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Risk-sharing Agreements: Country Experiences and Challenges

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Overview

Risk-sharing agreements (RSAs) are in use across much of Europe. While their particular objectives and formats differ, the overarching aim of such agreements is to tackle issues of uncertainty (e.g., around clinical effectiveness, indication, and dosage) at the time of product launch. Within Europe, however, there is significant variation at the national level with respect to policy makers' views on RSAs. Some perceive RSAs as a means of mitigating uncertainty and improving patient access, and others point to the associated issues of poor supporting infrastructure, complex administrative challenges and high implementation costs. The purpose of this piece is to discuss the challenges and implementation nuances faced by policy makers in six European countries along these lines.

Introduction and Background[1]

Risk-sharing agreements (RSAs) have received increasing attention in recent years. Such agreements involve formal arrangements between payers and medical technology manufacturers when new products are launched, in an effort to facilitate patient access, manage costs and support the process of innovation. Manufacturers must demonstrate that the new technology provides additional benefits compared to existing therapies in order to obtain funding, but data is often insufficient in estimating the cost-effectiveness of the product in real-world clinical settings. This can create significant uncertainty around product performance at the time of launch. Payers must decide whether to fund therapies that may or may not be effective in the patient population, while manufacturers face the risk of low adoption rates and a subsequent reduction in projected revenues in the absence of reimbursement. In addition to therapeutic value, there may be uncertainty about the dose in daily practice.

As a result, both payers and manufacturers, operating in a risk averse environment, aim to reduce their exposure. One way to is through performance-based agreements where patients are monitored for data collection (from registries or through observational

[1] The following sources were referenced to develop this thought piece: Performance-Based Risk-Sharing Arrangements-Good Practices for Design, Implementation, and Evaluation: Report of the ISPOR Good Practices for Performance-Based Risk-Sharing Arrangements Task Force, http://www.ispor.org/TaskForces/documents/Performance-based-Risk-Sharing-Guidelines.pdf; Linking Payment to Health Outcomes: A taxonomy and examination of performance-based reimbursement schemes between healthcare payers and manufacturers, http://www.sciencedirect.com/science/article/pii/S0168851010000515; and Managed Entry Agreements for Pharmaceuticals: The European Experience, European Commission, http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/mea_report_en.pdf.

studies) while the technology is in use, thus changing how risk is managed across both payers and manufacturers. Risk-sharing schemes can take various forms, from outcomes-guarantee, conditional treatment continuation, and coverage with evidence development (CED), to finance-based schemes such as dose caps and price volume agreements (e.g. discounts, rebates). RSA's are also referred to as managed entry agreements (MEAs) in literature[2]. For the purposes of this analysis these aforementioned terms are all grouped under the term 'risk-sharing agreements' or RSAs.

Recent reports from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the European Commission[3] allude to the challenges inherent in such schemes, including the high cost of administration, lengthy negotiations, unclear success metrics and overly complex agreements. Price discounts, a simpler form of such arrangements, are often labeled 'risk-sharing', though payment is not directly tied to product performance. A number of country examples of RSAs have been previously documented, but little is known about their actual implementation and levels of adoption, recent developments or future plans. The question is whether RSAs help achieve the objectives for which they were implemented in the first place: namely, patient access, cost containment or support for innovation.

The LSE Summit

The LSE Summit on Risk-sharing and Managed Entry Agreements in London[4] provided a platform for European countries to share their experiences, evaluate potential synergies, and reflect on policy implications. The presentations and panel discussions included payers, industry manufacturers, academics and policymakers from Italy, Poland, the UK, Sweden, Netherlands, Novartis and the OECD. Each country approaches risk-sharing schemes differently, but cross-country observations can be made nonetheless. Country overviews of RSAs have been mentioned in previous reports such as from the ISPOR Task Force and European Commission. This analysis focuses on the nuances between countries and the specific challenges they face, illustrated by several examples.

[2] See HMI document "Taxonomy of Risk-Sharing Arrangements" for more information (http://centres.insead.edu/healthcare-management-initiative/thought-pieces/index.cfm).
[3] Performance-Based Risk Sharing Arrangements – Good Practices for Design, Implementation, and Evaluation: Report of the ISPOR Good Practices for Performance-Based Risk-Sharing Arrangements Task Force, ISPOR Task Force Reports; and Managed Entry Agreements for Pharmaceuticals: The European Experience, European Commission.
[4] For further information on the Summit, please visit: http://www.lse.ac.uk/businessAndConsultancy/LSESummit/riskSharing/home.aspx.

Country-level views and analyses

In the **UK,** risk-sharing schemes are referred to as patient access schemes (PAS). Following the introduction of a pharmaceutical price regulation scheme (PPRS) in 2009, the Department of Health asked NICE to set up a patient access schemes liaison unit (PASLU) to advise on PASs proposed by manufacturers. The multiple sclerosis (MS) drugs risk-sharing scheme, launched prior to 2009 (before the regulatory framework was created) has not only been widely discussed but well documented in numerous subsequent articles. Its aim was to monitor outcomes in a 10-year observational study for a cohort of patients receiving drug treatment. The drugs were priced at market levels, with an agreement to adjust future prices if outcomes turned out to be worse than predicted. While the initial assessment showed that the scheme has yielded several benefits for patients as well the scientific community, it also revealed the clinical and operational complexity of RSAs. Methodological problems around model design, administration costs and logistical delays were observed during the initial analysis of the first two years. It remains to be seen whether the drugs are currently priced at value and whether the uncertainty of the scheme's real-world cost-effectiveness can be resolved[5].

As highlighted by the principal investigator of the risk-sharing scheme, Jackie Palace from Oxford University, the MS scheme raised a number of issues: (i) operational complexity should not be underestimated – patient recruitment began too early before a setup was in place, (ii) while funds were allocated for administration, 'there was no explicit funding for sites', (iii) issues relating to governance. The need for continuous validation of the models and assumptions and 'sustained education' about the scheme in helping keep people informed and interested were among the important lessons learnt. The majority of schemes in the UK are financially based, involving discounts, rebates or dose capping, due to concerns over the administrative burden on the NHS as well as manufacturers. There is currently only one scheme in operation – Velcade (bortezomib) for multiple myeloma – involving an outcomes component.

In **Sweden**, the Dental and Pharmaceutical Benefits Agency (TLV) evaluates cost effectiveness, decides on reimbursement status and sets prices for prescription drugs used in outpatient settings. In cases where drugs are granted conditional reimbursement, manufacturers may be asked to collect additional real-world data and to

[5] For further details on the study design and analyses, see BMJ articles, Multiple Sclerosis Risk Sharing Scheme: Two Year Results of a Clinical Cohort Study with Historical Comparator, http://www.ncbi.nlm.nih.gov/pubmed/19955128; and UK Multiple Sclerosis Risk-sharing Scheme: A New Natural History Dataset and an Improved Markov Model, http://bmjopen.bmj.com/content/4/1/e004073.full.

resubmit the cost-effectiveness model for evaluation by the TLV. Sweden appears to have engaged in 15 RSAs as of November 2011, with all involving CED rather than financial agreements. Over the years there has been a reduction in the number of schemes requiring 'non-interventional study' or additional data, implying an overall shift toward less complex agreements. Conditional reimbursement can depend on a number of parameters, including the number of patients using the product, sales volume, treatment duration and dosage, patient characteristics, and presentation of evidence of effect from randomized controlled trials (RCTs), as well as new health economic models, evidence of effect and non-interventional study. The first appear to be easily derived from the existing prescription registry, while the latter two are considered more difficult to obtain and interpret.

The example of a DPP4 inhibitor,[6] Januvia (sitagliptin), highlighted another unique set of issues that may emerge from RSAs. As a first-in-class drug, there was a high level of uncertainty concerning its long-term effects, but Januvia was granted general reimbursement conditional (on evidence development) that the manufacturer provide additional data – the number of patients with hypoglycemias per annum, time-to-treatment with insulin compared to other treatments, and quality of life (QoL) data from a Swedish setting – within three years. The manufacturer's report was based on a systematic review and a cross-sectional study with EQ-5D (an instrument used to measure health outcomes) of Swedish patients, but both components were found to have problems. The systematic review revealed that the hypoglycemia was defined differently in different studies, and that the manufacturer used the definition of mild hypoglycemia from one source and the cost of treating mild hypoglycemia from another, leading to the underestimation of the cost/QALY (Quality-adjusted life year)[7] value for Januvia. In addition, while the quality data showed a correlation between hypoglycemia and QoL, methodological problems made it difficult to draw firm conclusions about the nature of this relationship. Questions about Januvia's cost-effectiveness remain unanswered and a reassessment by TLV is currently underway. Sweden's experience with RSAs reveals that CED schemes may enable patient access, but TLV must still find efficient ways of dealing with products with uncertainties or lacking evidence.

[6] Dipeptidyl peptidase-4 or DPP-4 inhibitors are a class of medicine used to increase the level of insulin for the treatment of type 2 diabetes.
[7] QALY is a measure of health status used to assign a value to health outcomes in cost-effectiveness analyses. It accounts for the quality as well as quantity (years) of life lived. For more information, see http://onlinelibrary.wiley.com/doi/10.1111/j.1524-4733.2009.00515.x/full.

In **Italy**, when drug reimbursement is granted on a conditional basis, the arrangement can take one of many MEA forms, including RSAs, cost sharing, budget caps, price-volume agreements (PVAs), payment by results, and monitoring registries in order to manage uncertainty around utilization and cost-effectiveness. Italy relies on its drug registries, which are among the most advanced in the EU, for implementing MEAs. These are designed to track patient eligibility for drugs and treatment pathways in order to evaluate real-world effectiveness, gather epidemiological data as well as information for a safety profile, and collect information that may have been overlooked in the initial evaluation. Most importantly, they enable the Italian Medicines Agency (AIFA) to monitor appropriateness of use according to approved indications. The data is owned by AIFA, while maintenance fees are subsidized by manufacturers. Registries cover a number of disease areas including anti-diabetics, oncology drugs, orphan drugs, and ophthalmic medicines, to name a few. According to the ISPOR Task Force report, monitoring registries are used for 78 therapeutic indications, or 66 active compounds; 28 are part of a conditional reimbursement scheme such as cost sharing, risk-sharing or payment by results, though all include an outcomes component whereby efficacy is monitored and treatment is dependent on a positive response to the drug. In parallel, Italy has implemented another initiative, known as the 'Regional Dashboard' (CIRR), allowing for analyses and interpretation of data collected across registries, regional customization, and comparisons to national benchmarks. Key conclusions to emerge from the Italian experience focus on the need for collaboration and communication between the various stakeholders, collective involvement in the design of clinical trials, and the harmonization of clinical trial procedures.

In **The Netherlands**, the Health Insurance Board (CVZ) advises the ministry of health on drug reimbursement decisions. From 2006 to 2011, coverage with evidence development schemes was applied only to high-cost and orphan drugs in hospital settings. These were granted temporary coverage for four years conditional on clinical effectiveness data being collected; if the drug was cost-effective it continued to receive funding. Caroline van der Meijden from CVZ, acknowledged that their initial results and experience were 'not very positive', and that the scheme was 'more coverage than evidence development'. Although real-world data was collected for 14 drugs, the results did not provide additional information regarding therapeutic benefit, nor did they help with health economic evaluations. CED schemes posed challenges for the Dutch system as a result of inconsistency in methods for data collection, missing data, small sample

sizes of patients, problems in measuring QoL, and difficulties in ceasing reimbursement of drugs at the end of four years (if they showed no benefit). Successful implementation, according to CVZ, will depend on simpler schemes which impose less of an administrative burden, the creation of indication-based registries (which can be used for comparator data when new drugs are launched), and a continued focus on the cost/QALY value as an ROI measure in patients. As far as future plans for the Dutch healthcare system are concerned, they will continue to engage in further MEAs, beyond CED, to include performance- and financial-based agreements.

In **Poland**, a new reimbursement law implemented in 2012 provides the legal framework for implementing RSAs. Prior to this, most arrangements were non-binding 'gentlemen's agreements'. Information on the number and nature of risk-sharing agreements is kept confidential, but it would appear that approximately 200 agreements may be in place, though different dosages of the same therapy count as separate schemes, so there is potential for over-estimation. The vast majority of the current schemes are financially-based – they involve simple discounts to make products available at lower cost. The introduction of outcomes-based schemes depends on the MOH's confidence in monitoring treatment, as registries are currently maintained by private institutions and NGOs; a lack of trust in outcomes data provided by private and NGOs firms is of primary concern to the MOH. In addition, the registry data is not shared with public entities. Other elements to support RSAs, such as 'e-prescribing' and 'e-registries', are a work-in-progress due to issues of compatibility and operability with outcomes-based schemes.

An Industry Perspective

Novartis, which has implemented a number of risk-sharing schemes (i.e. Lucentis in the U.S. and Xolair in France), supports pragmatic schemes to manage issues of access but insists that the burden of additional data collection be closely evaluated against the value generated from further evidence. Given the challenges associated with evidence collection, simple discount schemes are increasingly popular, particularly in the UK. Christophe Carbonal, Head of Market Pricing at Novartis, argued such schemes also enable patient access, and that the cost of collecting information may outweigh the value of the information obtained.

The issue of confidentially is a concern. In order for manufacturers to successfully engage in RSAs, a level of confidentiality must be accepted among stakeholders. (For

example, the Japanese national health authorities cannot ask for information on ongoing RSA schemes in other countries). It is felt that there is value to generating additional information and that complex schemes can be pursued so long as they are considered in the wider context of other programmes. The European Federation of Pharmaceutical Industries and Associations (EFPIA), for example, has identified a need to explore ways in which registries and data collection mechanisms at the national and European levels can be leveraged in Europe.

Summary

While countries employ different forms of RSAs to achieve different goals, a number of cross-country trends are worth noting. In addition to issues of uncertainty in cost-effectiveness and access to medicines, countries engage in RSAs to obtain discounts on drugs. In fact, simple discount schemes are more prevalent than schemes requiring data collection. Most policymakers, however, argue that if RSAs are designed and implemented meticulously, they can be of significant value to payers, manufacturers and patients. Real-world data is often collected through registries or observational studies, i.e. non-interventional study, but clearly some countries (e.g. Italy) are more advanced in their efforts to develop and manage registries than others. Italy's indication-based registries appear to successfully help track data for the purposes of post-launch evaluations and analyses, and other European countries such as the Netherlands are evaluating the use of registries at the national level.

While it has been extensively documented that evidence development requires significant resources – financial and otherwise – it appears that most of these countries are engaged in MEAs, and will continue to be so for the foreseeable future.