess real-world data, as well as how to calculate and evaluate total cost associated with treatment.
- Developing/updating all regulations and legislations that support access to the market.
- Engagement of patient advocacy groups for RSA approval [1].

CONCLUSION

Risk-sharing agreements (RSAs) are used as effective tools for improving patients' access to innovative treatments, and for containing continuous increases in health expenditure and rising costs of healthcare and innovative medicines in KSA. Regardless of the challenges associated with implementation of such agreements, there are recognized advantages in the adoption of RSAs to patients, payers and manufacturers. The utilization of RSAs in KSA is limited, but it has shown a growing trend in the past few years. To facilitate the implementation of RSAs, there is need to consider several factors such as data collection, transparency, and regulations. Continuous and sustained assessment of implemented RSAs will improve future agreements.

DECLARATIONS

Acknowledgements

None provided.

Funding

This work was supported by Researchers Supporting Project (number RSP2023R76), King Saud University, Riyadh, Saudi Arabia.

Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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REFERENCES

- Gray AL. *Pharmaceutical pricing and reimbursement policies: perspectives for the future*. *J Pharm Policy Pract* 2015; 8(1): 1-2.
- Pritchett L, Wiesinger A, Faria-Billinton E, Brown A, Murray G, Stoor L, Nwogu G. *A review of guidelines and approaches to performance-based risk-sharing agreements across the UK, Italy, and the Netherlands*. *Value Health* 2015; 18(7): A568.
- Gonçalves FR, Santos S, Silva C, Sousa G. *Risk-sharing agreements, present and future*. *Ecancermedalsci* 2018; 12.
- 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: 33-38.
- NICE. *The NICE glossary*. NICE Website, 2019.
- De Pourville G. *Risk-sharing agreements for innovative drugs: a new solution to old problems?* *The Euro J Health Econ* 2006; 7: 155-157.
- Ehret J, Williams D. *European pharmaceutical pricing and reimbursement conference*. *Expert Rev Pharmacoecon Outcomes Res* 2009; 9(1): 37-39.
- Espín J, Rovira J, García L. *Experiences and impact of European risk-sharing schemes focusing on oncology medicines*. Brussels: Commissioned by the European Commission, Directorate-General Enterprise, 2011.
- Vogler S, Paris V, Panteli D. *In Ensuring access to medicines: How to redesign pricing, reimbursement, and procurement?* E. Richardson, W. Palm, and E. Mossialos, Editors. 2018.
- Pickin M, Cooper CL, Chater T, O'Hagan A, Abrams KR, Cooper NJ, Boggild M, Palace J, Ebers G, Chilcott JB, et al. *Multiple sclerosis risk-sharing scheme monitoring study—early results and lessons for the future*. *BMC Neurol* 2009; 9(1): 1-8.
- Towse A, Garrison LP. *Can't get any satisfaction? Will pay for performance help? Toward an economic framework for understanding performance-based risk-sharing agreements for innovative medical products*. *Pharmacoecon* 2010; 28: 93-102.
- Al-Omar HA, Attuwajiri AA, Aljuffali IA. *Pharmaceutical companies' views on a health technology assessment (HTA) entity in Saudi Arabia*. *Saudi Pharm J* 2020; 28(6): 662-668.
- Al-Omar HA, Alghannam HH, Aljuffali IA. *Exploring the status and views of managed entry agreements in Saudi Arabia: mixed-methods approach*. *Expert Rev Pharmacoecon Outcomes Res* 2021; 21(4): 837-845.
- KPMG. *Kingdom of Saudi Arabia Budget Report; A review of KSA 2019 budget and recent economic developments 2018*.
- International C. *Kingdom of Saudi Arabia Healthcare Overview | The Pulse: 8th Edition*. Colliers International KSA Healthcare Overview 2018.
- Bawazir S. *Saudi Arabia Pharmaceutical Country Profile, in Saudi Food and Drug Authority in collaboration with the World Health Organization 2012*, Saudi Food and Drug Authority: World Health Organization website.
- De Pourville G. *Risk-sharing agreements for innovative drugs: a new solution to old problems?* *The Eur J Health Eco* 2006; 7: 155-157.
- Kanavos P, Ferrario A, Tafuri G, Siviero P. *Managing risk and uncertainty in health technology introduction: the role of managed entry agreements*. *Global Policy* 2017; 8: 84-92.
- Adamski J, Godman B, Ofierska-Sujkowska G, Osińska B, Herholz H, Wendykowska K, Laius O, Jan S, Sermet C, Zara C, et al. *Risk sharing arrangements for pharmaceuticals: potential considerations and recommendations for European payers*. *BMC Health Services Res* 2010; 10(1): 1-6.
- Neumann PJ, Chambers JD, Simon F, Meckley LM. *Risk-sharing arrangements that link payment for drugs to*

- health outcomes are proving hard to implement. *Health Affairs* 2011; 30(12): 2329-2337.
21. Tuffaha HW, Scuffham PA. The Australian managed entry scheme: are we getting it right? *Pharmacoecon* 2018; 36(5): 555-565.
22. Ferrario A, Arāja D, Bochenek T, Čatić T, Dankó D, Dimitrova M, Fürst J, Greičiūtė-Kuprijanov I, Hoxha I, Jakupi A, et al. The implementation of managed entry agreements in Central and Eastern Europe: findings and implications. *Pharmacoecon* 2017; 35: 1271-1285.
23. Klemp M, Fronsdal KB, Facey K. What principles should govern the use of managed entry agreements? *Int J Technol Assess Health Care* 2011; 27(1): 77-83.