The Impact of Two Pharmaceutical Risk-Sharing Agreements on Pricing, Promotion, and Net Health Benefits

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ABSTRACT

Objectives: Health insurers are increasingly making use of risk-sharing agreements with drug manufacturers to manage uncertainties regarding the costs and effectiveness of new drugs. Several risk-sharing models exist including those based on sales volume, achievement of clinical thresholds, and achievement of cost-effectiveness thresholds. The objective of this article is to compare two risk-sharing arrangements and to investigate conditions under which each is preferable from the perspective of the payer and the manufacturer.

Methods: We develop two two-period models to compare two risk-sharing arrangements between a payer and a drug manufacturer in which there is uncertainty about the effectiveness of the new drug. In the first risk-sharing agreement, the drug is listed on a formulary in the first period but delisted in the second period if the net monetary benefit in the first period is negative. In the second risk-sharing agreement, the manufacturer pays a rebate in each period if the net monetary benefit in that period is negative.

Results: We show that the relative performance of the two arrangements depends on several factors and that neither arrangement is always preferred. Additionally, we are able to identify situations in which a payer and a manufacturer would prefer the same plan and other situations in which the two parties would disagree on which plan was most desirable.

Conclusions: Because neither risk-sharing arrangement is always preferred, payers and manufacturers must carefully consider the characteristics of their individual situation when entering into such contracts.

Keywords: pharmaceutical advertising, pharmaceutical pricing, rebates, risk sharing.

Introduction

Prescription drug spending is the fastest rising component of overall health-care spending in many countries. Among Organisation for Economic Co-operation and Development countries, drug spending increased by an average of 6.1% annually from 1998 to 2005 and in most countries outpaced growth in total health-care spending and growth in overall Gross Domestic Product [1]. The increases in prescription drug spending may be due to increased sales of existing drugs as well as increasing availability of new and expensive drugs [2]. For example, some new drugs such as enzyme replacement therapies, cancer drugs, and the “biologics” can cost more than $100,000 per year.

To manage the costs and risks associated with new and expensive drugs, many payers have instituted formulary approval guidelines. Formulary submission guidelines requiring a cost-effectiveness analysis and a budget impact analysis are common. Nevertheless, the future effectiveness and demand for a drug are unknown at the time that formulary listing decisions are made, meaning that estimates of sales volume, effectiveness or cost-effectiveness may not be achieved. Several “risk-sharing” arrangements have been developed to spread the risks associated with drug budgets, effectiveness and cost-effectiveness between payers and manufacturers and thus alleviate some of the concerns about uncertainty.

There are several different forms of risk-sharing agreements. Taylor et al. describe a risk-sharing system in which a new drug is entered into the health-care system on a trial basis [3]. If the drug achieves its target outcomes, then it will be funded on an ongoing basis. If it does not, then it will be removed from the health-care system and the manufacturer must pay the costs incurred to date [3]. A similar idea can be used at the level of the individual patient in which all patients are given a new drug for a trial period. Those who respond according to predefined clinical criteria would be allowed to continue, although those who do not respond would switch to an alternate treatment and have their drug costs up to that point reimbursed by the manufacturer. This is similar to the recently announced model for bortezomib (Velcade) in the United Kingdom [4]. Price-volume agreements are widely used [5], and much has been written about the UK National Health Service (NHS) risk-sharing plan for multiple sclerosis which involves the monitoring of patients for 10 years and payment of a rebate if a predetermined cost-effectiveness threshold is not achieved (e.g., [6,7]).

Although some see such risk-sharing arrangements as an innovative solution to a difficult problem, there are criticisms of some of the specific arrangements. Sudlow and Counsell, for example, criticized a risk-sharing plan between the UK NHS and the manufacturers of interferon beta and glatiramer acetate [7]. They argued that the money “would be better spent on independent research” as it pushes drugs with only limited, biased, and short-term data to the market prematurely.

Despite the growing use of risk-sharing arrangements and their intuitive appeal to policy makers, there has been little academic research on the topic. Zaric and O’Brien [8] analyzed a manufacturer’s optimal response to a price-volume agreement. Claxton [9] discussed value-based pricing, in which manufacturers set prices according to known willingness-to-pay levels. Coyle et al. [10] discussed the concept of stratified cost-effectiveness analysis as a way for payers to set limited use conditions to maximize net benefits. Zaric [11] generalized the approach of Coyle et al. [10] to allow for continuously variable strata. This model was used to address the question of how a manufacturer would optimally set prices and limited use conditions in anticipation of limited use conditions being imposed by a payer.
Comparing Risk-sharing Agreements

Several other risk-sharing frameworks are possible [12] but there appears to be little, if any, publicly available formal analysis of these options.

A complicating factor in the design of risk-sharing agreements is the fact that promotional campaigns, such as advertising to physicians, direct-to-consumer advertising, physician detailing, sponsoring research studies, and educational seminars, all of which can increase sales, can take place after formulary decisions have been made. Research consistently shows that pharmaceutical advertising is effective in increasing sales (e.g., [13,14]). Promotional effort could lead to off-label use, use outside of that specified by limited use conditions, use in groups where cost-effectiveness has not been demonstrated, or use that exceeds amounts predicted in the original budget impact analysis.

In this article, we compare two risk-sharing arrangements: delisting after a trial period and rebates based on net monetary benefit (NMB). The objective of this article is to compare the two arrangements and to investigate conditions under which either risk arrangement is preferable from the perspective of the payer and the manufacturer. Our analysis includes explicit modeling of the effect of marketing efforts by manufacturers. To our knowledge, there is no research that considers how manufacturers are likely to make pricing and marketing decisions in the presence of risk-sharing agreements.

Basic Model

We develop two two-period models of risk-sharing contracts between a manufacturer and a payer. The manufacturer has developed a new drug and wants to include it on the payer’s formulary. In both models, the manufacturer chooses the price as well as the level of promotional effort in period $i$, $i = 1, 2$, to maximize the expected net present value of total profit. All notations are summarized in Table 1.

Before period 1, the manufacturer submits an application for the drug to be included on the payer’s formulary. The application includes the price, $p$, for both periods. We assume that payer enforces the constraint, $p^{\text{Min}} \leq p \leq p^{\text{Max}}$, where $p^{\text{Min}}$ and $p^{\text{Max}}$ are exogenous. We use the term “marketing” to refer to all promotional activities, including but not limited to advertising, promotion, and physician detailing, which serve to increase total sales. Let $m_i$ be the amount spent on marketing and let $N_i(p, m_i) = nkm_i^{1/2}p^{-1/2}$ be the total market size in period $i$ as a function of marketing effort and price, where $n$ represents the population size and $k$ is a constant representing the maximum fraction of the market that could ever be reached (and thus $n \times k$ is the maximum market size). This demand curve is a special case of a Cobb–Douglas demand function [15] with $a = 1/2$, $b = -1/2$.

Let $E_i$ be the average incremental effectiveness of the new drug per person, relative to the current standard of care. We assume that, because the drug is new, the only information available $E_0$, is derived from the clinical trials leading to regulatory approval of the drug. We assume that $E_i$ is a measure of effectiveness, such as life years or quality-adjusted life years. Nevertheless, $E_i$ could also be measured in any units that describe health benefits, including symptom-free days or various disease-specific measures, such as tumor size or viral load, provided that the payer values such benefits. Because of the limited scope and the controlled conditions of such trials, the true effectiveness of the drug in the population covered by the payer is unknown and $E_i$ is thus considered to be a random variable. Let $f_i(·)$ and $F_i(·)$ be the probability density function and cumulative density function of $E_i$. The distribution of $E_i$ could be used in setting $p^{\text{Max}}$ and $p^{\text{Min}}$, for example, by requiring a minimum probability that the new drug would be cost-effective.

Let $C$ be the incremental change in the cost of other healthcare consumption due to the use of this drug, per person. The term $C$ includes the cost of health care displaced (or added) as a result of the new drug but does not include the cost of the new drug itself. The incremental cost $C$ can be positive or negative depending on whether the new drug leads to increased or reduced expenses in the future. For example, a situation where a relatively inexpensive drug prevents the need for expensive surgery could result in $C < 0$, whereas a situation in which the new drug must be administered intravenously in a hospital setting could result in $C > 0$.

Let $\lambda$ be the payer’s willingness to pay for each unit of benefit (in the same units as used for $E_i$) and $U$ be the number of units of the drug consumed per patient in period $i$. We define the total NMB in period $i$ as $\text{NMB}_i = N_i(p, m_i) \times (E_i - C - pU) = (\text{market size}) \times (\text{average NMB per person})$.

We analyze two risk-sharing arrangements based on NMB, delisting and rebates, defined as follows.

**Delisting**

The drug is sold in period 1 at price $p$. If $\text{NMB}_1 < 0$, then the drug is delisted and not sold in period 2. Otherwise, the manufacturer is allowed to continue to sell the drug at price $p$ in period 2 (i.e., the drug is delisted if the net monetary benefit in the first period is negative).

**Rebates**

The drug is sold in each period at price $p$. In either period, if $\text{NMB}_i < 0$, then the manufacturer pays a rebate $R_i = -\text{NMB}_i$; if $\text{NMB}_i > 0$, then there is no rebate (i.e., if the NMB is negative in any period, then the manufacturer pays a rebate that is exactly large enough to make the NMB equal to zero).

In this model, “risk” is defined by uncertainty in effectiveness ($E_i$). In particular, the risk is that effectiveness is not high enough to allow the new drug to demonstrate “value for money” (through positive net benefits). This risk is shared in the first contract by

<table>
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<td>Manufacturer’s objective</td>
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<tr>
<td>Manufacturer’s decisions</td>
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<td>Calculated quantities</td>
<td>$N_i(p, m_i)$, $E_i(1)$, $\text{NMB}_i$, $E_i$</td>
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<tr>
<td>Parameters</td>
<td>$i$, $\lambda$, $C$, $U$, $E_i$, $f_i$, $\alpha$, $\beta$, $a$, $b$, $s_1$, $s_2$, $s_3$, $\delta$</td>
</tr>
<tr>
<td>Ratios</td>
<td>$p$, $p^{\text{optimal}}$, $\text{NMB}^{\text{total}}$, $\text{NMB}^{\text{optimal}}$</td>
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CDF: cumulative density function; PDF: probability density function.
Table 2  Optimal solutions for the case of $E(U(\alpha, \beta))$

<table>
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<th>Delisting</th>
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<tr>
<td>$E(\Pi)^*$</td>
<td>$\frac{1}{2}(Unk)^2 \frac{\lambda(p-\beta-\alpha)-\delta C + \delta \lambda \beta}{2U} \left(1+\delta \frac{\delta \lambda \alpha - C}{\lambda(p-\beta-\alpha)}\right)$</td>
</tr>
<tr>
<td>$p^*$</td>
<td>$(\lambda(p-\beta-\alpha)-\delta C + \delta \lambda \beta )/2U$</td>
</tr>
<tr>
<td>$m_1^*$</td>
<td>$(Unk)^2 \frac{\lambda(p-\beta-\alpha)-\delta C + \delta \lambda \beta}{2U}$</td>
</tr>
<tr>
<td>$m_2^*$</td>
<td>$(Unk)^2 \frac{\lambda(p-\beta-\alpha)-\delta C + \delta \lambda \beta}{2U}$</td>
</tr>
<tr>
<td>$P(\text{delisted})$</td>
<td>$\left(\frac{1}{\lambda(p-\beta-\alpha)}\right) \left(\frac{1}{2\lambda} \frac{\lambda(p-\beta-\alpha)(1+\delta) + \delta C - \delta \lambda \alpha}{C p U} \right)$</td>
</tr>
<tr>
<td>$E(R)</td>
<td>$</td>
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(A1) and (A2) above are formal statements of optimization problems in which the manufacturer chooses $p$, $m_1$, and $m_2$ to maximize a profit function subject to constraints on price.

Analysis

Results in this section are based on a special case in which effectiveness, $E_v$, is uniformly distributed between $\alpha$ and $\beta$, $\beta \geq \alpha \geq 0$, in both periods (i.e., $F(e) = (\alpha - \alpha)/(\beta - \alpha)$). With this additional assumption, it is straightforward to find the optimal price ($p^*$), marketing effort in each period ($m_1^*$ and $m_2^*$), and expected profit ($\Pi^*$). The results shown in Table 2 are for $C \leq \frac{1}{16}(\alpha \beta + \beta)$ and $p^* = (\lambda \beta - C)/U$. When $p^* > p^\text{Max}$ (i.e., a rebate is always paid). This case will be discussed separately in the Model Extensions section. If $C > \frac{1}{16}(\alpha \beta)$, then the value of $p^*$ calculated in Table 2 would always be larger than $p^\text{Max}$. Nevertheless, the formula for $p^*$ was generated under the assumption that $p^* < p^\text{Max}$.

It is not possible to derive meaningful algebraic comparisons between A1 and A2. Thus, we compared the two risk-sharing arrangements numerically. We constructed an example with base case parameter values $n = 1000$, $k = 0.005$, $U_1 = U_2 = 100$, $\lambda = 50,000$, $C = 1000$, $\delta = 1$, $\alpha = 0.5$ and $\beta = 1$. Preliminary analysis demonstrated the importance of $C$, $\lambda$, and the ratio $\alpha/\beta$ so our presentation will focus on these three parameters. For the uniform distribution, when $\alpha = 0$ (i.e., when average benefits are always positive), the ratio $\alpha/\beta$ can be interpreted as a measure of the magnitude of the uncertainty in effectiveness; when $\alpha/\beta$ is small, $\alpha$ is much smaller than $\beta$ and uncertainty in effectiveness is large because there is a wide range of possible effectiveness values, whereas $\alpha/\beta$ is large, there is relatively little uncertainty in effectiveness because there is a narrow range for possible effectiveness values. We set $p^\text{Max} = (\lambda \beta - C)/U$ and $p^\text{Max} = \max((\alpha - \alpha)/(\beta - \alpha), 0)$. These definitions ensure that $0 \leq q \leq 1$ (i.e., a technical constraint to ensure that the probability of observing negative NMB in the first period is between 0 and 1) and that $p^* \leq 0$. We define $p^*$ as the ratio of the manufacturer’s optimal profit under A2 to the optimal profit under A1, $B^*$ is the ratio of total expected benefits purchased by the payer under A2 to total benefits purchased under A1 when the manufacturer chooses price and marketing effort optimally, and $S^*$ as the ratio of the optimal market size in the first period under A2 to the optimal market size in the first period under A1.

We first evaluated $S^*$ for different values of $C$ and $\alpha/\beta$ (Fig. 1). The optimal market size under A1 is constant with respect to requiring the drug to be pulled from the market if it cannot demonstrate value for money in the first period. Risk is shared in the second contract by requiring the manufacturer to pay a rebate to the payer in each period if positive net benefits are not observed. Both contracts depend on the NMB in each period. The expression for NMB can be rearranged to see that the NMB is negative if $E < (C + pU)/\lambda$. Let $q$ be the probability that the drug is delisted at the end of period 1 in A1, given by $q = \int f_1(e) de_1$ (i.e., $q$ is the probability that the effectiveness is less than $(C + pU)/\lambda$). Let $E[R]$ be the expected rebate in period 1 in A2, given by $E[R] = N_c(p, m_1) \times \int \left(\frac{C + pU - \lambda \alpha}{\lambda(p - \beta - \alpha)}\right) f_1(e) de_1$ (i.e., $E[R]$ is the weighted value of the rebate for all instances in which the effectiveness is less than $(C + pU)/\lambda$).

Let $p_1$, be the manufacturer’s profit in period 1, and let $\Pi_1$ be the total two-period profit. We assume that the unit production cost is small and can be ignored, and we ignore allocated fixed costs. Let $\delta$ be the one-period discount factor (where $\delta = \frac{1}{1 + d} = d$).

In A1, profit in each period is given by $\pi_1 = pUN_1(p, m_1) - m_1 = \text{price} \times \text{units/person} \times \text{market size} - \text{market cost} - \text{rebate}$, and total profit is $\Pi = \pi_1 + \delta(1-q)\pi_1$, i.e., profit in the first period plus the discounted profit in the second period, multiplied by the probability that the drug does not get delisted.

In A2, profit in each period is given by $\pi_1 = pUN_1(p, m_1) - m_1 - R_1 = \text{price} \times \text{units/person} \times \text{market size} - \text{marketing cost} - \text{rebate}$

and total profit is $\Pi = \pi_1 + \delta\pi_1$. To determine the optimal price and marketing effort, the manufacturer solves the following optimization problems:

\begin{align}
(\text{A1}) \quad & \text{max } \Pi = pUN_2(p, m_1) - m_1 + \delta(1-q)pUN_1(p, m_1) - m_1) \\
& \text{s.t. } p^\text{Max} \leq p \leq p^* \\
(\text{A2}) \quad & \text{max } \Pi = pUN_2(p, m_1) - m_1 - E[R_1] + \delta[pUN_1(p, m_1) - m_1 - E[R_1]] \\
& \text{s.t. } p^\text{Max} \leq p \leq p^* 
\end{align}
Comparing Risk-sharing Agreements

Figure 1 Ratio of optimal market sizes.

Figure 2 shows \( P^* \) for different combinations of willingness to pay (\( \lambda \)) and nondrug incremental costs (\( C \)). Positive values of \( C \) are shown in Figure 2a and negative values of \( C \) are shown in Figure 2b. Several points are not shown in Figure 2a, corresponding to cases in which there is no feasible solution. For example, when \( C = -25,000 \), indicating cost savings, \( S^* \) is approximately 0.85, whereas when \( C = 25,000 \) the market size ratio is approximately 0. Thus, when rebates are used and there are high nondrug incremental costs and high uncertainty in effectiveness, price and marketing effort will be chosen so that there will be very low sales volume.

For positive \( C \) (Fig. 2a), the ratio \( P^* \) is increasing in \( \lambda \) and decreasing in \( C \). Thus, as the payer’s willingness to pay for benefits increases, the manufacturer is more likely to prefer rebates over delisting, and as the nondrug incremental costs increase, the manufacturer is more likely to prefer delisting over rebates. For all cases, \( P^* \) increases in \( \lambda \) and reaches a maximum value of approximately 1.12. The ratio \( P^* \) may be greater than or less than 1, which suggests that the preferred alternative, from the manufacturer’s perspective, depends on the relationship between \( C \) and \( \lambda \). In instances where \( P^* < 1 \), \( P^* \) can be significantly less than 1, whereas in instances where \( P^* > 1 \), the ratio tends to be close to 1. This suggests that, although it is possible for either contract to be better for the manufacturer, a risk-averse manufacturer may prefer delisting over rebates when \( C > 0 \).

Figure 2b shows \( P^* \) for cases when \( C < 0 \) (i.e., use of the new drug leads to cost savings elsewhere). In all instances of \( P^* > 1 \) suggesting that the manufacturer always earns higher profits with rebates compared with delisting when the nondrug incremental costs are negative. Each curve is nonmonotonic (neither strictly increasing nor strictly decreasing) in \( \lambda \) and peaks at approximately 1.14 before sloping down again to approximately 1.12. This results in \( P^* \) also being nonmonotonic in \( C \).

Figure 3 shows \( B^* \) and \( P^* \) as functions of \( \alpha/\beta \) for different values of \( C \). Four regions are labeled on the graphs. In region A which only occurs for the case of \( C = 10,000 \) in Fig. 3c), \( B^* \) and \( P^* \) are both less than 1, indicating that the payer purchases fewer total benefits and the manufacturer earns lower profits under A2 than under A1. In region B, \( B^* \geq 1 \) and \( P^* \leq 1 \), indicating that the payer purchases more benefits and that the manufacturer earns lower profits under A2 than under A1. In region C, \( B^* \) and \( P^* \geq 1 \), meaning that both benefits and profits are greater under A2 than under A1. Finally, in region D, \( P^* \geq 1 \) and \( B^* \geq 1 \). If a new drug had characteristics such as range of effectiveness and nondrug incremental cost, which placed it in zone A, then both parties would likely prefer a delisting arrangement over a rebates arrangement. If the contract fell in zone C, then both parties...
would likely prefer a rebates arrangement. If the contract fell in zone B or zone D, then the two parties would likely disagree on which option was preferable.

The existence of the four regions of Figure 3 with their different interpretations suggests that manufacturers and payers may have differing perspectives on which arrangement is preferred. There are two reasons why these disagreements may arise. There may be a difference of perception or estimation, in which the two parties disagree on the parameter estimates and hence on the region. Alternately, there may be an intrinsic difference between the contracts in which both parties agree on all parameter estimates, but these estimates place the contracts in region B or D.

Figure 4 shows $P^*$, $B^*$ and the value of the incremental cost-effectiveness ratio (ICER) in the optimal solution to A1 divided by $\lambda$ as a function of $\alpha/\beta$ for $C = 0$ and $\lambda = 50,000$. Graphs for other values of $C$ are qualitatively similar and offer similar insights. The graph for the optimal ICER under A2 divided by $\lambda$ is not shown because, with the rebate policy that we consider, this ratio is always less than 1. Additionally, it varies in a narrow range between 0.89 and 0.99 for this particular example. Four regions are shown on the graph corresponding to the regions between the points where one of these lines crosses 1. In regions B and C, both parties prefer A2 because $P^*$ and $B^*$ are both greater than 1. Although the manufacturer prefers A1 in region A, the expected ICER throughout this region exceeds $\lambda$, and the payer would purchase more health benefits under A2. In contrast, in region D, the manufacturer would prefer A2, and the ICER of A2 is less than $\lambda$ throughout this region.

To better understand Figure 4, we describe two instances in greater detail. We note that under A1, optimal marketing effort ($m^*$) and market size ($N^*$) are independent of model parameters $\alpha$, $\beta$, $C$ and $\lambda$. This is not the case for A2 because $m^*$, and hence $N^*$, both depend on the expected rebate ($E[R]$) which is a function of $\alpha$, $\beta$, $C$ and $\lambda$.

First, consider $\alpha/\beta = 0.1$ (i.e., relatively high uncertainty about future effectiveness) with other parameters as in the base case. Under delisting, it is optimal to set a price of approximately 95% of the upper limit $p_{\text{Max}}$. This results in the expected ICER in the first period being 1.7 times greater than $\lambda$ and a 94% chance that the drug will be delisted at the end of the first period. Under rebates, the optimal price is only 67% of $p_{\text{Max}}$. The manufacturer spends much less on marketing under rebates compared with delisting, resulting in a total market size that is only 73% as large under rebates as under delisting. The benefits purchased in period 1 are thus only 73% as great as under delisting but the total expected benefits purchased over both periods under rebates is greater than under delisting because the drug is always sold in both periods under rebates, yet has only a 6% chance of being available in the second period under delisting. The expected rebate is relatively high at 27% of total sales because uncertainty about effectiveness is high.

Next, consider $\alpha/\beta = 0.8$ (i.e., relatively low uncertainty in effectiveness). Under delisting, the optimal price is 80% of the
maximum, resulting in a probability of being delisted of 0 (i.e., the price is set so that, regardless of effectiveness, it would be cost-effective). Under rebates, the optimal price is higher and set at approximately 90% of the maximum possible price. The manufacturer spends slightly more on marketing under rebates than under delisting. The net result of the higher price (which reduces demand) and greater marketing expenditures (which increase demand) is a market size that is 97% as large under rebates as under delisting. Because the probability of being delisted under delisting is 0, the expected total benefits are 97% as great under rebates as they are under delisting. Because there is little uncertainty in effectiveness, the expected rebate is only 3% of sales in rebates.

**Model Extensions**

**No Upper Bound on Prices**

The above analyses all made use of an upper bound \( p^{\text{Max}} \) on prices for both contracts. For the case of delisting, it is necessary to have an upper limit on price because without an upper limit it would be optimal for the manufacturer to set an arbitrarily high price, thus earning arbitrarily large profits in period 1, while ignoring period 2. However, when rebates are used, the rebates may induce the manufacturer to self-regulate when setting prices. We investigated whether there would be instances under rebates when it would be optimal to choose a price so that a rebate is always paid (i.e., to choose \( p^* > p^{\text{Max}} - (\beta \bar{B} - C[U]) \)).

Our analysis suggests that it would never be optimal to choose \( p > p^{\text{Max}} \). When \( p < p^{\text{Max}} \), corresponding to the case examined in earlier sections, the solution \( p^* = p^{\text{Max}} \) is possible but this will not be the solution in general.

A potential concern among policy makers and formulary managers about the use of rebate schemes is that they will merely encourage manufacturers to set high prices, always pay rebates, and extract the payer’s full willingness to pay for benefits. The above analysis suggests that the optimal price will always result in the payer receiving some net monetary benefit, except for the special case where there is no uncertainty in effectiveness, which is likely to be the exception rather than the rule. This result occurs because demand in this model is price sensitive, and beyond a certain point, increases in price are offset by decreases in demand.

**More Than Two Periods**

We extended the model to a multiperiod framework to investigate whether some of the results obtained previously were a result of using a two-period framework rather than to features of the risk-sharing arrangements themselves. This could be particularly important in the case of delisting, where it may make sense in a two-period model to sacrifice sales in the second period in exchange for a higher price in the first period. For longer time horizons, this behavior may cease to be optimal as the value of the future sales that are sacrificed would increase.

First, consider rebates. For rebates, the extension to multiple periods does not change the optimal values \( p^* \) and \( m^* \). This is because the optimal marketing is the same in each period \( (m_1^* = m_2^* = \ldots = m_T^*) \) and the problem reduces to the same two-variable problem as in the two-period model.

Next, consider delisting. We are able to extend the time horizon to infinitely many periods. This could serve as an approximation to a case with a very long remaining time horizon or a high discount rate (i.e., low \( \delta \)). In this case, we find that there are only two possible optimal solutions: either set \( p^* = p^{\text{Max}} \) or set \( p^* = p^{\text{Max}} \). When \( p^* = p^{\text{Max}} \), this ensures that the drug is never delisted and is sold in every period. When \( p^* = p^{\text{Max}} \), the drug is always delisted after the first period. The manufacturer will earn the largest possible profit in the first period and ignore all future periods. The first result, setting \( p^* = p^{\text{Max}} \) to ensure sales in every period when the length of the time horizon grows, seems intuitive, but the latter result does not so we explore it in more detail.

One condition in which it is optimal to ignore future periods is \( \beta (1 - \delta) \geq \alpha \) and \( C \geq 0 \), which corresponds to positive non-drug incremental costs and maximum possible effectiveness substantially larger than the minimum possible effectiveness (i.e., relatively large uncertainty in effectiveness). A subcase is \( \delta = 1 \) (no discounting), \( \alpha = 0 \) (some possibility of no benefits) and \( C = 0 \) (nondrug incremental costs are positive). A second condition is \( \delta = 1 \) (no discounting) and \( C = \alpha a \geq 0 \) (nondrug incremental costs are greater than willingness to pay for the lowest possible level of benefit).

**Other Changes in the Basic Model Setup**

In the analysis presented thus far, we have assumed that \( E_t \) is uniformly distributed, \( C_i = C \), and \( N_i(p, m) = nkm^i(p^{1/2}) \). We also investigated generalizations of these assumptions. In particular, we let \( E_t \) be normally distributed rather than uniformly distributed; we defined the incremental cost per person \( C_i \) as \( C_i(N_i) = C_i + \gamma N_i \); and we considered two new forms for the demand function, a more general multiplicative model, \( N_i(p, m) = nkm^i \gamma p^{-\alpha} \), \( 0 < \alpha < 1 \), and a linear model, \( N_i(p, m) = h_i + sm_i^2 - sp_i \), \( 0 < \alpha < 1 \), \( b > 0 \), \( s_1 > 0 \).

The new incremental cost function \( C_i(N_i) \) may be an increasing or decreasing function of the number of individuals using the new drug. If \( \gamma > 0 \), then the incremental cost \( C_i(N_i) \) is an increasing function of the number of users. This may occur if the new drug is used in progressively more marginal groups as the market expands. If \( \gamma < 0 \), then the incremental cost \( C_i(N_i) \) is decreasing. This may occur if there are positive network effects (e.g., drugs that treat communicable diseases) or if providers become more experienced with the drug and thus able to derive economies of scale as they expand to larger numbers of patients.

It is not possible to obtain algebraic solutions using either demand curve. However, both rebate schemes reduce to twovariable optimization problems for which solutions can be obtained through an exhaustive search of all possibilities within realistic bounds. In the case of delisting, the two variable problem is obtained by finding \( m_i^* \), then substituting \( m_i^* \) into \( \Pi \) and searching over values of \( m_i \) and \( p_i \); in the case of rebates, the two-variable problem is obtained by observing that \( m_i^* = m_i^* \), substituting \( m_i^* \) into \( \Pi \), and searching over values of \( m_i \) and \( p_i \). Although the actual solution values differ from those presented in previous sections, the qualitative insights are similar and are not presented.

**Discussion**

In this article, we developed models to evaluate two different risk-sharing agreements. We compared the two agreements analytically and using several numerical examples, and we suggested a number of extensions to the basic two-period model. Our analysis demonstrated the many complex trade-offs involved in various risk-sharing arrangements and the viability of using a combination of analytic and numeric techniques to understand and compare different risk-sharing arrangements.

This analysis has yielded several important insights. First, neither of the two arrangements that we evaluated would always be preferred by either the payer or the manufacturer. This was shown through the different zones in Figure 3, each of which is
interpreted differently by each party. The different interpretations could arise from disagreements about various parameter estimates or features of the agreements themselves. The possibility of conflicting preferences would likely continue to hold true using more realistic assumptions and may also hold true for other specifications of risk-sharing plans. There are also instances when both parties would agree as to which option was preferable, also shown in Figure 3. In zone A, both parties would be better off with delisting, and in zone C both parties would be better off with rebates.

Second, two important factors in determining the performance of the risk-sharing plans are uncertainty in the outcomes and nondrug incremental costs (expressed in our model by $\alpha$ and $\beta$, respectively). It may be necessary to have good estimates of the values of these quantities to properly understand the impact of a newly proposed risk-sharing agreement. Third, a potential concern about the impact of rebate schemes is that the optimal response by manufacturers will be to set a high price and always pay a rebate, leaving the payer with no net monetary benefit. However, we found that this behavior would not be optimal, suggesting that the concern is unfounded. Fourth, although delisting puts an incentive on the manufacturer to choose a low price and thus maximizes the probability of remaining on the formulary, there are instances when it is optimal for the manufacturer to set the price as high as possible and ignore the second period. Indeed, even when we extended the time horizon to an infinite period model we identified conditions under which it would be optimal for the manufacturer to ignore all future periods.

The two arrangements that we considered place different incentives on the manufacturer. Under delisting the payer uses the threat of delisting to prevent the manufacturer from setting too high a price. The manufacturer must consider the trade-off between expected profit in period 1 and total expected profit in later periods when determining the price and marketing effort. Under rebates, the rebate is nonnegative by definition so the payer is guaranteed a positive or zero NMB, regardless of the price or the true effectiveness. In this case, the manufacturer’s choice for price involves a balance between market size (lower price means larger demand) and profit per unit sold (higher price means higher per-unit profit).

Two recent articles that describe pharmaceutical risk-sharing contracts in general, discuss some of the reasons why these contracts may be useful, and discuss potential difficulties in implementing them [16,17]. The authors offer differing conclusions, with one article arguing that “it is not clear that risk-sharing will be accepted”, and that risk-sharing agreements will probably only be attractive in specific limited situations [17], and the other concluding that “risk-sharing plans . . . may become a staple feature of the market [16].” Our analysis suggests that differing interpretations about the desirability of a particular contract may be expected.

Our model makes use of the general variable $m$, to represent all possible promotional activities. There are several ways in which drug manufacturers can promote their products. Manufacturers traditionally target their advertising efforts toward physicians using journal advertising and detailing. Although such campaigns are widely used and have been proven highly successful in promoting sales [18], drug manufacturers are increasingly using direct-to-consumer advertising (DTCA) to promote their drugs directly to the consumers [19]. Recent research suggests that patients will respond to advertisements by requesting specific drugs from their physicians, and that many physicians will prescribe requested drugs even if they would not prescribe them otherwise [20,21]. DTCA campaigns may also put pressure on the public payers to cover the advertised drugs.

The models and analysis that we presented are intended for risk-sharing agreements with either public sector payers or private sector payers, that are very large and include most local patients. This is because of the inclusion of the promotional effort term. Physician detailing and direct to consumer advertising would be a large component of promotional effort. In regions where manufacturers have agreements with several payers and physicians treat patients who belong to several different plans, it would be difficult to target that effort to the intended patient-plan combinations.

Transaction and monitoring costs may be important when considering adopting a risk-sharing plan, and it would be important to consider these costs in a comparison of “risk-sharing” versus “no risk-sharing.” However, we ignored these costs in our analysis because we compared two risk-sharing contracts, both of which would involve monitoring of effectiveness.

There are several possible extensions for this model. We compared only two forms of risk-sharing agreement but several other forms could be considered, such as the bortezomib “warranty” model used by the NHS or price-volume agreements which are used by several payers. We assumed the same distribution for effectiveness in both periods. However, the effectiveness observed in the first period would probably provide some information about the effectiveness in the second period and therefore reduce the uncertainty in effectiveness in that period.

We assumed that $E_1$ and $E_2$ were independent but they may be correlated. Market size in second period is may be a function of $m_1$ as well as $m_2$, as early investments might not yield a benefit until later periods. We assumed that the only source of uncertainty was the effectiveness of the drug. However, for a new drug there could also be uncertainty regarding incremental costs and market size, as well as other factors. We assumed that the manufacturer would know the payer’s willingness to pay $\lambda$ with certainty, but the manufacturer may only be able to guess this value based on past experience or results of similar decisions, if they are publicly available. As a model simplification, we assumed that $E_1$ was the only stochastic term. However, there are likely to be many uncertain parameters including sales volume and cost. Future research can incorporate these additional sources of uncertainty.

Drugs are becoming increasingly expensive, and drug spending is growing faster than the economy as a whole in many countries, straining public health-care budgets in the process. If a payer believes that it is taking on too much risk by adding a drug to a formulary then this may restrict its ability to reimburse drugs that could be effective or cost-effective under different circumstances. If a manufacturer believes that it is taking on too much risk then it may avoid listing drugs on certain formularies even though listing could be profitable under different circumstances. As drugs become more expensive, continued research on the design and implementation of risk-sharing contracts will become increasingly important to continue ensured access.

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Comparing Risk-sharing Agreements

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