How Risky Is That Risk Sharing Agreement? Mean-Variance Tradeoffs and Unintended Consequences of Six Common Risk Sharing Agreements

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Abstract

Background. Pharmaceutical risk sharing agreements (RSAs) are commonly used to manage uncertainties in costs and/or clinical benefits when new drugs are added to a formulary. However, existing mathematical models of RSAs ignore the impact of RSAs on clinical and financial risk. Methods. We develop a model in which the number of patients, total drug consumption per patient, and incremental health benefits per patient are uncertain at the time of the introduction of a new drug. We use the model to evaluate the impact of six common RSAs on total drug costs and total net monetary benefit (NMB). Results. We show that, relative to not having an RSA in place, each RSA reduces expected total drug costs and increases expected total NMB. Each RSA also improves two measures of risk by reducing the probability that total drug costs exceed any threshold and reducing the probability of obtaining negative NMB. However, the effects on variance in both NMB and total drug costs are mixed. In some cases, relative to not having an RSA in place, implementing an RSA can increase variability in total drug costs or total NMB. We also show that, for some RSAs, when their parameters are adjusted so that they have the same impact on expected total drug cost, they can be rank-ordered in terms of their impact on variance in drug costs. Conclusions. Although all RSAs reduce expected total drug costs and increase expected total NMB, some RSAs may actually have the undesirable effect of increasing risk. Payers and formulary managers should be aware of these mean-variance tradeoffs and the potentially unintended results of RSAs when designing and negotiating RSAs.

Keywords

compound distribution, formulary, managed entry agreement, mean-variance tradeoff, patient access scheme, portfolio risk, price-volume agreement, risk sharing agreement

Introduction

Several contracts between payers and drug manufacturers have emerged in efforts to manage the costs and/or uncertainties associated with introducing new drugs to formularies.1-4 These contracts are used in several countries.3-10 The contractual mechanisms include simple price reductions, price-volume agreements, and complex value-based schemes, as well as contracts involving dose caps or trial periods. There is a broad terminology used to discuss these contracts including risk sharing agreements, product listing agreements, patient access schemes, value-based pricing, outcomes-based contracting, managed entry agreements, and risk sharing agreements, with terminology varying by the structure of the agreements (e.g., financial v. outcomes-based contracts) and geography. Although terminology varies, we use the term “risk sharing agreement” (RSA), consistent with recent literature.1

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Despite the widespread use of RSAs, one study of RSAs in the United Kingdom found that “there was no consensus over which of the schemes was best,” and a survey of RSAs used in Asian countries “did not identify which strategies are most effective in promoting cost containment and/or greater access.” The large number of RSAs in existence, along with the variations in their structure and use, lead to questions about the relative advantages of each type. In particular, it would be useful for payers and formulary managers to know whether there are situations that call for the use of one type of RSA instead of another, and what tradeoffs are involved in choosing each contract. However, there are very few empirical studies that demonstrate the impact of RSAs. There are practical challenges to conducting empirical research in this area as specific contract details are often confidential, and there is typically only one agreement in place in any jurisdiction for a specific drug/payer combination, which limits the ability to conduct direct comparisons. We are not aware of any empirical studies that involve direct comparisons of RSAs.

The literature contains several mathematical models of RSAs. Two simulation models were used to estimate the impact of RSAs in which the manufacturer of a biologic used in the treatment of rheumatoid arthritis would rebate the payer for the cost of first-line treatment for patients who discontinued treatment within 3 months of treatment initiation. Three studies investigate the impact of price-volume agreements and outcomes-based RSAs on the incentives of either the manufacturer or the payer. Mahjoub et al. investigated the impact of the time to evaluate clinical response on a manufacturer’s profit in an outcomes-based RSA. Zaric and O’Brien investigated whether implementing a price-volume agreement leads to more accurate budget impact forecasts from manufacturers. Gavious et al. investigated a setting where the manufacturer and payer simultaneously provide a volume estimate, and the risk sharing mechanism involves payments from the manufacturer to the payer as well as payment from the payer to the government. There are several game-theoretic models of RSAs. Zhang et al. develop a game-theoretic model to investigate the optimal design of a price-volume agreement when there is asymmetric information about market size, and Levaggi and Pertile investigate value-based pricing in the presence of asymmetric information about the benefit of new drugs.

We are aware of three studies that directly compare different types of RSAs. Zaric and Xie develop two two-period models, one of an outcomes-based RSA and the second of a delisting arrangement. Levaggi compares an uncertain “listing process” with a value-based RSA, and Critchley and Zaric extend Levaggi’s analysis to include promotional effort by the manufacturer.

Prior mathematical models of RSAs do not consider the importance of variability in outcomes—the models described above evaluate expected outcomes of RSAs but do not consider variability. However, tradeoffs between expected return and risk have long been recognized as important in finance and other fields. Thus, in this article we develop a common modeling framework that can be used to compare outcomes for several different types of RSAs when market size, benefit per patient, and cost per patient are all uncertain. We use the model to evaluate the impact of six different RSAs on the mean and variance of total drug costs, the mean and variance of net monetary benefits (NMB), the probability that drug costs exceed an arbitrary threshold, and the probability of negative NMB. These results are important to several entities directly involved in or effected by formulary decisions and RSA negotiations, including payers, formulary managers, and manufacturers.

From a technical standpoint, our model has two novel features. First, our model makes use of compound random variables, which are often used to model total claim size in insurance and risk analysis applications, but to our knowledge, have not previously been used to examine the impact of RSAs. Second, our model explicitly considers risk and variability in RSA outcomes and thus addresses an important gap in the literature.

**Modeling Risk Sharing Agreements**

In this section, we introduce a model of spending and health benefits following the introduction of the new drug. We introduce six special cases of the model, which allow us to evaluate drug spending and NMB under commonly used RSAs. Notation is summarized in Table 1. Let $E[\cdot]$ and $Var[\cdot]$ denote the mean and variance of a random variable.
At the time that a new drug is introduced to a formulary the number of patients and the amount of drug consumed per person are unknown. Let $N \sim \text{Binomial}(n, p)$ be a random variable representing the number of patients who will use the new drug, with $E[N] = \mu_N$ and $\text{Var}[N] = \sigma^2_N$. Let $D_i \sim \text{i.i.d.}$ random variables representing the units of drug consumed by person $i$ if there was no RSA in place, $i = 1, \ldots, N$. This amount is based on clinical guidelines but still varies throughout the population for several reasons: dosing guidelines may be based on factors that vary throughout the population leading to variation in consumption; some patients may experience toxicity or intolerance, leading to discontinuation; some patients may experience clinical success and remain on the drug for a very long time; and real-world prescribing practice may deviate from clinical guidelines. Let $p$ be the price of the drug per unit. Let $B_i$ be i.i.d. random variables representing the incremental health benefits per person using the drug, and let $C_i$ be i.i.d. random variables representing the incremental cost per person not including drug costs ("nondrug costs"). $i = 1, \ldots, N$. Nondrug costs include items like costs to administer treatment, costs of managing adverse events, and potential costs avoided if the drug prevents the need for other treatments (e.g., readmissions). Let $\mu_B$, $\mu_C$, and $\mu_D$ be the means of $B_i$, $C_i$, and $D_i$, respectively, and let $\sigma^2_B$, $\sigma^2_C$, and $\sigma^2_D$ be the variances of $B_i$, $C_i$, and $D_i$, respectively. Let $r_{jk}, j, k \in \{B, C, D\}$, be the pairwise correlations between the benefit, nondrug cost and drug cost for all individuals (i.e., $r_{BD} = r_{DB}$ is the correlation between health benefit and drug consumption).

Let $TD$ be the total cost of the new drug paid for by the payer if there is no RSA in place, and let $TB$ and $TC$ be the total incremental benefits and total incremental nondrug costs, respectively, among all individuals who receive the new drug. These quantities are defined using compound random variables $^{34,35}$ as

\[
    TD = p \sum_{i=1}^{N} D_i, \\
    TB = \sum_{i=1}^{N} B_i, \quad \text{and} \quad TC = \sum_{i=1}^{N} C_i. 
\]

Let $\lambda$ be the payer’s willingness to pay (WTP) for health benefits, and let $\text{NMB}$ be the net monetary benefit from the new drug, $^{36}$ given by

\[
    \text{NMB} = \sum_{i=1}^{N} (\lambda B_i - C_i - pD_i) = \lambda TB - TC - TD. 
\]
We use this framework to model costs, benefits, and NMB for two reasons:

1. This framework allows us to model uncertainty in the size of the patient population for a new drug; the drug consumption per person; and the actual benefits experienced per person. Uncertainty in these quantities has been noted among the reasons for implementing RSAs\(^{37-39}\) or implied by the structure of some RSA contracts (e.g., uncertainty in clinical success for bortezomib\(^{40}\)). In addition, this allows us to represent total drug cost \(TD\) and NMB as random variables.

2. It provides a common, flexible method to estimate the impact of RSAs in which differences in outcomes between RSA contracts are due to contract parameters rather than realizations of random variables.

We model six different RSAs. Examples of each are described elsewhere.\(^{4}\)

- **Price reduction:** There is a price reduction of \(s\) so that the drug price is reduced from \(p\) to \((1 - s)p\), \(0 \leq s \leq 1\). This changes the total drug cost to \(TD' = (1 - s)TD\).

- **First doses free:** There is no payment for the first \(u\) doses for each patient after which the payer pays the full price for the drug. The number of doses paid for by the payer for individual \(i\) becomes

\[
D'_i = \begin{cases} 
0 & D_i \leq u \\
D_i - u & D_i > u = \max\{D_i - u, 0\}
\end{cases}
\]

and the total drug cost becomes \(TD'_i = p \sum_{i=1}^{N} D'_i\).

- **Last doses free:** The payer pays the full price for the first \(v\) doses, and there is no payment for any doses beyond the \(v\)th dose for each patient. The number of doses paid for by the payer for individual \(i\) becomes

\[
D'_i = \begin{cases} 
D_i & D_i \leq v \\
v & D_i > v = \min\{D_i, v\}
\end{cases}
\]

and the total drug cost becomes \(TD'_i = p \sum_{i=1}^{N} D'_i\).

- **Clinical threshold RSA:** If the benefit for a patient is less than a threshold \(t \geq 0\) then the payer does not pay for the drug; otherwise the payer pays the full price. Let \(I_{B_i \geq t}\) be an indicator variable that indicates whether clinical success was achieved, defined as

\[
I_{B_i \geq t} = \begin{cases} 
1 & B_i \geq t \\
0 & \text{otherwise}
\end{cases}
\]

and let \(\phi = E[I_{B_i \geq t}]\) be the probability of clinical success.

The total drug cost becomes \(TD'' = p \sum_{i=1}^{N} D_i I_{B_i \geq t}\).

- **Price-volume agreement (PVA):** If total drug sales volume exceeds a rebate level \(L, L \geq 0\), then there is a rebate at rate \(\alpha\) on all excess units, \(0 \leq \alpha \leq 1\). If total drug sales are below the rebate level \(L\), then there is no rebate. This changes the total drug cost to

\[
TD'^{pva} = \begin{cases} 
TD & \text{if } \sum_{i=1}^{N} D_i \leq L \\
p \left[ \sum_{i=1}^{N} D_i - \alpha \left( \sum_{i=1}^{N} D_i - L \right) \right] & \text{if } \sum_{i=1}^{N} D_i > L
\end{cases}
\]

This can be rewritten as \(TD'^{pva} = TD - Rpva\) where \(Rpva = \max\{\alpha p \left( \sum_{i=1}^{N} D_i - L \right), 0\}\).

- **Cost-effectiveness RSA:** If \(NMB < 0\), then the manufacturer pays a rebate which ensures that the NMB is never negative. Let \(R^{ce} = \max\{-NMB, 0\}\) be the rebate, which results in \(TD'^{ce} = TD - R^{ce}\) and \(NMB^{ce} = \max\{NMB, 0\}\).

In each case, \(NMB\) is calculated by substituting the appropriate expression for \(TD\) into (1). For example, \(NMB^{ce} = \lambda TB - TC - TD'^{ce}\). In the remainder of the article we refer to the first three RSAs as “simple RSAs,” and we refer to \(s, u, v, \phi, \alpha\), and \(L\) as “RSA parameters.”

We analyze the performance of each RSA with respect to six outcomes: expected total drug cost; variance in total drug costs; probability that total drug costs exceed any given threshold; expected NMB; variance in NMB; and probability that NMB is positive.

Before analyzing the impact of these RSAs we formally state five assumptions:

**Assumption 1:** \(E[TB] \geq E[TC]\).

**Assumption 2:** Conditional on receiving formulary listing, none of the RSAs defined above has an impact on the distribution of \(N\).

**Assumption 3:** None of the RSAs defined above has an impact on the distributions of \(B, C,\) or \(D\).

**Assumption 4:** All else equal, formulary managers prefer contracts that result in lower expected costs and lower variability in outcomes.
Assumption 5: The distributions of $B$, $C$, and $D$ are continuous and differentiable everywhere.

Assumption 1 means that we only consider drugs that would be cost-effective if they were free. If this were not true, then there is no way that the drug could be made cost-effective through any of the RSA contracts examined in this article. Assumption 2 states that the RSA mechanism does not have an impact on the number of individuals who use the drug. This is reasonable if the drug treats a limited and very clearly defined condition, or if there are no competitors. We relax this assumption in a later section where we investigate whether RSAs change the incentives for promotion. Assumption 3 states that the RSA mechanism does not have any impact on the distributions of the incremental benefit of the drug, the nondrug costs among individuals who use the drug, and the amount of drug consumer per person. This is reasonable if dosing and drug usage guidelines are exogenous and based on clinical guidelines and not affected by the existence of an RSA. Assumption 4 is consistent with discussions of mean-variance tradeoffs in finance, and the results from a survey of payer and manufacturer representatives from the United States and the European Union. Assumption 5 is made to simplify the formal proofs.

Impact of RSAs on Drug Costs and Total Net Monetary Benefits

In this section, we examine the impact of each of the six RSAs defined in the previous section.

Mean, Variance, and Distribution of Total Drug Costs

We first analyze the impact of the RSAs on total drug cost. We focus on mean and variance of total drug costs because two objectives of RSAs are reduced costs and reduced uncertainty in costs. In Proposition 1, we state the impact of each RSA on drug costs compared to a scenario with no RSA in place. All formal proposition statements and proofs are shown in the supplemental appendix.

Proposition 1: Relative to having no RSA in place,

i. The expected total drug cost is reduced by each RSA.

ii. Variance in total drug costs may increase or decrease using a cost-effectiveness RSA or a clinical threshold RSA. For all other RSAs the variance in total drug costs is reduced.

iii. The probability that drug costs exceed any given threshold is reduced by each RSA.

The three properties discussed in Proposition 1 are desirable to payers and formulary managers in that they can help reduce costs (part i), make costs more predictable (part ii), and reduce the likelihood of exceeding a fixed budget (part iii). Conditional on a drug being listed, all six RSAs reduce total expected drug costs and reduce the probability that drug costs exceed some threshold. Of note, the price-reduction RSA, which should be the simplest to implement, leads to both a reduction in drug costs and a reduction in the variability in drug costs relative to not having an RSA in place.

A potentially unexpected result in Proposition 1 is that variance in drug costs may actually increase when using a cost-effectiveness RSA or a clinical threshold RSA. In both cases this happens because the variance in costs depends on other random variables. In the case of a cost-effectiveness RSA, the variance in total drug costs also depends on the health benefits, non-drug costs, and the WTP threshold, all of which contribute to total drug cost through the rebate term. For the intuition, consider the case when $C_i = 0$ (i.e., no non-drug costs; Appendix Figure A1). If the probability of a rebate is very low, then $\text{Var}[TD^{ce}] \approx \text{Var}[TD]$, but if there is a high probability of a rebate then $\text{Var}[TD^{ce}] \approx \text{Var}[\lambda TB] = \lambda^2 \text{Var}[TB]$, which may exceed $\text{Var}[TD]$. For a clinical threshold RSA we can show, for the special case of no correlation between $D_i$ and $B_i$, that the RSA can lead to an increase in variability in total drug costs when the following conditions are all true: there is little uncertainty in the number of patients; little uncertainty in the drug volume consumed per patient; and a high probability of clinical success (shown in the appendix and discussed further in the examples section). Conversely, when $\sigma^2_D > \mu_\lambda$ then the clinical threshold RSA reduces variance in total drug costs relative to not having an RSA in place.

In Proposition 2, we state that there can be multiple ways to structure RSAs to have the same expected costs.

Proposition 2: Equivalence of RSAs.

i. RSA parameter values can always be found such that a price reduction, first doses free, last doses free, clinical threshold, and PVA have the same expected total drug costs.

ii. If the expected total drug cost in a cost-effectiveness RSA is positive, then RSA parameter values can be
found to set the expected total drug costs equal to any of the other RSAs.

This result is important for two reasons. First, it allows a formulary manager who is only interested in the expected total drug costs the flexibility to choose any of the six RSAs studied in this paper and achieve equivalent results. Second, it allows for “fair” comparisons between RSAs when there are multiple objectives (such as the mean and variance in total drug costs). If Proposition 2 did not hold, then comparisons among RSAs would need to consider the preferences of decision makers over multiple outcomes (e.g., by specifying a utility function). Thus, Proposition 2 is the basis to interpret the next result.

In Proposition 3, we formally state that some RSAs with equivalent expected total drug costs can be rank-ordered in terms of their effect on variance in drug costs.

**Proposition 3: Rank-ordered variance in total drug costs.**

Suppose that RSA parameters have been chosen so that the expected total drug costs are the same with a price reduction, first doses free, last doses free, and clinical threshold RSA. Then the variance in total drug costs can be ranked. In particular, a last doses free RSA always has the lowest variance in total drug costs, and a price reduction RSA always has the second lowest variance in total drug costs. If drug consumption per person and incremental benefits obtained per person are independent, then a clinical threshold RSA has the highest variance in total drug costs in this group.

Proposition 3 says that when $D_i$ and $B_i$ are independent (i.e., $r_{BD} = 0$), then variance in total drug costs can be ranked for all four RSAs as follows:

$$
Var[TD^c] \geq Var[TD^f] \geq Var[TD^r] \geq Var[TD^l].
$$

(2)

When $D_i$ and $B_i$ are not independent then only the two rightmost inequalities hold. Since the clinical threshold RSA and the three simple RSAs all have only one parameter it is not surprising that they have different variances in total drug costs when these parameters are chosen so that they are equivalent in a different outcome (expected total drug costs in this case). However, it may be surprising that for any choice of parameters resulting in equivalent expected total drug costs, the variance in drug costs can be ranked, and the ranking is always the same.

This ranking in variance should be important to payers and formulary managers because two objectives of RSAs are reduced costs and reduced uncertainty in costs—consistent with Assumption 4 and portfolio theory. If these are the only two criteria that formulary managers care about, then there is no reason to choose a RSA with relatively high variance in total drug costs rather than an RSA with relatively lower variance in total drug costs. A formulary manager who chose a high-variability option would need to have criteria other than total expected drug costs and variability in total drug costs. For example, the ranking in (2) suggests that a last doses free RSA dominates a price reduction RSA in terms of the impact on expected costs and variability in costs. However, ease of implementation might justify a preference for a price reduction over a last doses free RSA.

**Mean, Variance, and Distribution of NMB**

In this section, we analyze the impact of the six RSAs on NMB. The results mirror those presented in the previous section. In Proposition 4, we state the impact of each RSA on NMB compared to a scenario with no RSA in place. These results may be of interest in settings where cost-effectiveness is formally considered as part of the formulary approval process (e.g., public drug plans in Canada).

**Proposition 4:** Relative to having no RSA in place,

i. The expected NMB increases under each RSA.

ii. The variance in NMB is reduced for a cost-effectiveness RSA, and may increase or decrease for all other types of RSAs.

iii. Each RSA reduces the probability of experiencing negative NMB.

As with expected costs, all six RSAs have two desired effects on NMB: they all lead to an increase in expected NMB and they all reduce the probability of experiencing negative NMB. As in Proposition 1, there is a counterintuitive result regarding variability in NMB. For five of the six RSAs considered, implementing an RSA can increase the variability in NMB relative to not having an RSA in place. Thus, an RSA that reduces costs and reduces uncertainty in costs can increase uncertainty in NMB.

In Proposition 5, we formally state that RSA parameters can always be found so that the RSAs have equivalent expected NMB, and in Proposition 6, we state that the variance in NMB can be ranked for some RSAs.
Table 2  Base Case Parameter Estimates for Numerical Examples\textsuperscript{a}

| Parameter                                                                 | Value                  | Source                                  |
|--------------------------------------------------------------------------|------------------------|-----------------------------------------|
| Payer willingness to pay per QALY gained                                 | 50,000                 | Assumed                                 |
| Drug price per day                                                       | 375                    | Pan-Canadian Oncology Drug Review\textsuperscript{53} |
| Population size ($N$)                                                    | Gamma distributed      | Distribution assumed; parameters derived from Borg et al.\textsuperscript{54} |
| Drug use per person ($D_i$)                                               | a = 19.926 b = 6.399   | Distribution assumed; parameters derived from Borg et al.\textsuperscript{54} |
| Incremental health benefit per person ($B_i$)                           | Normal distribution    | Distribution assumed; parameters derived from Borg et al.\textsuperscript{54} |
| Incremental nondrug cost per person ($C_i$)                             | Normal distribution    | Distribution assumed; parameters derived from Borg et al.\textsuperscript{54} |
| Correlations between variables                                          | $\rho_{BC} = 0$        | Assumed; varied in sensitivity analysis |
| Expected units sold                                                      | $Q = 12,751$           | Derived from equation (A2)              |
| Distribution of total drug costs in the absence of an RSA               | $E[TD] = 4,781,672$    | Derived from equations (A2) and (A3) using the parameters above |
| Distribution of NMB in the absence of an RSA                            | $E[NMB] = -1,824,874$  | Calculated                              |
| Distribution of NMB in the absence of an RSA                            | $SD[NMB] = 248,430$    | Calculated                              |

NMB, net monetary benefit; QALY, quality-adjusted life year; RSA, risk sharing agreement.

\textsuperscript{a}Parameter values of D, B, and C are the result of several intermediate calculations. Rounded values are shown in the table.

**Proposition 5:** Equivalence of RSAs.

RSA parameter values can always be found so that the expected NMB is the same for any pair of RSA contracts among those studied in this paper.

**Proposition 6:** Rank-ordered variance in total NMB.

Suppose that RSA parameters are such that the expected NMB is the same using a price reduction, first doses free or last doses free RSA. If the drug cost per person is independent of the health benefits and the nondrug costs per person, then the variance in total drug costs can be ranked. In particular, a last doses free RSA has the lowest variance in NMB, a price reduction has the second lowest variance, and a first doses free RSA has the greatest variance.

Mathematically, the result of Proposition 6 is

$$\text{Var}[NMB^f] \geq \text{Var}[NMB^p] \geq \text{Var}[NMB^l].$$  \hspace{1cm} (3)

The implications of Proposition 6 are similar to Proposition 3: If a formulary manager cares about expected NMB and variability in NMB, then it is unclear why they would choose an RSA that results in high variability in NMB (i.e., a first doses free RSA) when they could choose one that results in the same expected NMB and lower variability in NMB. As is the case with total drug costs, the last doses free RSA dominates the price reduction RSA, but ease of implementation may justify a preference for a price reduction RSA. We note that the ordering of the first doses free, last doses free, and price reduction is the same for total drug costs (2) as it is for NMB (3). Thus, a decision maker who is only considering these three RSAs and who is only concerned with the mean and variance of total drug costs and NMB should always weakly prefer a price reduction RSA versus a first doses free RSA, and should always weakly prefer a last doses free RSA versus a price reduction RSA.

**Examples**

We illustrate with several examples. Our base case parameters (Table 2) are based on introducing pomalidomide plus dexamethasone for the treatment of relapsed and/or refractory multiple myeloma\textsuperscript{41} to a small patient population, such as a Canadian province. Multiple myeloma represents approximately 1.5% of all new cancer cases in Canada.\textsuperscript{42} In 2020, there are expected to be 3400 total
new cases in Canada, and in 2017 there were approximately 1210 cases in Canada’s largest province. As there are multiple treatments for this indication, it is not expected that all patients would receive pomalidomide. The examples are intended to be illustrative: the objective of this section is to highlight the differences among the RSAs and to illustrate the results of the previous sections, not to make a specific prediction. We use the standard deviation as the measure of variability in our examples so that variability is expressed in the same units as the mean. Let $SD_{TD}$ and $SD_{NMB}$ refer to the standard deviation in $TD$ and $NMB$, respectively. Let $Q = \mu_D \mu_N$ be the expected drug volume.

Figure 1a shows the values of $u$ and $v$ in a first doses free and last doses free RSA, respectively, that are required to achieve any price reduction. The figure shows that, as stated in Proposition 2, any price reduction can be achieved by either of these RSAs through appropriate choice of parameters. For example, giving the first 50 units of the drug for free results in the same expected total drug costs as a price reduction of approximately 40%; giving the drug for free after consumption of 150 units results in the same expected total drug costs as a price reduction of approximately 5%. Figure 1b shows, for three different PVA threshold levels, the values of the PVA rebate rate required to achieve a given price reduction. For a PVA to achieve the same expected total drug cost as a price reduction RSA with a price reductions of more than 50% (i.e., $s \geq 0.5$), the PVA would require rebate rates greater than 100% and/or rebate levels lower than half the expected total sales volume.

Proposition 5 states that we can find RSA parameter values to yield the same expected total NMB. In Table 3, we show combinations of parameters required to achieve $E[NMB] = 0$ for different combinations of the drug price and willingness to pay. For each case where the drug would not be cost-effective, the RSA parameters are set so that the expected cost of the drug is reduced enough to make the drug cost-effective with the given RSA. These examples demonstrate that RSAs can be made equivalent through careful selection of parameters and that there are multiple methods of achieving any given objective.

In the previous sections, we stated that the impact of the RSA contracts on variability in total drug cost and NMB could be mixed. In the remaining examples, we illustrate this finding by examining the ratio of the standard deviation in a given outcome (total drug cost or NMB) when an RSA is in place to the standard deviation when an RSA is not in place. Let $f_{TD}^k = SD[TD]/SD[TD]$ be the ratio of the standard deviation in total drug costs with RSA $k$ to the standard deviation in total drug costs when there is no RSA in place. If the ratio $f_{TD}^k < 1$ then the RSA has reduced variability in total drug costs; if $f_{TD}^k > 1$ then the RSA has increased variability in total drug costs.
Table 3 RSA Parameters to Achieve $E[NMB] = 0$ for Different Values of Price ($p$) and WTP ($\lambda$)\(^a\)

| $\lambda$ | p = 375 | p = 500 | p = 1000 |
|-----------|---------|---------|----------|
| 20,000    | price reduction | $s = 0.843$ | $s = 0.882$ | $s = 0.941$ |
|           | first doses free | $u = 112.4$ | $u = 120.4$ | $u = 136.9$ |
|           | last doses free | $v = 20.0$ | $v = 15.0$ | $v = 7.5$ |
|           | PVA ($\alpha = 100\%$) | $L = 2004$ | $L = 1503$ | $L = 751$ |
| 50,000    | price reduction | $s = 0.382$ | $s = 0.536$ | $s = 0.768$ |
|           | first doses free | $u = 48.6$ | $u = 68.4$ | $u = 99.9$ |
|           | last doses free | $v = 79.1$ | $v = 59.1$ | $v = 29.6$ |
|           | PVA ($\alpha = 100\%$) | $L = 7884$ | $L = 5914$ | $L = 2957$ |
| 75,000    | price reduction | No RSA needed$^b$ | $s = 0.248$ | $s = 0.624$ |
|           | first doses free | $u = 31.6$ | $u = 79.8$ | $u = 99.9$ |
|           | last doses free | $v = 97.5$ | $v = 47.9$ | $v = 29.6$ |
|           | PVA ($\alpha = 100\%$) | $L = 9591$ | $L = 4795$ | $L = 2495$ |
| 100,000   | price reduction | No RSA needed | No RSA needed | $s = 0.480$ |
|           | first doses free | $u = 61.2$ | $u = 66.4$ | $u = 99.9$ |
|           | last doses free | $v = 66.4$ | $v = 47.9$ | $v = 29.6$ |
|           | PVA ($\alpha = 100\%$) | $L = 6632$ | $L = 2495$ | $L = 10320$ |
| 150,000   | price reduction | No RSA needed | No RSA needed | $s = 0.192$ |
|           | first doses free | $u = 24.4$ | $u = 106.4$ | $u = 136.9$ |
|           | last doses free | $v = 106.4$ | $v = 47.9$ | $v = 29.6$ |
|           | PVA ($\alpha = 100\%$) | $L = 10320$ | $L = 4795$ | $L = 2495$ |

RSA, risk sharing agreement; WTP, willingness to pay.

\(^a\)For each case where the drug would not be cost-effective, the RSA parameters are set so that the expected cost of the drug is reduced enough to make the drug cost-effective with the given RSA.

\(^b\)"No RSA Needed" is indicated if $E[NMB] \geq 0$ for the specific combination of price and WTP.

Figure 2 (a) $f_{TD}^k$ for price reduction, first doses free, last doses free, clinical threshold, and cost-effectiveness RSA as a function of the price reduction ($s$). Parameters of the first doses free, last doses free, and clinical threshold RSAs are adjusted so that they all have the same expected total drug costs as a price reduction RSA for each level of price reduction. (b) $f_{TD}^k$ for a PVA and cost-effectiveness RSA as a function of the rebate rate ($\alpha$). For the PVA, three lines are shown corresponding to rebate levels of $L = 1.1Q$, $L = Q$, and $L = 0.75Q$. 
In Figure 2a, we show $f_{TD}^k$ as a function of the level of price reduction in a price reduction RSA. To ensure fair comparisons, parameters for a first doses free, last doses free, and clinical threshold RSA are set so that these three RSAs have the same expected total drug cost as a price reduction RSA for any given price reduction (i.e., for any price reduction $s$ shown on the horizontal axis of the graph, parameters $u$, $v$, and $f$ were chosen so that the corresponding RSAs have the same expected total drug costs). For this set of parameters, all RSAs result in a reduction in the standard deviation in total drug costs. The standard deviations in total drug costs are ordered as predicted by Proposition 3. In this example, and others that were explored with different parameterizations, the price reduction, first doses free, and last doses free RSA all had similar performance.

In this example, the cost-effectiveness RSA yields approximately a two thirds reduction in the standard deviation in total drug costs. The line is flat ($f_{TD}^c = 66\%$ everywhere) since there are no parameters to adjust in this RSA. The other RSAs all have $f_{TD}^k > 66\%$ for small price reductions and $f_{TD}^k < 66\%$ for large price reductions. The vertical line shows the magnitude of the price reduction required for a price reduction RSA to be cost effective (i.e., to have NMB = 0). This example shows that the cost-effectiveness RSA can result in a reduction in variability in total drug costs; that the other RSAs can all be constructed so that the new drug is cost-effective on average; and that for large a price reduction, the simple RSAs have lower variability in total drug costs than the cost-effectiveness RSA.

In Figure 2b, we show $f_{TD}^{pre}$ as a function of the rebate rate for three values of the rebate level for a PVA. The figure illustrates the relationship between the rebate rate ($a$) and the rebate level ($L$). If the rebate level is less than the expected drug volume, then a PVA can have a significant impact on the standard deviation in total drug costs, whereas when the rebate level exceeds the expected total sales volume, which would allow for a buffer on expenditures, then a PVA has a more modest effect on variability in total drug costs.

In Proposition 1, we stated that variability in drug costs could increase when using either a clinical threshold RSA or a cost-effectiveness RSA. In Figure 3a, we show $f_{TD}^{ct}$ as a function of the probability of success ($\Phi$) for different levels of the standard deviation in the number of patients $\sigma_N$. For this example only, we relax the assumption that the number of patients follows a Poisson distribution and allow $\sigma_N$ to be different than $\mu_N$. This allows us to isolate the effect of uncertainty in the number of patients. As predicted, for low variability in the number of patients (i.e., low $\sigma_N$) and a high probability of clinical success, $f_{TD}^{ct}$ may exceed 100%, indicating greater variability in total drug costs with a clinical threshold RSA than without an RSA in place. The probability of success at which $f_{TD}^{ct} = 100\%$ (i.e., $\phi_2$ as defined in the proof of Proposition 1 in the appendix) decreases as $\sigma_N$ decreases. For the
lowest value of \( \sigma_N \), the standard deviation of total drug costs with an RSA can be more than twice as large as the standard deviation in total drug costs when there is no RSA in place. Thus, for intermediate levels of clinical success, the clinical threshold RSA may have the unintended consequence of increasing the variability in total drug costs.

In Figure 3b, we show the impact of a cost-effectiveness RSA on variability in total drug costs (i.e., \( f_{CE}^{TD} \)) as a function of the WTP for health benefits for different values of the coefficient of variation in the distribution of health benefits (\( c_B = \sigma_B / \mu_B \)). This example illustrates the interaction between WTP and the coefficient of variation of health benefits on the ratio \( f_{CE}^{TD} \). For low values of WTP, the standard deviation in drug costs is approximately zero since there is almost always a rebate (i.e., at low WTP the drug would rarely be seen as cost-effective), resulting in low effective drug costs and hence low variability in total drug costs. For high WTP, the standard deviation in drug costs is approximately the same as if there were no RSA in place (i.e., \( f_{CE}^{TD} \approx 1 \) for high WTP) since there is almost never a rebate. For intermediate levels of WTP there is sometimes a rebate. By definition of the cost-effectiveness RSA, when a rebate occurs, drug costs are equal to the monetary value of health benefits accrued, and thus variability in drug costs is determined primarily by the health benefits. In this example, the ratio \( f_{CE}^{TD} \) can exceed 1.5 when there is high variability in benefits per person.

We also observe that \( f_{CE}^{TD} \) is increasing in the coefficient of variation in the distribution of health benefits.

We also investigate the impact of each RSA on variability in NMB. Let \( f_k^{NMB} = SD[NMB^k] / SD[NMB] \) be the ratio of the standard deviation of NMB with RSA \( k \) in place to the standard deviation of NMB where there is no RSA in place. Figure 4 illustrates two of the results of Proposition 4. First, both panels show that variability in NMB does not increase when using a cost-effectiveness RSA. Second, both panels illustrate that for the other RSAs it is possible to have a higher standard deviation in NMB with an RSA in place than without (Figure 4a for a price reduction RSA and Figure 4b for a PVA). Other RSAs are not shown as their performance was similar to that of a price reduction.

In additional analyses (not shown) we found that the correlations between drug costs, incremental benefits, and incremental nondrug costs (i.e., the values of \( \rho_{BD}, \rho_{BC}, \) and \( \rho_{DC} \)) did not have an important impact on the performance of the RSAs. These values are likely difficult to measure. Although they may be important in probabilistic sensitivity analysis, our analysis suggests that it is not necessary to know their true values when planning an RSA. Also, in Proposition 3 we stated that \( \text{Var}[TD^r] \geq \text{Var}[TD'] \) when \( D_r \) and \( B_r \) are independent. Although we are only able to algebraically prove this result for that special case, in numerical analyses we are not able to find examples where this is not true.

Figure 4  (a) Ratios \( f_k^{NMB} \) and \( f_{CE}^{NMB} \) as functions of WTP (\( \lambda \)). \( f_{CE}^{NMB} \) is shown for three levels of the price reduction (\( s \)). (b) Ratios \( f_k^{NMB} \) and \( f_{CE}^{NMB} \) as a function of WTP (\( \lambda \)) for different levels of the rebate level relative to total drug volume. For \( f_{CE}^{NMB} \) three lines are shown corresponding to levels of \( L = 0.75Q, L = Q, \) and \( L = 1.1Q \).
Risk Sharing Agreements and Incentives for Promotion

Assumption 2 stated that the RSAs do not have an impact on the distribution of $N$. We relax this assumption and investigate whether, conditional on listing, implementing an RSA changes the incentives to expend promotional effort. Let $m$ be a decision variable representing the amount of money expended to increase $\mu_N$, and let $m^*_k$ be the optimal level of promotional effort by the manufacturer when RSA $k$ is in place, $k \in \{p,f,l,ct,pva,ce\}$.

Proposition 7: If marketing effort can increase the expected total market size then the optimal level of marketing spending by the manufacturer is lower under each RSA than it would be when there is no RSA in place (i.e., $m^*_k \leq m^*_0$, $k \in \{p,f,l,ct,pva,ce\}$).

Corollary 1: When the manufacturer can exert promotional effort to increase market size, the expected number of patients using the new drug and expected total drug spending are lower with an RSA in place than they would be with no RSA in place.

Formally, Proposition 7 states that $m^*_k \leq m^*_0$, $k \in \{p,f,l,ct,pva,ce\}$. This occurs because the RSAs make promotional effort less attractive by reducing the average profit of each unit sold, and as a result promotional spending is reduced. This finding is consistent with Critchley and Zaric\(^{32}\) who found that optimal promotional effort was reduced through various RSAs. It follows that the total market size and expected total drug spending are reduced (Corollary 2). We can also relax the assumption that the existence of the RSA does not change the distribution of $D$. The analysis and results are very similar to the case just presented and is omitted. The case where $m$ can simultaneously increase both $\mu_N$ and $\mu_D$ requires many additional assumptions to derive analytical results and is not considered here.

Discussion and Conclusions

In this article, we develop a model in which the number of patients, the amount of drug consumed by each patient, and the benefits achieved by each patient are not known at the time that a formulary listing decision must be made. We investigate the impact of six common RSAs on drug expenditures and NMB. Our analysis adds to existing literature by explicitly considering the impact that RSAs have on variability in costs and NMB, which, to our knowledge, has not been addressed by previous mathematical models of RSAs. In addition, the model is flexible and could contribute to future analyses of other RSA contracts.

Our analysis yields several insights:

1. All six RSAs considered in this article can reduce expected total drug costs, reduce the probability that total drug costs exceed any threshold, increase expected NMB, and reduce the probability of negative NMB. Thus, a decision maker whose objective is one of these four measures can achieve success with any of the six RSAs studied in this article.

2. Since the parameters of the RSAs can be adjusted so that any pair of RSAs has the same expected NMB, a decision maker whose objective is expected NMB can design RSA contracts in such a way that they should be indifferent between RSAs. Similarly, the parameters of all RSAs except a cost-effectiveness RSA can be adjusted so that they have the same expected total drug costs. Thus, a decision maker whose objective is expected total drug costs can design RSA contracts in such a way that they should be indifferent between those five RSAs.

3. For some RSAs, if they are designed so that they have the same expected performance, then they can be ranked in terms of their impact on variability in these outcomes. This applies to the price reduction, first doses free, and last doses free RSA when considering NMB, and also includes the clinical threshold RSA when considering total drug cost. Decision makers should only consider high-variability contracts if factors other than cost and variability influence their decisions.

4. The cost-effectiveness RSA and the clinical threshold RSA can both increase variability in total drug costs relative to not having an RSA in place, and all RSAs except the cost-effectiveness RSA can increase variability in NMB relative to not having an RSA in place. Decision makers should be aware of this potential unintended consequence when negotiating RSA contracts.

5. The clinical threshold RSA may seem appealing because it promises “pay-for-performance,” in that drug costs are only incurred when clinical success is achieved. However, this RSA can have the unintended consequence of increasing variability in both total drug costs and NMB.

6. None of the RSA contracts analyzed in this article provide an incentive for manufacturers to counteract the RSA by increasing their level of marketing spending.
In a survey of pharmaceutical decision makers in Europe, 85% of respondents indicated that they believed that “innovative agreements” might be preferable to simple price reductions if they could offer a greater reduction in cost or could be better at managing uncertainty. However, there is some evidence to suggest that payers do not fully benefit from more complex RSAs due to administrative burden, and a review of performance-based RSAs in Italy confirmed that the administrative burden of implementing RSAs may be high. Arguments are often made that financial-based RSAs are preferred over other RSAs because they are easier to implement. Our study adds that a simple price reduction is also better at reducing variability in total drug costs and variability in NMB than a clinical threshold RSA and a first doses free RSA, and has mixed results when compared to a PVA or a cost-effectiveness RSA; and that the clinical threshold RSA, cost-effectiveness RSA, and PVA may all have unintended consequences. Thus, new and innovative RSA designs may not be in the best interest of those formulary managers who are trying to manage costs and uncertainty.

This study has limitations. Assumption 3 states that the RSA mechanism does not have any impact on the distributions of the incremental benefit of the drug, the nondrug costs among individuals who use the drug, and the amount of drug consumed per person. This may not hold if a particular RSA is accompanied by efforts to improve adherence. However, the results of Propositions 2, 3, 4, and 6 would still hold as one could find RSA parameters so that the RSA had the same expected total drug cost or expected total NMB. Some authors have argued that price controls may inhibit innovation. This is outside the scope of the current analysis. However, many of the results in this article focus on comparisons between RSAs given the decision to implement one.

There are many promising directions for future research. We assumed that the costs and benefits for each patient were independent of the number of patients. This assumption could be relaxed to allow benefits to vary in the number of patients, which may be reasonable if patients who are less likely to benefit were reached when the total number of patients is large. We investigated a small number of RSA structures. One of the key results of this article is that, in some circumstances, RSAs can be ranked for decision makers who care about the mean and variance in total drug costs and NMB. Future research may consider the use of utility functions to combine outcomes in cases where a ranking is not possible, or in cases where a decision maker is also concerned about other outcomes. The approach taken in this article can be easily adapted to consider more complex arrangements, such as progressively larger discounts in volume, applied at an individual or population level. The approach used in this article can also be extended to include parameter uncertainty.

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**Supplemental Material**

Supplemental material for this article is available on the Medical Decision Making Policy & Practice website at https://journals.sagepub.com/home/mpp.

**References**

1. Antonanzas F, Juárez-Castelló C, Lorente R, Rodríguez-Ibeas R. The use of risk-sharing contracts in healthcare: theoretical and empirical assessments. *Pharmacoconomics*. 2019;39(12):1469–83.
2. Carlson JJ, Gries KK, Yeung K, Sullivan SD, Garrison LP Jr. Current status and trends in performance-based risk-sharing arrangements between healthcare payers and medical product manufacturers. *Appl Health Econ Health Policy*. 2014;12(3):231–8.
3. Ferrario A, Araja D, Bochenek T, et al. The implementation of managed entry agreements in Central and Eastern Europe: findings and implications. *Pharmacoconomics*. 2017;35(12):1271–85.
4. Adamski J, Godman B, Ofierska-Sujkowska G, et al. Risk sharing arrangements for pharmaceuticals: potential considerations and recommendations for European payers. *BMC Health Serv Res*. 2010;10:153.
5. Vergheese NR, Barrenetxea J, Bhargava Y, Agrawal S, Finkelstein EA. Government pharmaceutical pricing strategies in the Asia-Pacific region: an overview. *J Mark Access Health Policy*. 2019;7(1):1601060.
6. Robinson MF, Mihalopoulos C, Merlin T, Roughead E. Characteristics of managed entry agreements in Australia. *Int J Technol Assess Health Care*. 2018;34(1):46–55.
7. National Institute for Health and Care Excellence. Patient access schemes liaison unit [cited July 26, 2016]. Available from: https://www.nice.org.uk/about/what-we-do/patient-access-schemes-liaison-unit/list-of-technologies-with-approved-patient-access-schemes
8. Han E, Park SY, Lee EK. Assessment of the price-volume agreement program in South Korea. *Health Policy*. 2016;120(10):1209–15.
9. Garattini L, Curto A. Performance-based agreements in Italy: “trendy outcomes” or mere illusions? *Pharmacoconomics*. 2016;34(10):967–9.
10. Navarria A, Drago V, Gozzo L, et al. Do the current performance-based schemes in Italy really work? “Success
fee”: a novel measure for cost-containment of drug expenditure. *Value Health*. 2015;18(1):131–6.
11. Williamson S, Thomson D. A report into the uptake of patient access schemes in the NHS. *Clin Pharm*. 2010;2:268–70.
12. Tilling K, Lawton M, Robertson N, et al. Modelling disease progression in relapsing-remitting onset multiple sclerosis using multilevel models applied to longitudinal data from two natural history cohorts and one treated cohort. *Health Technol Assess*. 2016;20(81):1–48.
13. Clopes A, Gasol M, Cájol R, et al. Financial consequences of a payment-by-results scheme in Catalonia: gefitinib in advanced EGFR-mutation positive non-small-cell lung cancer. *J Med Econ*. 2017;20(1):1–7.
14. Gamba S, Pertile P, Vogler S. The impact of managed entry agreements on pharmaceutical prices. *Health Econ*. 2020;29(Suppl 1):47–62.
15. Lorente R, Antonanzas F, Rodríguez-Ibeas R. Implementation of risk-sharing contracts as perceived by Spanish hospital pharmacists. *Health Econ Rev*. 2019;9(1):25.
16. Nazareth T, Ko JJ, Sasane R, et al. Outcomes-based contracting experience: research findings from US and European stakeholders. *J Manag Care Spec Pharm*. 2017;23(10):1018–26.
17. Ferrario A, Kanavos P. Dealing with uncertainty and high prices of new medicines: a comparative analysis of the use of managed entry agreements in Belgium, England, the Netherlands and Sweden. *Soc Sci Med*. 2015;124:39–47.
18. Antonanzas F, Juarez-Castello C, Rodriguez-Ibeas R. Should health authorities offer risk-sharing contracts to pharmaceutical firms? A theoretical approach. *Health Econ Policy Law*. 2011;6(3):391–403.
19. Soini E, Asseburg C, Taiha M, Puolakka K, Purcaru O, Luosujärvi R. Modeled health economic impact of a hypothetical certolizumab pegol risk-sharing scheme for patients with moderate-to-severe rheumatoid arthritis in Finland. *Adv Ther*. 2017;34(10):2316–32.
20. Fagnani F, Pham T, Claudepierre P, et al. Modeling of the clinical and economic impact of a risk-sharing agreement supporting a treat-to-target strategy in the management of patients with rheumatoid arthritis in France. *J Med Econ*. 2016;19(8):812–21.
21. Mahjoub R, Odegaard F, Zaric GS. Health-based pharmaceutical pay-for-performance risk-sharing agreements. *J Operat Res Soc*. 2014;65(4):588–604.
22. Zaric GS, O’Brien BJ. Analysis of a pharmaceutical sharing agreement based on the purchaser’s total budget. *Health Econ*. 2005;14(8):793–803.
23. Gavious A, Greenberg D, Hammerman A, Segev E. Impact of a financial risk-sharing scheme on budget-impact estimations: a game-theoretic approach. *Eur J Health Econ*. 2014;15(5):553–61.
24. Barros PP. The simple economics of risk-sharing agreements between the NHS and the pharmaceutical industry. *Health Econ*. 2011;20(4):461–70.
25. Mahjoub R, Odegaard F, Zaric GS. Evaluation of a pharmaceutical risk-sharing agreement when patients are screened for the probability of success. *Health Econ*. 2018;27(1):e15–e25.
26. Adida E. Outcome-based pricing for new pharmaceuticals via rebates. *Manag Sci*. Published online August 6, 2020. doi:10.1287/mnsc.2019.3574
27. Osler W, Martagan T, Tang CS. *Improving Access to Rare Disease Treatments: Subsidy, Pricing, and Payment Schemes*. SSRN; 2019. Available from: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3481150
28. Zhang H, Zaric GS, Huang T. Optimal design of a pharmaceutical price-volume agreement under asymmetric information about expected market size. *Product Oper Manag*. 2011;20(3):334–46.
29. Levaggi R, Pertile P. Value-based pricing alternatives for personalised drugs: implications of asymmetric information and competition. *Appl Health Econ Health Policy*. 2020;18(3):357–62.
30. Zaric GS, Xie B. The impact of two pharmaceutical risk-sharing agreements on pricing, promotion, and net health benefits. *Value Health*. 2009;12(5):838–45.
31. Levaggi R. Pricing schemes for new drugs: a welfare analysis. *Soc Sci Med*. 2014;102:69–73.
32. Critchley GJ, Zaric GS. The impact of pharmaceutical marketing on market access, treatment coverage, pricing, and social welfare. *Health Econ*. 2019;28(8):1035–51.
33. Markowitz H. Portfolio selection. *J Finance*. 1952;7(1):77–91.
34. Pekoz E, Ross SM. Compound random variables. *Prod Eng Inform Sci*. 2004;18:473–84.
35. Bowers NL, Gerber HU, Hickman JC. *Actuarial Mathematics*. Society of Actuaries; 1986.
36. Tambour M, Zethraeus N, Johannesson M. A note on confidence intervals in cost-effectiveness analysis. *Int J Technol Assess Health Care*. 1998;14(3):467–71.
37. Dunlop WCN, Staufler A, Levy P, Edwards GJ. Innovative pharmaceutical pricing agreements in five European markets: a survey of stakeholder attitudes and experience. *Health Policy*. 2018;122(5):528–32.
38. Rotar AM, Preda A, Loblova O, et al. Rationalizing the introduction and use of pharmaceutical products: the role of managed entry agreements in Central and Eastern European countries. *Health Policy*. 2018;122(3):230–6.
39. Morel T, Arickx F, Befrits G, et al. Reconciling uncertainty of costs and outcomes with the need for access to orphan medicinal products: a comparative study of managed entry agreements across seven European countries. *Orphanet J Rare Dis*. 2013;8:198.
40. Mayor S. Drugs “refund” scheme proposed for England and Wales. *BMJ*. 2007;334(7605):1181.
41. Miguel JS, Weisel K, Moreau P, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2013;14(11):1055–66.
42. Brenner DR, Weir HK, Demers AA, et al. Projected estimates of cancer in Canada in 2020. *CMAJ*. 2020;192(9):E199–E205.

43. Canadian Cancer Society. Multiple myeloma statistics [cited August 19, 2020]. Available from: https://www.cancer.ca/en/cancer-information/cancer-type/multiple-myeloma/statistics?

44. Myeloma Canada. Canadian statistics for multiple myeloma [cited August 19, 2020]. Available from: https://www.myelomacanada.ca/en/about-multiple-myeloma/what-is-myeloma/statistics.

45. Roy A, Kish JK, Bloudek L, et al. Estimating the costs of therapy in patients with relapsed and/or refractory multiple myeloma: a model framework. *Am Health Drug Benefits*. 2015;8(4):204–15.

46. Briggs AH, Weinstein MC, Fenwick EAL, et al. Model parameter estimation and uncertainty: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force—6. *Value Health*. 2012;15(6):835–42.

47. Thorp H, Hughes C. Administrative burden trends in NHS funding: patient access schemes. *Clin Pharm*. 2010;2:319–22.

48. Department of Health. Hints and tips for companies considering a Patient Access Scheme (PAS) proposal in England [cited January 12, 2021]. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/217037/PAS-Good-Practice-Guidance.pdf.

49. Caffrey M. Aetna, Merck reach value-based deal on diabetes drugs and collaborate on wellness [cited July 14, 2020]. Available from: https://www.ajmc.com/focus-of-the-week/aetna-merck-reach-value-based-reimbursement-deal-on-diabetes-drugs-to-collaborate-on-wellness-initiative.

50. Abbott TA, Vernon JA. The cost of US pharmaceutical price regulation: a financial simulation model of R&D decisions. *Manag Dec Econ*. 2007;28:293–306.

51. Shaikh M, Del Giudice P, Kourouklis D. Revisiting the relationship between price regulation and pharmaceutical R&D investment. *Appl Health Econ Health Policy*. Published online July 15, 2020. doi:10.1007/s40258-020-00601-9.

52. Vernon JA. Examining the link between price regulation and pharmaceutical R&D investment. *Health Econ*. 2005;14(1):1–16.

53. Pan-Canadian Oncology Drug Review. pCODR Expert Review Committee (pERC): initial recommendation [cited January 12, 2021]. Available from: https://www.cadth.ca/sites/default/files/pccdrid/pccdrid-pomalyst-mm-in-rec.pdf.

54. Borg S, Nahi H, Hansson M, Lee D, Elvidge J, Persson U. Cost effectiveness of pomalidomide in patients with relapsed and refractory multiple myeloma in Sweden. *Acta Oncol*. 2016;55(5):554–60.