4-23-2014 12:00 AM

Modeling Pharmaceutical Risk-Sharing Agreements

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A thesis submitted in partial fulfillment of the requirements for the Doctor of Philosophy degree in Business

MODELING PHARMACEUTICAL RISK-SHARING AGREEMENTS

(Thesis format: Integrated Article)

by

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Graduate Program in Business Administration

A thesis submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy

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Abstract

Many new and expensive drugs have been introduced in the past 10 years. However, at the time of introduction, the effectiveness of these drugs outside of clinical trials is often unknown. This creates a risk to third-party payers, as the outcome of these drugs in real-world practice is uncertain at the time of introduction. A pay-for-performance risk-sharing agreement is a type of contract that shares part of this risk with the manufacturer by linking the performance of a drug to the manufacturer's revenue. This dissertation consists of three essays to examine the performance of two types of pharmaceutical pay-for-performance risk-sharing agreements.

In my first essay I examine the performance of a pay-for-performance risk-sharing agreement in which patients are assessed at some evaluation time to determine their response to the drug. The manufacturer rebates to the payer a proportion of the sales from all patients excluding the sales from those responding at the evaluation time. I model disease progression using a continuous time Markov chain with uncertain transition rates. I address the following questions regarding the performance of this agreement: What is the optimum evaluation time and under what conditions will the manufacturer make a profit? What is the distribution of the manufacturer's profit resulting from different sources of uncertainty?

In the second essay I extend the model developed in the first essay to calculate the net monetary benefits of the payer and identify the conditions under which both parties have incentives to introduce the new drug.

The third essay focuses on the analysis of a risk-sharing agreement in which patients are prescribed a drug only if their probability of response lies within a range of success probabilities. The payer determines this range such that the use of the drug is cost-effective. I generalize from the existing literature by allowing the rebate to be different from the price of the drug and incorporating two types of administrative costs. I seek to answer two important policy questions: First, under what conditions does the payer benefit from the agreement? Second, under what conditions does the agreement become welfare-improving?

Keywords

Risk-sharing, Pay-for-performance, Pharmaceutical, Healthcare, Disease Progression Model, Net Monetary Benefit, Operations Research, Management Science, Health Economics

Co-Authorship Statement

I hereby declare that this thesis incorporates some material that is a result of joint research. Essay 1 was in the Journal of the Operational Research Society co-authored with Dr. Gregory S. Zaric and Dr. Fredrik Odegaard. As the first author, I was in charge of all aspects of the project including formulating research questions, literature review, research design, analyzing the secondary data, and preparing the first complete draft of the manuscript. With the above exception, I certify that this dissertation and the research to which it refers, is fully a product of my own work. Overall, this dissertation includes 3 original papers, with the first essay already published in an academic journal.

Essay 1 – Status: In Press

Mahjoub R, Odegaard F, Zaric GS, Health-based pharmaceutical pay-for-performance risk-sharing agreements, In Press (Published Online, Sep. 11, 2013), *Journal of the Operational Research Society (JORS)*

Acknowledgments

I would like to thank my supervisor, Dr. Greg Zaric and my co-supervisor, Dr. Fredrik Odegaard, for their invaluable support and guidance throughout my PhD research studies. I would also like to thank the supervisory committee and members of the examining board for their valuable feedback. Last but not least, I would like to thank my wife and my daughter, without whom this achievement would not have been possible.

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Introduction

When a new pharmaceutical treatment is introduced by a drug manufacturer, insurance providers, also known as "third-party payers" or "payers", need to decide whether to cover it for reimbursement. Those treatments approved for reimbursement are included in a list called formulary. Owing to the rising expenditures on pharmaceuticals in general and on the personalized and specialized drugs in particular, the decision criteria for adding new drugs on formularies have evolved by including economic considerations into the evaluation process in addition to the clinical merits (Hoffman et al., 2012; OECD, 2005). For instance in Australia the cost-effectiveness assessment is called a "fourth hurdle" process - in addition to safety, efficacy, and quality- for adding new drugs to the national formulary (Lopert and Elshaug, 2013).

Some countries with publicly funded healthcare have established agencies to determine whether new pharmaceutical treatments should be listed in public formularies. Examples of such agencies are National Institute for Health and Care Excellence (NICE) in the UK and Pharmaceutical Benefits Advisory Committee (PABC) in Australia.

In Canada, every province or territory has its own publicly funded drug plan. For instance, the Ontario Drug Benefit (ODB) program covers most of the cost of 3,800 prescription drug products listed on the ODB formulary (MOHLTC, 2014). In 2002 the Common Drug Review (CDR) process was established at the Canadian Agency for Drugs and Technologies in Health (CADTH). According to CADTH, the following objectives are defined for CDR process: to reduce duplication of reviews by jurisdictions, to provide equal access to timely, evidence-based information, and to consolidate the submission filing process for

pharmaceutical manufacturers. CDR also provides formulary listing recommendations to the participating federal, provincial, and territorial publicly funded drug plans (CADTH, 2014; Clement et al., 2009).

Contrariwise, there is no national agency yet in the US to provide cost-effectiveness review for formulary listing decisions although a US legislation was introduced in 2008 to create a public-private comparative effectiveness institute (NIH, 2014; Clement et al., 2009). However, formularies as well as pharmacy and therapeutic committees that oversee them are present in US hospitals and outpatient drug plans (Schiff et al., 2012).

The composition of committees that oversee the formularies can vary across jurisdictions. The Medical Technologies Advisory Committee (MTAC) that advises NICE on coverage decisions is composed of 25 independent specialists in medical technology and health economics. Additionally for each technology assessment, a lead team of 8 members including analysts, advisors, and patient experts will be assigned (NICE, 2013). On the other hand, the Canadian Drug Expert Committee (CDEC), which is the advisory body to CADTH's CDR process, is composed of 9 specialists in medical technology and health economics and 2 members of the public (CADTH, 2014; Clement et al., 2009).

Expensive Drugs with Unproven Effectiveness

In the past 10 years several expensive drugs have been introduced into the pharmaceutical market. Some examples include carfilzomib for relapsed and refractory multiple myeloma, costing $10,000 (USD) per 28-day cycle (Stenger, 2012); pralatrexate for patients with

relapsed or refractory peripheral T-cell lymphoma, costing $67,500 (USD) per each 7-week cycle (Hui et al., 2012); and bevacizumab for the treatment of breast, colon, lung, and brain cancer, costing up to $100,000 (USD) a year (Jirillo et al., 2008). At the time of introduction, the effectiveness of these drugs has been shown within clinical trials. Thus, the outcome of these drugs is uncertain in real-world practice ex-ante (Mullins et al., 2010). Third-party payers are concerned about this uncertainty when making formulary listing decisions. This is owing to the fact that there is a risk of making a type I error, i.e., incorrectly paying for a costly drug (or treatment) whose incremental benefit is not worth the additional cost (Towse and Garrison, 2010).

When facing this uncertainty, a risk-averse payer has several options. Eckermann and Willan (2007) suggest the following set of alternatives: 1) Adopt the new treatment irreversibly (e.g., by including it on the formulary). 2) Adopt the new treatment but seek more evidence, implying that the decision can be reversed if there is not enough evidence to support the cost-effectiveness of the new treatment. 3) Decline to adopt the treatment and wait for further evidence. Towse and Garrison (2010) identify "risk sharing" as a fourth option, where the payer adopts the new treatment and at the same time links collected evidence on the performance of the treatment to the manufacturer's revenues through a contract. Performance-based risk-sharing can also be attractive to the manufacturer, as it signals confidence in product quality when the product quality is not fully observable to the decision maker or payer (Cook et al., 2008).

In the context of this dissertation, I define a "pay-for-performance risk-sharing agreement" as a contract between a healthcare payer and a drug manufacturer in which a healthcare payer agrees to pay for a medicine based on a successful or agreed-upon clinical outcome. If the outcome is unsuccessful, then the payer must be reimbursed according to the conditions specified in the risk-sharing agreement.

There are several types of risk-sharing agreements. Adamski et al. (2010) provide a detailed review of the risk-sharing agreements implemented globally, and Carlson et al. (2010) provide a taxonomy of performance-based reimbursement schemes between healthcare payers and manufacturers. Each type of risk-sharing agreement has unique mechanics, including the set of contract parameters that generate the specific dynamics for that agreement. Zaric et al. (2013) provide a literature review on risk-sharing agreements modeling. They present several examples of different types of risk-sharing schemes illustrating the broad scope of these types of contracts.

Pay-for-performance Risk-sharing Examples

I provide a short description of some examples of risk-sharing agreements implemented in the UK, the US, and Italy.

Bortezomib for Multiple Myeloma

The National Health Service (NHS) in the UK and the drug manufacturer for bortezomib entered into a risk-sharing agreement in 2007. Under this agreement, the NHS agreed to pay for four cycles of treatment for patients suffering from multiple myeloma who met the

following criteria: 1) Bone transplant was not a treatment option. 2) At least one other treatment had been unsuccessful. After four cycles of treatment, the impact of treatment was measured by a serum monoclonal protein (M protein) test. If the test demonstrated effectiveness (defined for this agreement as a 50% or more reduction in M protein), then treatment could be continued and further cycles would be funded by the NHS. However, if the treatment was not successful, then it would be stopped, and the drug manufacturer would reimburse the NHS for the cost of the first four cycles (NICE, 2007).

Under this risk-sharing scheme the list price of £762 per 3.5 mg vial of bortezomib was not affected, although the effective price paid to the manufacturer by the NHS was close to £300 for the first four cycles of treatment (Carlson et al., 2010). This was owing to the fact that about 60% of patients did not respond to the drug (Richardson et al., 2003) and therefore the total sales for those non-responding patients were rebated.

Beta Interferon and Glatiramer Acetate for Multiple Sclerosis

In 2002, the National Institute for Health and Care Excellence of the UK recommended that beta interferon and glatiramer acetate should not be used by the NHS for the treatment of multiple sclerosis (MS) because of uncertainty in the long-term cost-effectiveness of those drugs (NICE, 2002). Against this backdrop, the UK government and several drug manufacturers entered into a risk-sharing agreement that allowed coverage of these drugs for the treatment of MS conditional on a 10-year monitoring study to collect data on the progression of disease in treated patients. According to this scheme, the collected data would be reviewed every two years and, based on the effectiveness results for every individual drug,

the drug manufacturers agreed to adjust the drug price to the NHS to ensure a maximum cost-effectiveness ratio of £36,000 per quality-adjusted life year evaluated over a 20-year horizon (Boggild et al., 2009; HSC, 2002).

Gene-expression Profiling Test

In 2007, United Healthcare in the US and Genomic Health entered into a performance-based agreement for a gene-expression profiling test priced at $3,460 (USD) per test. The test is designed to identify for women with breast cancer for whom chemotherapy would be unlikely to be beneficial (NIH, 2007). According to this risk-sharing scheme, both parties would monitor the results and, if a large number of patients for whom chemotherapy was not beneficial were still receiving the treatment, then they would renegotiate the price (Cook et al., 2008).

Nilotinib for Chronic Myeloid Leukemia

Based on a performance-based risk-sharing agreement with the Italian Medicines Agency in 2009, the drug manufacturer for nilotinib, a drug used for the treatment of chronic myeloid leukemia, agreed to refund the cost of the drug for every patient with an unsuccessful agreed-upon hematological response after one month (Carlson et al., 2010).

Lenalidomide for Multiple Myeloma

As part of a risk-sharing scheme agreed to in 2009 between the NHS and the manufacturer of lenalidomide for the treatment of multiple myeloma, the manufacturer will meet the cost of the drug after 26 cycles for patients who still remain on the treatment (NICE, 2009).

Media Coverage of Risk-Sharing

Prominent media coverage of the pay-for-performance risk-sharing agreements outlines the debate about the merits of these types of contracts. For example, the risk-sharing schemes for beta interferon, bortezomib, and lenalidomide were broadly covered by the media in the UK (BBC News, 2009; BBC News, 2007; BBC News, 2002). In an interview with a medical expert regarding the risk-sharing scheme for lenalidomide, the scheme was presented as the type of model that should be used for other drugs going forward (BBC News, 2009).

On the academic side there is increasing attention to these agreements within the literature. Carlson et al. (2010), for example, see a promising future for performance-based risk-sharing agreements owing to the increasing number of these agreements implemented over the past 10 years. There are, however, challenges with regard to the successful implementation of these agreements. Neumann et al. (2011), for example, see "high transaction costs, the lack of acceptable outcome metrics, difficulties in determining treatment effects, and the absence of suitable data capture systems" as some of those challenges involved. Towse and Garrison (2010) agree that in principle risk-sharing can increase overall efficiency by providing manufacturers and payers with real options. However, they believe it is too early to conclude that the recent interest in these agreements will become a trend owing to the lack of empirical evidence on the success of the on-going schemes.

Overview of Thesis and Specific Essays

Given the diversity and complex dynamics of pay-for-performance risk-sharing schemes, the optimal solution for the payer or the drug manufacturer may not be obvious. Providing

insight into the dynamics of these agreements can lead to designing contractual solutions that render the use of these new expensive drugs cost-effective. Motivated by this idea, in this dissertation I examine the performance of two distinct types of health-based pharmaceutical pay-for-performance risk-sharing agreements.

The first type is based on the bortezomib risk-sharing scheme in the UK. In the first essay I examine the performance of a risk-sharing agreement similar to the bortezomib agreement from the perspective of the manufacturer. I assume that under this agreement, patients are assessed at some evaluation time to determine whether they are responding to the drug. The drug manufacturer rebates to the payer a proportion of the sales to non-responding patients. I use an underlying disease progression model to calculate the proportions (or numbers) of patients in each health state at each point of time. To incorporate uncertainty due to imprecision in measuring the response of patients to the drug, I use a continuous time Markov chain (CTMC) with three health states: "Sick", "Responding to drug", and "Progression of disease". By using the proportions of patients in each state at each point in time, I obtain the profit function and establish the optimization problem for the manufacturer. Then I address the following specific questions with regard to the performance of this risk-sharing agreement: What is the optimum evaluation time for the manufacturer if the rebate rate has been set by the healthcare payer? Under what conditions will the drug manufacturer make a profit? What is the distribution of the drug manufacturer's profit resulting from different sources of uncertainty? I illustrate analytical findings with a numerical model parameterized using data from the bortezomib phase II clinical trial (Richardson et al., 2003)

and perform a detailed sensitivity analysis for the manufacturer's optimal profit and optimal evaluation time with respect to the model parameters including the CTMC transition rates.

In the second essay I examine the performance of the bortezomib agreement from the payer's perspective. I extend the disease progression model developed in the first essay by adding a new state (i.e., "Death") and calculate the net monetary benefits of the payer that result from the risk-sharing agreement. Adding this new state enables the calculation of the cost and benefit of the new treatment for those patients for whom disease has progressed. I simplify and approximate the model by using a system of ordinary differential equations to calculate the proportions of patients in each health state at each point in time. I establish the optimization problem for the payer and identify the conditions under which both the payer and the pharmaceutical firm have incentives to introduce the new drug. I also investigate how different classifications of rebates for non-respondent patients affect the two parties.

In the third essay I discuss the second type of pay-for-performance risk-sharing agreement, which is based on a stylized model. Under this model, patients are prescribed a drug only if their probability of response to the drug lies within a range of probabilities of success between a lower and an upper cut-off probability. The payer determines these cut-off probabilities such that the use of the drug becomes cost-effective. The pharmaceutical firm provides the payer with a rebate for patients who do not respond to the drug. I generalize on Barros (2011) by means of allowing the rebate to be different from the price of the drug and by incorporating two types of administrative costs. To model patients' response to the drug, I use a simple disease progression model consisting of two states, i.e., response and failure.

I formulate the problem as a Stackelberg game in which the manufacturer acts as the leader and determines the optimal price for the drug to maximize its expected profit. Then the payer chooses the optimal cut-off probabilities to maximize its expected payoff. The problem is solved in reverse time sequence. Thus, in the first step of the analysis, I find the optimal decisions by the payer (i.e., cut-off probabilities) for a given price by solving the payer's optimization problem. In the second step of the analysis I find the drug manufacturer's optimal price for given optimal cut-off probabilities by solving the manufacturer's optimization problem. Then I seek to answer two important policy questions: First, does the payer benefit from the risk-sharing agreement? Second, is the risk-sharing agreement welfare-improving? I continue further by examining how administrative costs and distribution of the probability of response would affect the welfare-improving status of this type of risk-sharing compared with no risk-sharing.

In the final chapter of the thesis I give an overview of the main results from the analysis of the risk-sharing agreements discussed in this thesis and highlight the policy implications of their implementation. Then I conclude with a few suggestions on the directions for future research.

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Chapter 1

1 Health-based Pharmaceutical Pay-for-performance Risk-sharing Agreements

Many new drugs, such as biologics and cancer drugs, are very costly. However, their effectiveness outside of clinical trial settings is often uncertain at the time they gain market approval. This uncertainty may reflect a lack of real-world outcomes data, as opposed to clinical trial data, for a typical patient population. A risk-sharing agreement is a contract between a drug manufacturer and a healthcare payer to help manage uncertainties regarding the cost and effectiveness of those drugs. In this chapter, I model a risk-sharing agreement in which a proportion of total sales is rebated. I model disease progression using a continuous time Markov chain (CTMC) with uncertain transition rates. I examine the performance of this risk-sharing agreement from the manufacturer's perspective and investigate the conditions under which the manufacturer will make a profit. I illustrate with a numerical model parameterized using data from a phase 2 clinical trial of an oncology drug that was subjected to a risk-sharing agreement in the UK.

1.1 Introduction

In October 2006, the UK National Institute for Health and Care Excellence (NICE) recommended against coverage by the National Health Service (NHS) of the drug bortezomib (Velcade) for the treatment of multiple myeloma owing to its high price (BBC News, 2006; NICE, 2006). The manufacturer of the drug chose not to reduce the drug price but instead proposed to reimburse drug sales for those patients who did not show a meaningful clinical response (Garber and McClellan, 2007).

As a result, the NHS and the drug manufacturer entered into a pay-for-performance risk-sharing agreement in 2007. Under this agreement, the NHS agreed to pay for four cycles of treatment for patients suffering from multiple myeloma who met the following criteria: 1) Bone transplant was not a treatment option. 2) At least one other treatment had been unsuccessful. After four cycles of treatment, the impact of treatment was measured by a serum monoclonal protein (M protein) test. If the test showed effectiveness (defined for this agreement as a 50% or more reduction in M protein), then treatment could be continued and further cycles would be funded by the NHS. However, if the treatment was not successful, then it would be stopped, and the drug manufacturer would reimburse the NHS for the cost of the first four cycles (NICE, 2007).

A growing number of drugs that use advanced molecular biologic techniques ("biologics") are being introduced into the pharmaceutical market. These drugs often have list prices of several thousand to several hundred thousand dollars per patient per year. Some examples include trastuzumab (Herceptin), which is used to treat breast cancer, with an annual treatment cost of $48,000 (USD) per patient (FTC, 2009); bevacizumab (Avastin), which is used to treat colorectal cancer, with an annual treatment cost of $100,000 (USD) per patient (Sahr, 2009); and imiglucerase (Cerezyme), which is used to treat the metabolic disorder Gaucher's disease, with annual treatment costs of over $300,000 (USD) (Sahr, 2009).

At the time of the introduction of many of these drugs to the market, their effectiveness outside of clinical trial conditions is uncertain. Thus, when making funding decisions for these new drugs, this uncertainty creates the risk for the healthcare payers that the incremental benefits gained from these drugs will not be worth the additional cost. Pay-

for-performance has become an option for payers to manage this risk (Adamski et al., 2010). Under this model, a healthcare payer agrees to pay for a medicine based on a successful or agreed-upon clinical outcome. If the outcome is not achieved, then the payer must be reimbursed according to the conditions specified in the risk-sharing agreement between the payer and the drug manufacturer.

In this chapter, I model a risk-sharing scheme in which a proportion of total sales is rebated. I model disease progression and response to the drug with a CTMC. I assume that those who are responding to the drug at the evaluation time are eligible to continue receiving the drug, while a rebate is paid for all other individuals. I address the following specific questions with regard to the performance of this risk-sharing agreement, from the perspective of the drug manufacturer: What is the optimum evaluation time if the rebate rate has been set by the healthcare payer? Under what conditions will the drug manufacturer make a profit? What is the distribution of the drug manufacturer's profit resulting from different sources of uncertainty?

1.2 Related Literature

There are several types of risk-sharing agreements. Adamski et al. (2010) provide a detailed review of the risk-sharing agreements implemented globally, and Carlson et al. (2010) provide a taxonomy of performance-based reimbursement schemes between healthcare payers and manufacturers. Zaric et al. (2013) review some of the literature on risk-sharing agreement modeling, and they give examples of different types of risk-sharing schemes as an indication of the broadness of these types of contracts. Although risk-sharing agreements are becoming more common, only limited academic research exists on this subject. I identify two groups of papers on the subject: the first group

investigates risk-sharing agreements that are based on health outcomes, and the second group investigates agreements that are based on non-health outcomes, such as the drug's market share, sales volume, or duration of treatment.

1.2.1 Risk-sharing Based on Health Outcomes

Gandjour (2009) considered a risk-sharing agreement where a payer, who is risk-neutral in cost but risk-averse in health benefits, pays a discounted price when the observed effectiveness is less than expected. Zaric and Xie (2009) developed two-period models to compare two risk-sharing arrangements when there is uncertainty about the effectiveness of the new drug. In the first model, risk-sharing is operationalized by requiring the drug be pulled from the market if the net monetary benefit (NMB) is negative in the first period. In the second model, risk-sharing is operationalized by requiring the manufacturer to pay a rebate to the healthcare payer in each period when negative NMBs are observed. Zaric and Xie (2009) showed that the relative performance of the two arrangements depends on several factors and that neither arrangement is always preferred.

Lilico (2003) modeled the health benefits of a drug through lost earnings due to illness and calculated the utility to patients under two scenarios: with and without risk-sharing. He assumed that patients are risk-averse, that the pharmaceutical firm is risk-neutral seeking to maximize its profit, and that there is uncertainty regarding treatment outcomes. He investigated the conditions under which risk-sharing leads to increased profit for the firm and increased welfare for patients. He concluded that under risk-sharing firms get increased profit and patients get increased welfare, and that the gains are greater when the disease is harder to cure or when it takes longer to cure.

Barros (2011) analyzed the interactions between the NHS and the pharmaceutical industry with and without risk-sharing. The author developed a simple disease progression model, where patients respond successfully with probability π to a new treatment with a benefit $b>0$. He assumed the price is set by the drug manufacturer and calculated the utility for the payer (NHS) and the valuation of sales for the drug manufacturer for both scenarios. The results of this model showed that, depending on when a risk-sharing agreement is negotiated (i.e., before or after the price has been set for the drug), the agreement may increase or decrease the social welfare. Based on Barros (2011), Antonanzas et al. (2011) developed models to analyze scenarios with and without risk-sharing. Antonanzas et al. (2011) assumed that the price of the new drug is determined through a negotiation between the payer and the drug manufacturer. These authors explored how the optimal contract may depend on the trade-off among the monitoring costs, the marginal production cost, and the utility derived from treatment.

1.2.2 Risk-sharing Based on Non-health Outcomes

Zaric and O'Brien (2005) analyzed a drug manufacturer's optimal statement of total budget for a new drug under a price-volume agreement. Under the price-volume agreement, if the total cost of a drug is greater than the projected budget, then the manufacturer must reimburse the healthcare payer a portion α, $0<\alpha<1$, of the difference between the true drug expenditures and the stated budget. The authors showed that the manufacturer's optimal statement of total budget varies in unit price, unit cost, and the rebate proportion, which led the authors to argue that a single risk-sharing model would not be effective in all situations.

Zhang et al. (2011) developed a game theoretic model of price-volume agreement to investigate the optimal contract design in the presence of asymmetric information about the mean total demand. They considered a one-period problem in which the unit sales price and the rebate rate are offered by the payer to the manufacturer. The objective of the payer is to maximize its NMB, and the objective of the manufacturer is to maximize its profit. Among the findings in Zhang et al. (2011) are the following: an incentive-compatible contract always exists; the optimal price is decreasing in expected market size; and the rebate may be increasing or decreasing in the expected market size.

1.2.3 Uncertainty in Health Economic Evaluations

There are two types of uncertainty in health economic evaluations: first-order uncertainty and second-order uncertainty (Briggs et al., 2012; Halpern et al., 2000; Stinnett and Paltiel, 1997). The effectiveness of a drug for the treatment of a disease may vary from one patient to another within the patient population. This heterogeneity in patient response to treatments could be observed in numerous settings. For example, there may be heterogeneity in *delay until response* and *duration of response* to a drug. First-order uncertainty reflects the heterogeneity inherent in the stochastic nature of the response to the drug (Halpern et al., 2000; Stinnett and Paltiel, 1997). Second-order uncertainty arises mainly owing to a lack of evidence about outcomes in a typical patient population or under "real-world" conditions, as opposed to the sample of patients in a clinical trial (Mullins et al., 2010; Halpern et al., 2000). For example, a clinical trial might not reflect reality when the sample of patients is not fully representative of the patient population or when imprecisions occur in measuring the trial outcomes.

First-order uncertainty, which is inherent in most risk-sharing papers by assuming that response of patients to the drug is stochastic in nature, is modeled by defining probability distributions for health and/or non-health outcomes of the drug. An examination of second-order uncertainty is not as common in risk-sharing papers. Some examples include Barros (2011) and Antonanzas et al. (2011), who incorporated second-order uncertainty by assuming that the probability of treatment success is uncertain. Zhang et al. (2011) also incorporated second-order uncertainty by assuming an error term for the drug demand. In my model, first-order uncertainty is expressed by treating the proportion of patients in each health state at each point of time as a random variable. I incorporate second-order uncertainty by assuming that the rates at which patients move from one health state to another are uncertain due to errors in measuring the response to the drug.

1.2.4 Contributions of this Work

This chapter investigates optimal decision-making by a drug manufacturer in a risk-sharing agreement that is based on health outcomes of a new drug. Many of the other papers that investigated risk-sharing based on health outcomes used simple models of effectiveness, in which treatment is either a success or a failure (e.g., Barros (2011) and Lilico (2003)). In this chapter, I enrich modeling of patient response to the drug through a CTMC-based disease progression model. By using both analytical and numerical approaches, we gain insights into the performance of a risk-sharing agreement similar to the bortezomib agreement in the UK from the perspective of the drug manufacturer. Note that the mechanics of this type of risk-sharing agreement are different from those of the agreements discussed in the health-outcome–based papers of the literature review. This

difference makes a direct comparison of the results of this chapter with the results from those papers impossible.

This chapter makes three main contributions. First, to my knowledge, this is the first study to capture both first- and second-order uncertainty in the context of a risk-sharing agreement with a drug manufacturer using a CTMC disease progression model. Second, this is the first study to investigate the dynamics of a risk-sharing agreement, in which the evaluation time for the patients' response to the drug is one of the contract parameters. Third, this chapter specifies boundary conditions on the rebate rate, where the profit has an optimal solution or the profit becomes negative and thus the manufacturer has no incentive to participate.

Table 1-1: Table of decision variables and parameters

ITEMS	DESCRIPTIONS
α	Rebate rate (set by the healthcare payer)
T_E	Evaluation time (to be negotiated by firm and healthcare payer)
Λ_S, Λ_R	Random variables for the transition rates. Λ_S: from *S*, Λ_R: from *R* to *P*; λ_S, λ_R realized values
Θ_S	Given a transition from state *S* occurs, random variable for the probability that the destination is *R*; θ_S realized value
$S(t)$, $R(t)$, $P(t)$	Random variables for the proportions of patients in states *S*, *R*, and *P*, with uncertain parameters (first- and second-order uncertainty)
$S_1(t)$, $R_1(t)$, $P_1(t)$	Random variables for the proportions of patients in states *S*, *R*, and *P*, for a given set of parameters (i.e., first-order uncertainty only)
s, r, p	Values taken by the random variables $S(t), R(t),$ and $P(t)$ respectively
$\bar{S}(t), \bar{R}(t)$	Expected values of proportions of patients across states *S* and *R* at time *t*
M,C	Payment and marginal production cost for the drug per unit time
$\pi_\alpha(T_E)$	Manufacturer's profit for a given set of proportions of patients in states *S*, *R*, and *P* (first- and second-order uncertainty)
$\Pi_\alpha(T_E)$	Expected value of the manufacturer's profit with regard to first-order uncertainty for a given set of transition rates
T^*	Optimal evaluation time for $\Pi_\alpha(T_E)$
α_L	The lower threshold for α, for which $\partial\Pi_\alpha(T_E)/\partial T_E = 0$ at $T_E = 0$
α_∞	The threshold for rebate rate, above which the profit becomes negative as T_E approaches infinity.

1.3 Model

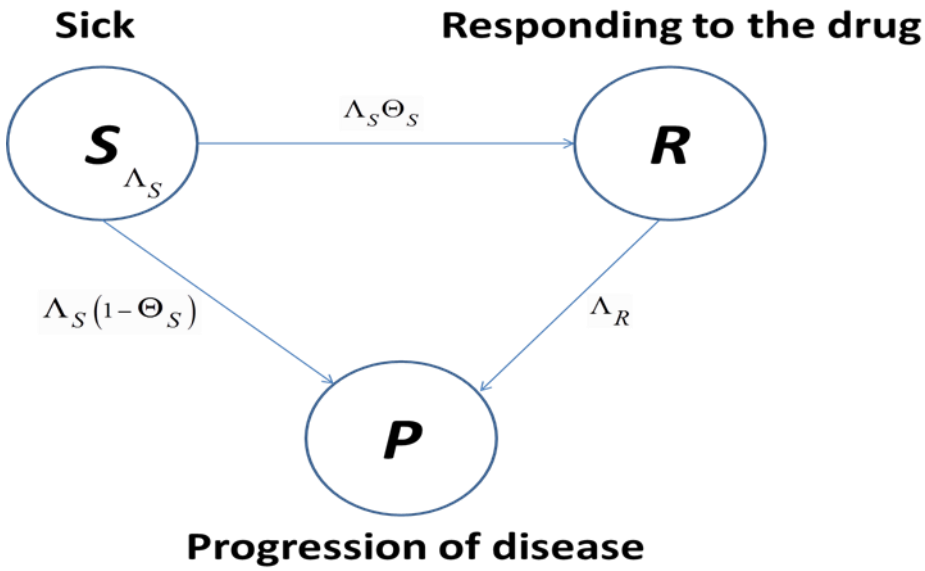
1.3.1 Disease Progression Model

My model captures heterogeneity in patient response to a drug (i.e., first-order uncertainty) by modeling disease progression as a CTMC with three states: "Sick" (*S*), "Responding to the drug" (*R*), and "Progression of disease" (*P*), where *P* is an absorbing state that includes death (Figure 1-1). We let $S(t)$, $R(t)$, and $P(t)$ denote the random variables for the proportions of patients at time *t* in state *S*, *R*, and *P*, respectively. We define Λ_S as the (random) transition rate from state *S* and Θ_S as the (random) probability

that the destination is *R* given that a transition from state *S* occurs. Thus, the probability that the destination is *P*, given that a transition from *S* occurs, is $1-\Theta_S$.

Transition rates of patients from state *S* to state *R* and from state *S* to state *P* are therefore given by $\Lambda_S\Theta_S$ and $\Lambda_S(1-\Theta_S)$, respectively. We let Λ_R denote the (random) transition rate from state *R* to state *P*. My model also captures the imprecision in measuring patient response to the drug (second-order uncertainty) by assuming that CTMC transition rates are uncertain (i.e., Λ_S, Θ_S, and Λ_R are random variables).

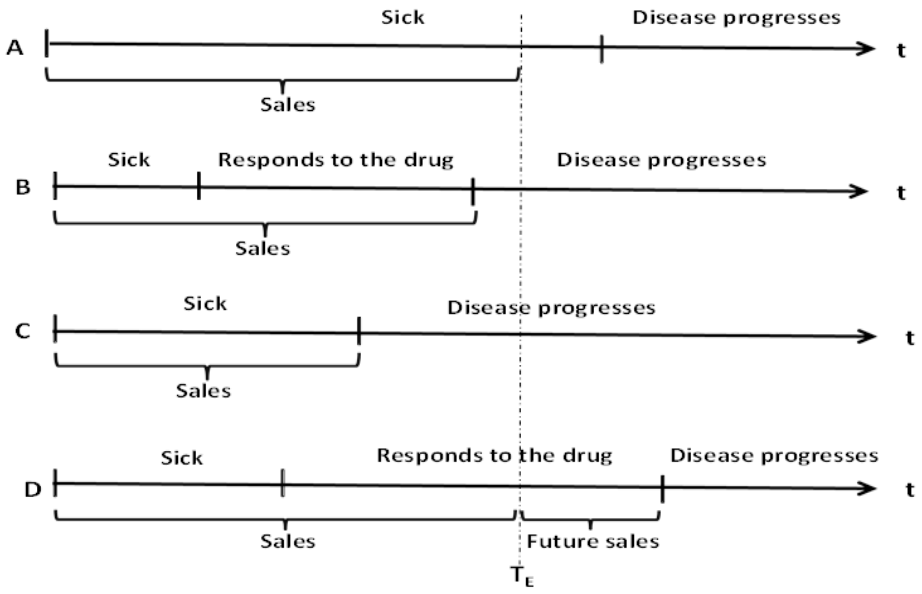
Figure 1-1: Disease progression model



1.3.2 Manufacturer's Profit

I assume that the administration of a new drug is subject to a pay-for-performance risk-sharing agreement between the drug manufacturer and a third-party payer. According to this agreement, patients start taking the drug at time $t = 0$ and stop receiving the drug as soon as the disease progresses (i.e., as soon as they enter state *P*, either from state *S* or state *R*). At a pre-specified time, $T_E > 0$, patients are evaluated to determine whether they are responding (and, hence, whether the drug has been successful). Patients who are not responding at T_E stop receiving the drug. The manufacturer must rebate the payer a proportion α, $0 \leq \alpha \leq 1$, of the total sales incurred until time T_E for two groups of patients: 1) patients who are not responding at T_E (Figure 1-2A); and 2) patients for whom the disease has already progressed by T_E (Figure 1-2B and 2C). Patients who are responding at T_E continue taking the drug, and the manufacturer continues to collect sales revenues beyond time T_E for as long as the patients continue to respond to the drug (Figure 1-2D).

Figure 1-2: Timeline scenarios for sales of the drug for every patient



I ignore sunk costs of R&D and consider marginal production and distribution cost only. Let M be the payment for the drug per unit of time, and let C be the marginal production and distribution cost of the drug per unit of time. I assume the rebate parameter α is set by the payer and that T_E is a parameter of the contract to be negotiated by the payer and manufacturer. Let $\pi_\alpha(T_E)$ be the manufacturer's expected profit from sales of the drug with regard to both first- and second-order uncertainty:

$$\begin{aligned}\pi_\alpha(T_E) = \; & E[\textit{Sales until } T_E] - E[\textit{Costs until } T_E] + E[\textit{Future sales after } T_E] \\ & - E[\textit{Future costs after } T_E] - E[\textit{Rebates}].\end{aligned} \quad (1)$$

In the Appendix, I describe how to calculate the five components of the expected value of the profit in (1) (See Equations [A1] to [A5]). These calculations involve multiple integrals over the state (S, R, P), time, and uncertain transition rates. Although there is no closed-form solution for the expected value, one way to estimate $\pi_\alpha(T_E)$ is through Monte Carlo simulation, which I show later in this chapter. By removing second-order uncertainty, we can simplify the problem and calculate the expected profit with regard to first-order uncertainty for a given set of transition rates.

1.3.3 Model When CTMC Transition Rates are Known

Let $\Pi_\alpha(T_E)$ be the expected profit with regard to first-order uncertainty for a given set of CTMC rates, λ_R, λ_S, and θ_S. For this given set of rates, let $S_1(t)$, $R_1(t)$, and $P_1(t)$ be the random variables for the proportions of patients in state S, R, and P at time t, respectively, and let s , r, and p denote the realized values at time t. The transition rate matrix of the CTMC model, G, is given for this set of parameters by:

$$G = \begin{pmatrix} -\lambda_S & \lambda_S\theta_S & \lambda_S(1-\theta_S) \\ 0 & -\lambda_R & \lambda_R \\ 0 & 0 & 0 \end{pmatrix}. \quad (2)$$

I calculate the corresponding instantaneous transition probability matrix $Q(t)$ of the CTMC as $Q(t) = e^{tG} = B\exp(Dt)B^{-1}$, where D is the diagonal matrix of the eigenvalues associated with transition rate matrix G, and B is its corresponding matrix of eigenvectors (Grimmett and Stirzaker, 2007). This calculation yields:

$$Q(t) = \begin{pmatrix} e^{-\lambda_S t} & A(e^{-\lambda_S t} - e^{-\lambda_R t}) & 1 + Ae^{-\lambda_R t} - (A+1)\, e^{-\lambda_S t} \\ 0 & e^{-\lambda_R t} & 1 - e^{-\lambda_R t} \\ 0 & 0 & 1 \end{pmatrix}, \quad (3)$$

where $A = \lambda_S\theta_S / (\lambda_R - \lambda_S)$ and $\lambda_R \neq \lambda_S$. For $\lambda_R = \lambda_S$, $A(e^{-\lambda_S t} - e^{-\lambda_R t})$ and $1 + Ae^{-\lambda_R t} - (A+1)\, e^{-\lambda_S t}$ become indeterminate in $Q(t)$, and instead, their limits as λ_R approaches λ_S (or vice versa) must be considered. For the remainder of this chapter, I ignore the special case of $\lambda_R = \lambda_S$.

Let $\mu(t) = (\bar{S}_1(t)\ \bar{R}_1(t)\ \bar{P}_1(t))$ be the vector of expected values of the proportions of patients in states *S*, *R*, and *P* at time *t* for the given set of rates. I assume that $\mu(0) = (1\ 0\ 0)$, as all patients are initially sick and untreated. I use the formula $\mu(t) = \mu(0)Q(t)$ (Grimmett and Stirzaker, 2007) to obtain the expected values of proportions across the CTMC states at time *t*:

$$\mu(t) = \left(e^{-\lambda_S t} \quad A(e^{-\lambda_S t} - e^{-\lambda_R t}) \quad 1 + Ae^{-\lambda_R t} - (A+1)\, e^{-\lambda_S t}\right), \quad (4)$$

where $\lambda_R \neq \lambda_S$.

Note that we could have used a system of linear differential equations to represent the disease progression model with constant flow rates between states. Solving this system of linear differential equation with the initial conditions of $s(0)=1$, $r(0)=0$, and $p(0)=0$ by standard techniques (Boyce and Diprima, 2009) yields the means, as shown in Equation (4). However, a deterministic model would not allow us to model first-order uncertainty and estimates variability in the number of patients in states.

In the Appendix, I show how to calculate the expected values of the five components of profit with regard to first-order uncertainty. Substituting Equations (A6) to (A10) for the expected values of the components of the profit given in (1) yields the expected profit with regard to first-order uncertainty for the given set of rates:

$$\Pi_{\alpha}(T_E)=\left((1-\alpha)M-C\right)\left(\frac{1}{\lambda_S}+\frac{\theta_S}{\lambda_R}\right)\left(1-\bar{S}_1(T_E)\right)+\alpha M\left(T_E+\frac{1}{\lambda_R}\right)\bar{R}_1(T_E), \qquad (5)$$

where $\lambda_R \neq \lambda_S$, and $\bar{S}_1(T_E)$ and $\bar{R}_1(T_E)$ are given by (4).

Although perhaps not immediate from (5), it should be intuitive that the expected profit is decreasing in the rebate rate α (see Lemma A1 in Appendix). The component $1-\bar{S}_1(T_E)$ in the first term of Equation (5) represents the expected value of the proportion of patients who are not in state *S* at the evaluation time T_E. The coefficient $\left((1-\alpha)M-C\right)$ represents the net profit generated by a patient per unit of time. Thus, the coefficient $\left((1-\alpha)M-C\right)/\lambda_S$ in (5) represents the mean net profit generated by a patient during his or her stay in state *S*. If $\left((1-\alpha)M-C\right)>0$, or alternatively, $\alpha<1-C/M$, then the profit is increasing in $1/\lambda_S$ (mean duration in state *S*). The coefficient $\left((1-\alpha)M-C\right)\theta_S/\lambda_R$ in

(5) represents the mean net profit generated by a patient during his or her stay in state *R*. Similarly, if $\alpha < 1 - C/M$, then the profit is increasing in θ_S (probability of response to the drug) and $1/\lambda_R$ (mean duration in state *R*). The component $\bar{R}_1(T_E)$ in the second term of (5) represents the proportion of respondents at T_E. The coefficient $M(T_E + 1/\lambda_R)$ consists of the two following portions of sales to a respondent at T_E: 1) sales up to T_E (i.e., MT_E); and 2) sales for the mean duration in state *R* (i.e., M/λ_R). Thus, $M(T_E + 1/\lambda_R)\bar{R}_1(T_E)$ in the second term of (5) corresponds to the sum of sales from all respondents at T_E. The rebate rate α in the second term is to compensate for double-counting the rebate corresponding to the respondents at T_E in the first term of (5). See Equations (A6) to (A10) in the Appendix for further details.

1.3.4 Optimal Profit

In order to find the optimum evaluation time to maximize the drug manufacturer's profit, we need to solve the following single-variable, non-linear optimization problem:

$$(\text{OP}) \quad \max_{T_E} \Pi_\alpha(T_E)$$
$$\text{s.t.} \quad T_E \geq 0$$

where $\Pi_\alpha(T_E)$ is the expected profit given in Equation (5).

For the manufacturer, there are trade-offs in choosing T_E under risk-sharing: if T_E is too short, the drug manufacturer does not have time to generate much profit. On the other hand, if T_E is too long, the manufacturer will have to pay a rebate to the payer for a high percentage of patients because all patients will eventually experience disease progression. Thus, the optimal value for the optimization problem (OP) is not obvious because the cost of evaluating too early should be balanced with the cost of evaluating too late. Let T^*

be the optimal evaluation time for (OP), i.e., the maximizer of $\Pi_\alpha(T_E)$ given by Equation (5). Although there is no closed-form solution to (OP), it can be shown that under certain conditions the profit function $\Pi_\alpha(T_E)$ is concave (see subsequent section and Lemma A3 in Appendix). It also follows from the implicit function theorem that T^* is decreasing in the marginal production cost C (see Lemma A4 in Appendix). Furthermore, it is possible to derive certain conditions regarding monotonicity of T^* as a function of the rebate rate α (see Lemma A5 in Appendix).

Moreover, when there is no risk-sharing agreement, α=0, and the rebate term in (5) is zero, we obtain the following expected profit:

$$\Pi_0(T_E) = (M - C)\left(\frac{1}{\lambda_S} + \frac{\theta_S}{\lambda_R}\right)(1 - \bar{S}_1(T_E)). \tag{6}$$

Since $\bar{S}_1(T_E)>0$ for all $T_E>0$, it follows that $\Pi_0(T_E)>0$ as long as $M>C$. It is also apparent from (6) that since the asymptotic $\bar{S}_1(T_E)$ is zero, the profit is maximized as T_E approaches infinity if there is no risk-sharing agreement.

1.3.5 Properties of the Optimal Profit

In this section, I investigate the conditions under which the drug manufacturer's expected profit is positive. The drug manufacturer incurs the highest rebate as T_E approaches infinity. The asymptotic expected value of the profit in (5) is given by:

$$\lim_{T_E \to \infty} \Pi_\alpha(T_E) = ((1-\alpha)M - C)\left(\frac{1}{\lambda_S} + \frac{\theta_S}{\lambda_R}\right). \tag{7}$$

From (7) it is obvious that the asymptotic profit would still be positive in spite of incurring the maximum rebate if the rebate rate were low enough, i.e., $\alpha < 1 - C/M$.

Thus, $\alpha_\infty = 1 - C/M$ is a threshold for the rebate rate, above which the profit becomes negative as T_E approaches infinity. It follows that if $M>C$, then α_∞ is always larger than zero and less than one, i.e., $\alpha_\infty \in (0,1)$. Even when $\alpha>\alpha_\infty$, the profit can still be positive for some $T_E<\infty$, namely if the number of patients responding to the drug at T_E is high enough and fewer rebates are therefore required.

Let α_L denote a threshold for the rebate rate, such that, for $\alpha=\alpha_L$, the slope of the expected profit function (5) is zero at T_E=0, i.e., $\partial \Pi_\alpha(T_E)/\partial T_E\big|_{T_E=0}=0$. This yields:

$$\alpha_L = \left(1 - \frac{C}{M}\right)\left(1 + \frac{\lambda_S \theta_S}{\lambda_R}\right). \tag{8}$$

When the rebate rate $\alpha<\alpha_L$, then the slope of the profit function is positive at T_E=0, which implies that the manufacturer's profit is positive for some $T_E>0$. From (8), we see that the threshold α_L is decreasing in the marginal production cost C and increasing in the quality characteristics of the drug (i.e., the response rate $\lambda_S\theta_S$ and the mean duration of response $1/\lambda_R$). Note that α_L does not necessarily have to be less than one. That is, even if $\alpha>1$, as long as $\alpha<\alpha_L$, the manufacturer can still make a positive profit and rebate more than sales of the drug collected from non-responding patients. From (8) it follows that if $\lambda_R < \lambda_S\theta_S(M-C)/M$, then $\alpha_L>1$. For instance, if $M>2C$ and $\lambda_S\theta_S > \lambda_R$, then $\alpha_L>1$.

Since $\lambda_S\theta_S / \lambda_R > 0$, it follows from (8) that $\alpha_\infty<\alpha_L$. Thus, a rebate rate $\alpha>\alpha_L$ implies that the profit of the manufacturer starts with a negative value and also ends asymptotically with a negative value as T_E approaches infinity. However, when $\alpha>\alpha_L$, it is still possible that the manufacturer's profit will be positive for some $T_E>0$ owing to the unimodal shape of $\bar{R}_1(T_E)$.

Let t_R be the time, at which the number of patients in state *R* is maximized, i.e., $\partial \bar{R}_1(t)/\partial t\big|_{t=t_R} = 0$. For $\lambda_R \neq \lambda_S$, this leads to $t_R = \left(\ln(\lambda_R) - \ln(\lambda_S)\right)/(\lambda_R - \lambda_S)$ (see Lemma A2 in Appendix). It can be shown that $\Pi_\alpha(T_E)$ is concave for $\alpha \leq \alpha_L$ and $t_R \leq T_E \leq 2t_R$ (see Lemma A3 in Appendix). Next, I describe the conditions for the existence of T^*, i.e., the optimal evaluation time for $\Pi_\alpha(T_E)$ given by Equation (5), as a function of *α, M, C,* and the transition-rate parameters.

Proposition 1:

(a) If $\alpha \leq \alpha_L$, then there is an optimal evaluation time $T^* > t_R$, such that $\Pi_\alpha(T^*) > 0$ is the global maximum.

(b) If $\alpha_\infty \leq \alpha \leq \alpha_L$, then there is a finite optimal evaluation time T^*, $t_R < T^* < \infty$, such that $\Pi_\alpha(T^*) > 0$ is the global maximum.

Since $\alpha_\infty < \alpha_L$, a rebate rate $\alpha \leq \alpha_L$ falls into one of the following categories: $\alpha < \alpha_\infty$, $\alpha = \alpha_\infty$, or $\alpha_\infty < \alpha \leq \alpha_L$. The interpretation for $\alpha < \alpha_\infty$ is that the net sales are greater than the rebate paid for a non-respondent patient per unit of time (i.e., $M - C > \alpha M$). It follows from part (a) of Proposition 1 that for $\alpha < \alpha_\infty$, there is a $T^* > t_R$ such that $\Pi_\alpha(T^*) > 0$ is the global maximum.

The condition $\alpha = \alpha_\infty$ can be interpreted as the manufacturer being at the breakeven point for a non-respondent patient per unit of time (i.e., $M - C = \alpha M$). It follows from part (b) of Proposition 1 that for $\alpha = \alpha_\infty$, there is always a finite T^*, such that $t_R < T^* < \infty$.

The interpretation for $\alpha > \alpha_\infty$ is that the net profit for a non-respondent patient in one unit of time is negative. In other words, the manufacturer is making a loss here by paying a

rebate (αM) that is larger than the profit $(M - C)$ per non-respondent patient. However, according to part (b) of Proposition 1, despite this loss situation, the manufacturer can still make a positive profit overall. This result arises owing to the fact that as long as $\alpha \leq \alpha_L$, the slope of $\Pi_\alpha(T_E)$ remains non-negative at T_E=0.

The condition $\alpha_\infty < \alpha \leq \alpha_L$ can also be rearranged and written as in the following ordering between the transition rates: $0 < \lambda_R \leq \lambda_S \theta_S (M - C) / \left(\alpha M - (M - C)\right)$. This gives the range of λ_R for which there is a finite $T^* > t_R$ under certain values for M, C, α, λ_S, and θ_S. For instance, if $M - C > \alpha M/2$ and $\lambda_S \theta_S > \lambda_R$, then there is a finite $T^* > t_R$ such that $\Pi_\alpha(T^*) > 0$ is the global maximum.

The condition for a finite T^* when $\alpha \geq \alpha_\infty$ can be explained as follows: As T_E approaches infinity, all patients become non-respondents and the manufacturer is overall at the breakeven point when $\alpha = \alpha_\infty$ or overall making a loss when $\alpha > \alpha_\infty$. This implies that for $\alpha \geq \alpha_\infty$, T^* needs to be finite in order to yield a positive optimal profit. The result $T^* > t_R$ in Proposition 1 can be interpreted as follows: The manufacturer prefers to wait at least until the number of responding patients is maximized.

In the numerical examples section that follows, I further explore the properties of the expected profit by running simulation and estimating the distribution of the profit at each evaluation time T_E.

1.4 Monte Carlo Simulation of Manufacturer's Profit

In order to simulate the manufacturer's profit with regard to both first- and second-order uncertainty, we need to estimate the parameters for the general model. In the following

section, I apply the approach of Welton and Ades (2005) to estimate the distributions for the transition rates Λ_R, and Λ_S and the probability of success Θ_S, using published data from a phase 2 clinical trial (Richardson et al., 2003).

1.4.1 Estimation of Transition Rate Distributions

Let e_S and e_R be the *total* patient-months of exposure observed in states *S* and *R* during the course of the trial, respectively. The exposure for a patient in a state, e.g., *S* or *R*, is the time the patient spends in that state during the course of the trial. The total exposure e_i, $i \in \{S,R\}$, is the sum of individual exposures for patients in state *i* and is equivalent to the area under the curve that plots the number of patients in the respective state at each point of time.

Let n_S and n_R be the *total* number of transitions during the course of the trial out of states *S* and *R*, respectively. According to the conjugacy property, I assume that the (random) rates Λ_S and Λ_R are gamma distributed with *prior* parameters of a_S and b_S, and a_R and b_R, respectively (Gelman et al., 2004). Let $n_{S,R}$ be the number of transitions from state *S* to state *R* during the course of the trial. Following Welton and Ades (2005), I assume that the distribution of Θ_S is *beta* with *prior* parameters a_Θ and b_Θ (again owing to the conjugacy property). I derive the following *posterior* distributions from their respective prior distributions by using the approach of Welton and Ades (2005):

$$\Lambda_R \sim Gamma\ (a_R + n_R, b_R + e_R), \tag{9}$$

$$\Lambda_S \sim Gamma(a_S + n_S, b_S + e_S), \tag{10}$$

$$\Theta_S \sim Beta(a_\Theta + n_{S,R}, b_\Theta + n_S - n_{S,R}). \tag{11}$$

I use the above formulas for the distributions of the CTMC parameters to illustrate with a number of examples the optimal evaluation time for a drug manufacturer who has entered a risk-sharing agreement similar to the bortezomib agreement in the UK for the treatment of multiple myeloma. I fit the disease progression model using data from a phase 2 clinical trial (Richardson et al., 2003), and calculate the profit function for the manufacturer under a number of different conditions.

1.4.2 Numerical Examples for Distributions

In Richardson et al. (2003), the Kaplan-Meier method was used to perform time-to-event analysis of the trial outcomes. The *time to first response* was defined as "the time from the initial administration of bortezomib to the first evidence of a confirmed response." The *duration of a response* was defined as "the time from the achievement of a response to progression." The *time to disease progression* was defined as "the time from the initial administration of bortezomib to disease progression."

In the trial, 202 patients enrolled between February and December 2001. Of these, 193 patients could be evaluated. Patients received eight cycles of treatment (i.e., 24 weeks or about six months) during the course of the trial. There were 67 patients (35%) with a complete, partial, or minimal response to the drug. Among the 67 respondents, the median *time to first response* was 1.3 months. The median *time to progression of disease* among all 202 patients was seven months. The median *time to progression* among patients with a complete or partial response to bortezomib alone was 13 months. The median *duration of the response* among the 67 patients with a complete, partial, or minimal response to bortezomib alone was 12 months.

I estimate the parameters λ_S, λ_R, and θ_S by using the data from the above-described clinical trial. I use the Kaplan-Meier plot of *time to progression of disease* in the 193 patients treated with bortezomib (plot A in Richardson et al. (2003)), and estimate the number of patients for whom the disease has not progressed yet for a number of points in time (i.e., number of patients in $R+S$). I also use the Kaplan-Meier plot of the duration of the response in the 67 respondents (plot B in Richardson et al. (2003)) and extract the cumulative number of patients for whom the disease has progressed after responding to the drug for a number of points in time (i.e., cumulative number of transitions from state *R* to state *P*).

According to the results of the trial, of 67 respondents, 50% responded by 1.3 months after the initial administration of bortezomib (i.e., about 34 patients). From Richardson et al. (2003), the response times are unclear for the remaining 33 respondents after 1.3 months from the start of the trial. I produced an initial estimate of cumulative number of transitions from *S* to *R* from month two onward using a weighted least-squares approach. According to the result of this estimate, it took all 67 respondents eight months from the beginning of the trial to respond to the drug. I then estimated the number of patients in state *R* and, consequently, the number of patients in state *S*, at a respective number of points in time.

I use Equations (10) and (11) to estimate the distributions for Λ_S and Θ_S. The figures for the number of patients in state *S* at the end of the trial suggest that $n_S = 168$ and $e_S = 1095.98$. Also, the cumulative number of respondents (i.e., cumulative transitions from state *R* to state *P*) suggests that $n_{S,R} = 67$. I use Equation (9) to estimate the

distribution of Λ_R. The cumulative numbers of patients with progression of disease out of the 67 respondents suggest that $n_R = 48$ and $e_R = 434$. In the absence of any prior data for the parameters of the distribution of Λ_S, Θ_S, and Λ_R, I assume that $a_S = b_S = 0.1$, $a_\Theta = b_\Theta = 1$, $d_{S,R} = d_{S,P} = 1$, and $a_R = b_R = 0.1$ (Welton and Ades, 2005). Thus, we obtain the following distributions:

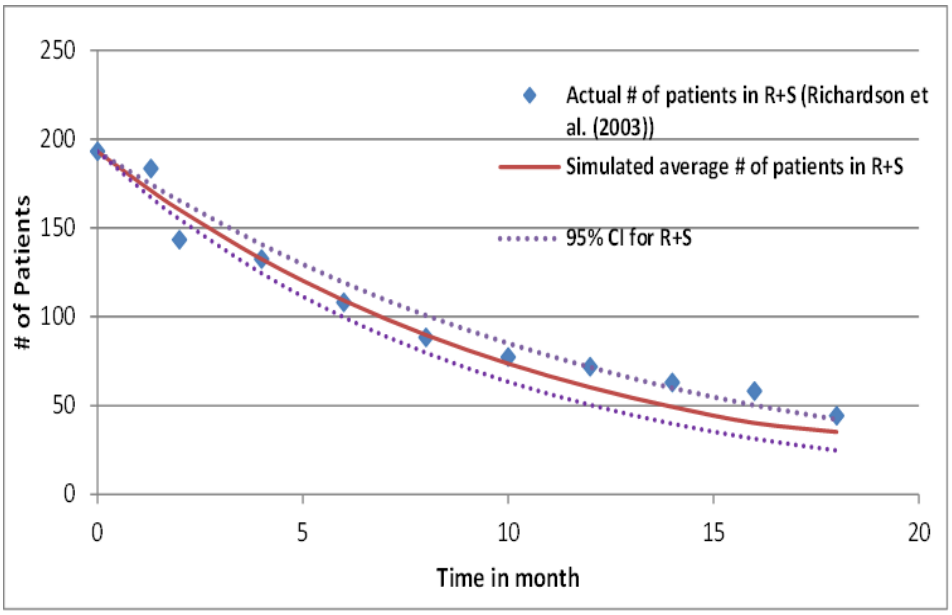
$$\Lambda_S \sim Gamma(168.1, 1096.1), \tag{12}$$

$$\Theta_S \sim Beta(68, 102), \tag{13}$$

$$\Lambda_R \sim Gamma(48.1, 434.1). \tag{14}$$

From distributions in (12) to (14), we obtain the following expected values and standard deviations for Λ_S, Λ_R, and Θ_S: $\bar{\lambda}_S = 0.15$, $\bar{\theta}_S = 0.4$, $\bar{\lambda}_R = 0.11$, and $\sigma_{\lambda_S} = 0.012$, $\sigma_{\theta_S} = 0.038$, $\sigma_{\lambda_R} = 0.016$. Figure 1-3 shows the actual numbers of patients without progression (i.e., patients who are in *S*+*R*), as well as the average numbers of those patients resulted by simulation at certain points of time. Figure 1-3 also shows the 95% confidence interval (CI) for the numbers of patients without progression. In the following section, I use the above-estimated distributions for the CTMC transition rates to estimate the distributions of the profit function for a number of numerical examples.

Figure 1-3: Simulated versus actual number of patients in state *R*+*S* at time *t*



1.4.3 Simulation of the Drug Manufacturer's Profit

I scale the price of the drug to one (M=1) and interpret the cost C as a proportion of M. I investigate profit for several combinations of α and C. For the base case, I assume that $C=0.3M$. Assuming a high production cost for the drug is because the production of new expensive drugs such as biologics is very costly and the populations of patients targeted for treatment by these specialized drugs are usually small. The time spent in state S and the time spent in state R follow exponential distributions with parameters Λ_S and Λ_R given by (12) and (14), respectively; the probability of response to the drug follows the binomial distribution Θ_S, given by (13).

I incorporate first-order uncertainty (i.e., stochastic nature of response of patients to the drug) by assuming that the duration of stay in sate S and the response time are distributed

according to exponential distributions with parameters λ_S and λ_R, respectively. Then I assume that the probability of response for each patient who leaves state *S* is also stochastic and distributed according to a Bernoulli distribution. I use the following steps to simulate the manufacturer's profit with regard to both first- and second-order uncertainty. First, I generate a set of CTMC transition rates from the distributions given by (12) to (14). Then, I use those values and simulate 1,000 times the response of a patient to the drug and calculate accordingly the manufacturer's profit. I repeat the above procedure 1,000 times. Figure 1-4 shows the expected values of the profit resulting from simulation, i.e., $\pi_\alpha(T_E)$, for α=70% and α=100% (dashed lines).

Figure 1-4: Simulated versus derived expected values of profit Equation (5), $\pi_\alpha(T_E)$ versus $\Pi_\alpha(T_E)$

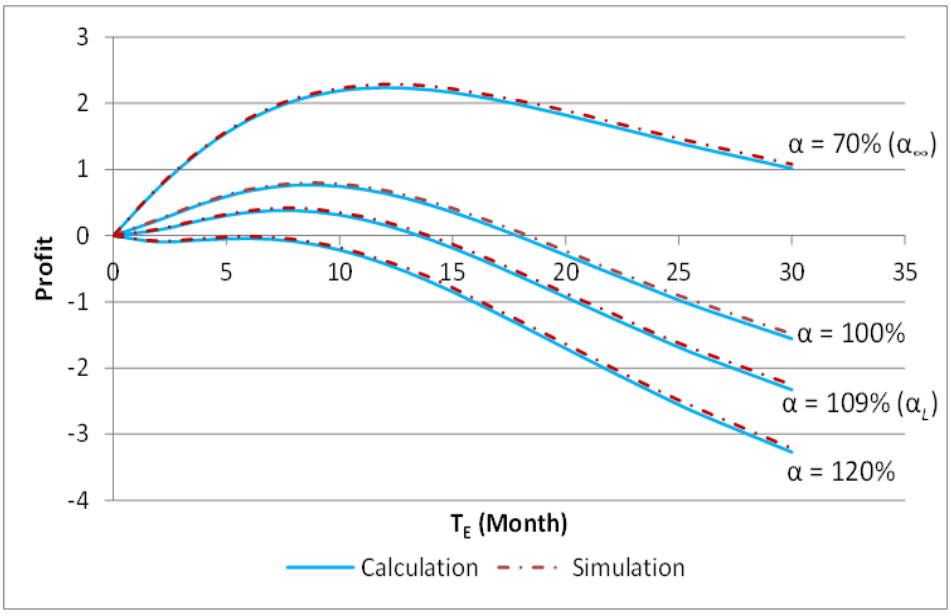


Figure 1-4 also shows the calculated expected values of the profit with respect to only first-order uncertainty, i.e., $\Pi_\alpha(T_E)$ based on λ_S=0.15, θ_S=0.4, and λ_R=0.11 (solid lines). It can be seen in Figure 1-4 that for various rebate rates, the expected values of the profit

including the optimal values estimated by $\pi_\alpha(T_E)$ are very close to the respective values calculated by $\Pi_\alpha(T_E)$. Therefore, the calculated expected value with the known CTMC parameters (as given in equation (5)) yields a good approximation to the model when there is no closed form solution for the expected value of the profit that results from incorporating both first and second-order uncertainty (i.e., $\pi_\alpha(T_E)$).

For the base case numerical illustration, α_∞=70%. I incorporate the expected values of the transition rates in Equation (8) to calculate the rebate rate lower threshold $\alpha_L \approx 109\%$. Figure 1-4 also shows the expected values of the profit for $\alpha = \alpha_\infty$, $\alpha = \alpha_L$, and for α= 120%.

Figure 1-5 shows the mean and 95% CI of the profit under the no-risk-sharing scenario (α=0) and under the risk-sharing scenario with α=100%. Figure 1-6 shows the mean and 95% CI of the manufacturer's loss at each evaluation time T_E when the profit under the risk-sharing scenario with α=100% is compared with the profit under the no-risk-sharing scenario, i.e., when the profit of the manufacture is calculated for α=0. In Figures 1-5 and 1-6, the expected values are obtained with regard to both first- and second-order uncertainty, whereas the 95% CI values are obtained with regard to second-order uncertainty only. Figure 1-6 shows that the loss is increasing in T_E for the parameters used in this example. According to Corollary 1 in the Appendix, the loss is increasing in T_E if $0.11\bar{R}_1(T_E) > (0.06 - 1/T_E)\bar{S}_1(T_E)$.

Figure 1-5: Mean and 95% CI for the profit with no risk-sharing (α=0) and with risk-sharing (α=100%)

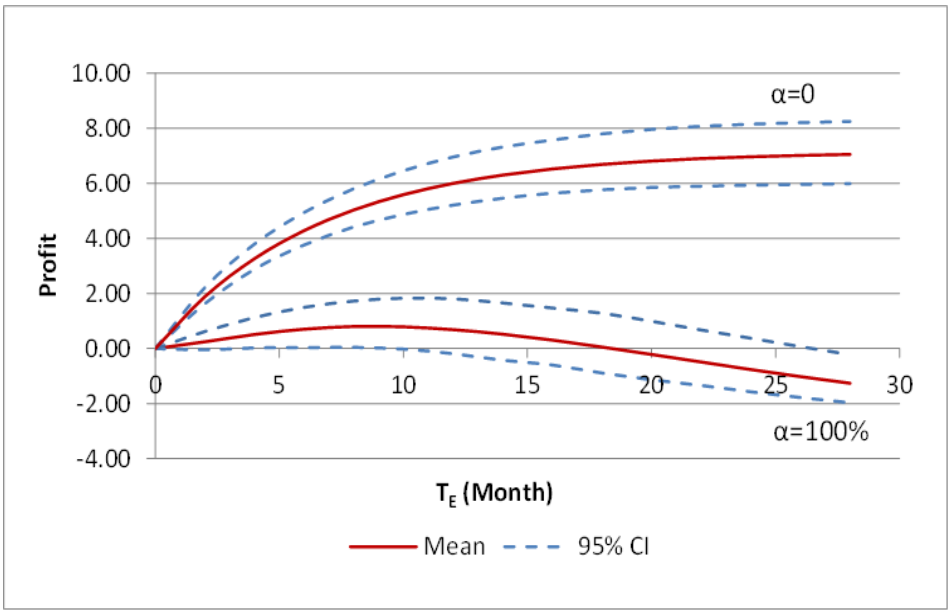
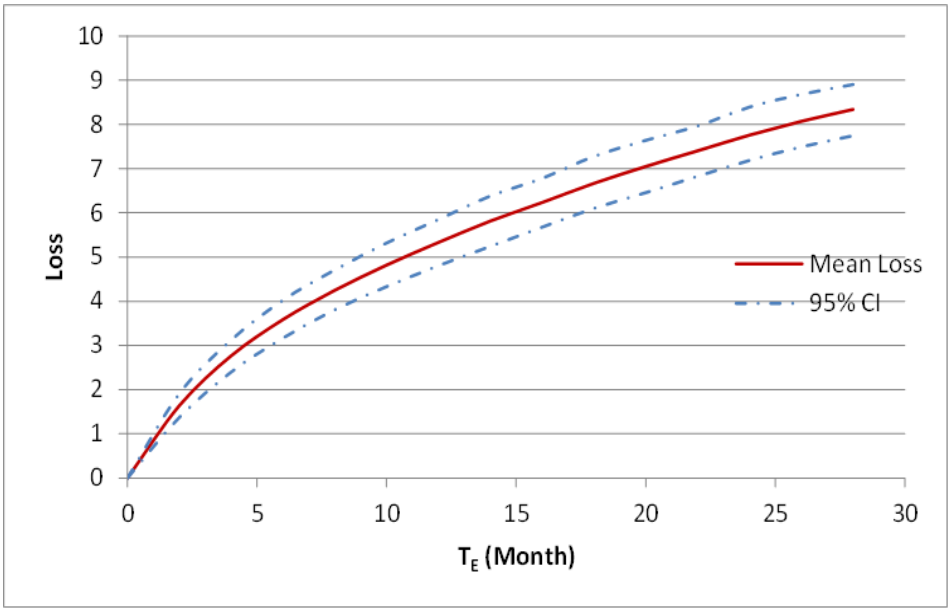


Figure 1-6: Mean and 95% CI for the manufacturer's loss due to risk-sharing with α=100% in comparison with no risk-sharing (α=0)



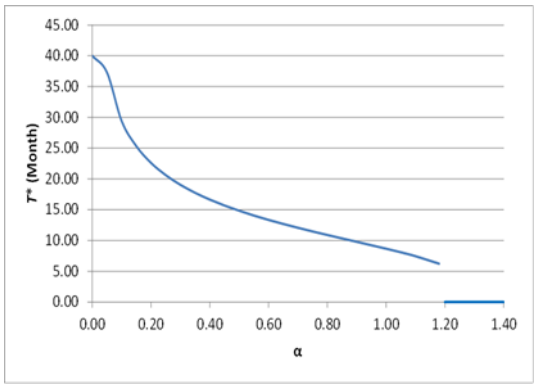
1.4.4 Sensitivity Analysis

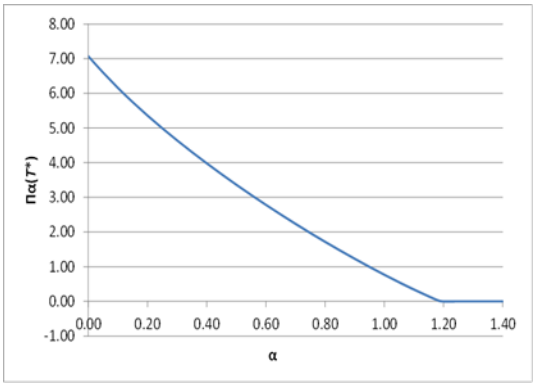
In the following section I investigate how T^* and the respective optimal profit $\Pi_\alpha(T^*)$ vary with the model parameters. As depicted in panel (a) of Figure 1-7, T^* is decreasing in the rebate rate α for the following reasons. A shorter evaluation time implies smaller sales of the drug because patients use the drug for a shorter period of time. Since the rebate is a proportion of the total sales, smaller sales implies a smaller rebate. Thus when α is large, a large rebate can be offset by smaller sales resulting from a shorter evaluation time.

Panel (b) of Figure 1-7 shows that $\Pi_\alpha(T^*)$ is also decreasing in α since for a larger α, the rebate is higher and thus the profit is smaller. It can be seen from panel (b) that for α≥120%, $\Pi_\alpha(T^*)=0$ at $T^*=0$, i.e., no feasible agreement is possible in this range of α. It can be verified that the results shown in Figure 1-7 (a) with respect to T^* for various rebate rates are consistent with the conditions stated in Proposition 1. The results shown in Figure 1-7 (a) are also consistent with Lemma 3, i.e., T^* is decreasing in rebate rate α as long as $0.11\bar{R}_1(T^*) > \left(0.06 - 1/T^*\right)\bar{S}_1(T^*)$.

Figure 1-7: Sensitivity analysis with regard to the rebate rate α (C=0.3M, λ_S=0.15, θ_S=0.4, and λ_R=0.11)

(a) Sensitivity analysis of T^* **(b) Sensitivity analysis of $\Pi_\alpha(T^*)$**

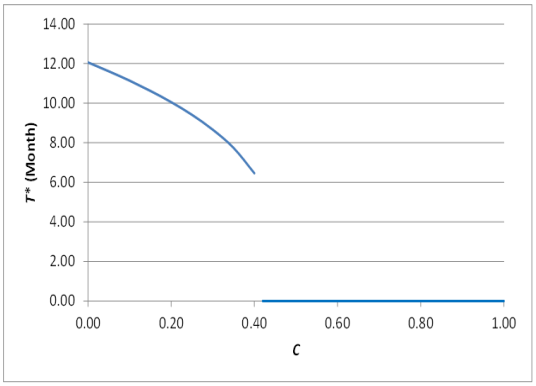


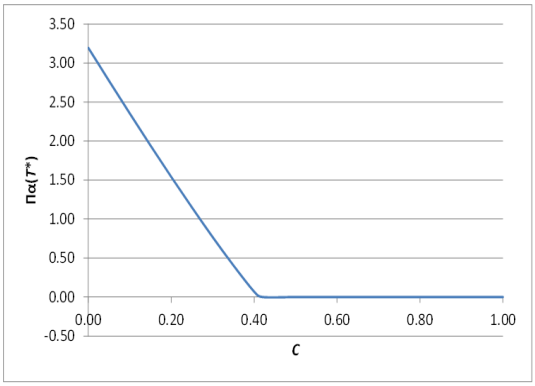


In panel (a) and (b) of Figure 1-8 we see T^* and $\Pi_\alpha(T^*)$ are both decreasing in C for reasons similar to those above regarding the rebate rate α. Panel (b) shows that for C>0.41, $\Pi_\alpha(T^*)$=0 at T^*=0, i.e., no feasible agreement is possible in this range of C.

Figure 1-8: Sensitivity analysis with regard to the marginal cost C (α=100%, λ_S=0.15, θ_S=0.4, and λ_R=0.11)

(a) Sensitivity analysis of T^* **(b) Sensitivity analysis of $\Pi_\alpha(T^*)$**





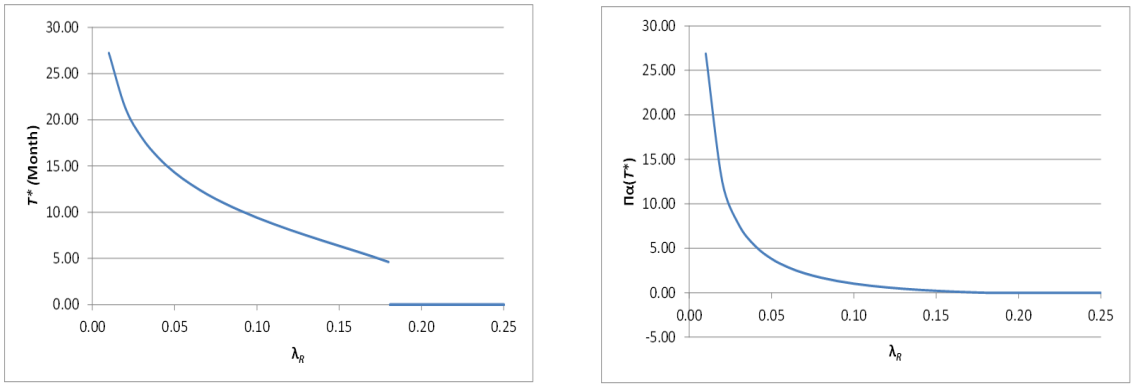
Panel (a) of Figure 1-8 shows the following results: T^*≈11 months for C=0.1M, T^*≈10 months for C=0.2M, T^*≈9 months for C=0.3M, and T^*≈7 months for C=0.4M. It can be

seen from the NICE guidelines for bortezomib that α=100% and the evaluation time is after four cycles of treatment with bortezomib (NICE, 2007). Four cycles is equivalent to 12 weeks, i.e., $T_E \approx 3$ months (Richardson et al., 2003). For all above-mentioned cases, except for the last case (i.e., $C=0.4M$), the drug manufacturer still makes profit with $T_E=3$ months. However, for example, for $C=0.1M$, the profit of manufacturer at the optimal evaluation time is more than two times higher than the profit after four cycles of treatment (i.e., 2.35 versus 1.11).

Figures 1-9 to 1-11 show the sensitivity analysis with regard to the CTMC rates (λ_R, θ_S, and λ_S, respectively).

Figure 1-9: Sensitivity analysis with regard to the transition rate λ_R (α=100%, $C=0.3M$, $\lambda_S=0.15$, and $\theta_S=0.4$)

(a) Sensitivity analysis of T^* **(b) Sensitivity analysis of $\Pi_\alpha(T^*)$**



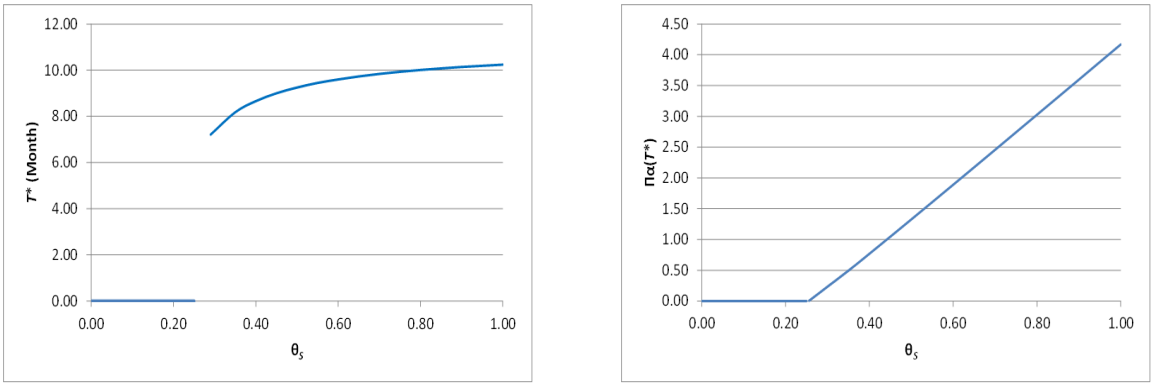
In panel (a) and (b) of Figure 1-9 we see both T^* and the optimal profit $\Pi_\alpha(T^*)$ are decreasing in λ_R. This is because a larger λ_R implies a shorter mean duration in state R per respondent ($1/\lambda_R$). A shorter mean duration in state R implies that the manufacturer prefers a shorter evaluation time such that more respondents can be measured at that

time. A shorter mean duration in R also implies a smaller profit such that for $1/\lambda_R \leq 5.3$ (i.e., $\lambda_R \geq 0.19$), $\Pi_\alpha(T^*)=0$ at $T^*=0$, i.e., no feasible agreement is possible in this range of λ_R.

In panel (a) and (b) of Figure 1-10 we see both T^* and the optimal profit $\Pi_\alpha(T^*)$ are increasing in θ_S. This is because a larger θ_S implies a higher proportion of respondents. Figure 1-10 shows that for $\theta_S \leq 0.25$, $\Pi_\alpha(T^*)=0$ at $T^*=0$, i.e., no feasible agreement is possible in this range of θ_S.

Figure 1-10: Sensitivity analysis with regard to the probability of response θ_S (α=100%, C=0.3M, λ_S=0.15, and λ_R=0.11)

(a) Sensitivity analysis of T^* **(b) Sensitivity analysis of $\Pi_\alpha(T^*)$**

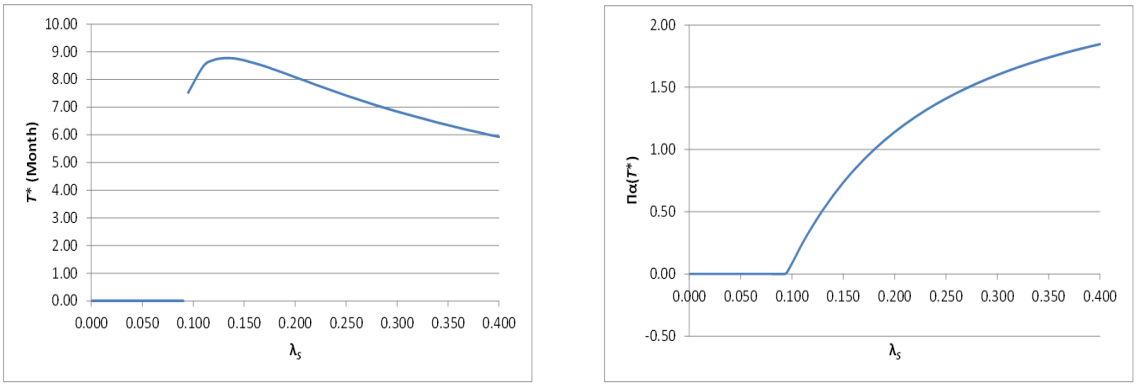


Finally in panel (a) of Figure 1-11, T^* is flat for small λ_S, increasing for intermediate λ_S, and decreasing for large λ_S. This relationship between T^* and λ_S can be explained as follows. If duration in state S is long (λ_S small), the manufacturer benefits by a long evaluation time so more patients move from S to R. However, if duration in state S is short (λ_S large), a long T_E can harm the manufacturer because a high proportion of patients have exited R.

In panel (b) of Figure 1-11, the optimal profit $\Pi_\alpha(T^*)$ is increasing in λ_S. This is because a shorter mean duration in state S (i.e., a larger λ_S) implies a higher number of respondents at the respective optimal evaluation time T^*. As shown in Figure 1-11, for $\lambda_S \leq 0.09$, $\Pi_\alpha(T^*)=0$ at $T^*=0$, i.e., no feasible agreement is possible in this range of λ_S.

Figure 1-11: Sensitivity analysis with regard to the transition rate λ_S (α=100%, C=0.3M, θ_S=0.4, and λ_R=0.11)

(a) Sensitivity analysis of T^* **(b) Sensitivity analysis of $\Pi_\alpha(T^*)$**



1.5 Conclusions and Future Research

I investigated the optimal evaluation time for a drug manufacturer under a pay-for-performance contract similar to the risk-sharing agreement used for bortezomib in the UK. The parameters used in this risk-sharing agreement can be categorized into two groups. The first group consists of the rebate rate α, the unit price of the drug M, and the evaluation time T_E. The parameters in this group are used to define the terms and conditions in the contract. The second group consists of the drug response rate $\lambda_S\theta_S$, the disease progression rate λ_R, and the drug production and distribution cost C. The parameters in this group are related to the characteristics of the drug and are generally

private information of the drug manufacturer. My analysis in this chapter reveals how different settings among the parameters of these two groups affect the profit and the optimal solution for the drug manufacturer.

My study highlights the trade-offs in negotiating this type of agreement. The analytical results supported by numerical examples in this study showed that, in many instances, the profit is non-monotonic for this type of risk-sharing agreement. Proposition 1 establishes boundary conditions on the rebate rate α, such that the status of the manufacturer's profit falls into one of the following two categories: 1) There is an optimal solution for the profit. 2) The manufacturer makes no profit and therefore would not participate. The following general rules can be derived with regard to the above mentioned categories: If $\lambda_S\theta_S$ is larger than λ_R and the rebate paid per patient (αM) is less than double the profit margin $(2\times(M-C))$, then there is an optimal solution for the drug manufacturer. On the other hand, if $\lambda_S\theta_S$ is smaller than λ_R and the rebate paid exceeds double the profit margin, then the drug manufacturer will make a loss. However, based on my numerical analysis (using data from the clinical trial of bortezomib), we observe that for low production cost C, the manufacturer makes a profit under most circumstances.

There are many promising directions for extending the model and for future research. The NICE assessment found that the incremental cost per quality-adjusted life year gained among patients with minimal response (i.e., a reduction of 25%-49% in serum M protein) would be very high (NICE, 2007). Thus, a potential extension to the model would be to assume a lower rebate rate for patients with minimal response compared with the rebate rate for non-respondents (i.e., patients with a reduction of less than 25% in serum M protein) and investigate the optimal solution under the new contract structure. I assumed

that the effectiveness of the drug was the only source of uncertainty. However, the cost of a new drug could be a source of uncertainty that could be incorporated in the model by assigning a probability distribution for that cost. The demand for the new drug can be incorporated in the model by assuming that the cohort size of patients administered the drug is a function of the price of the drug, the rebate rate, or both.

A limitation of this research is that it does not present the perspective of a second party, e.g., a healthcare payer, along with the drug manufacturer's perspective. Therefore, a potential area of future research would be to take a game theoretic approach in which a payer (e.g., NHS or a public drug plan) and a drug manufacturer are taking part. The first step to establishing this game is to find a suitable objective function for the payer. One possibility for the payer's objective function is to calculate the NMB of the payer by incorporating commonly accepted willingness-to-pay thresholds. The next step would be to specify the structure of the game and determine its respective incentive compatibility constraints. For instance it is possible to take a sequential approach such that for every rebate rate set by the payer, first the drug manufacturer determines the optimal price for the drug to maximize its profit. Then, the payer chooses the optimal evaluation time in order to maximize its NMB.

Appendix to Chapter 1

Calculation of the Expected Profit

In the following I show how to calculate the expected profit with regard to both first- and second-order uncertainty. Let $R(t)$ and $S(t)$ be the random variables for the proportions of patients in state S and R at time t, respectively, and let s and r denote the realized values. Let also Λ_S, Λ_R, and Θ_S be the random variables for the CTMC rates, and λ_S, λ_R, and θ_S be the realized values. Patients who are in state S (i.e., those who are taking the drug but have not yet responded to it) as well as patients who are in state R (i.e., those who are responding to the drug) contribute to the sales (and costs) of the drug until the evaluation time T_E. This leads to the following expressions for the terms in $\pi_\alpha(T_E)$:

$$E\left[Sales\ until\ T_E\right] = E\left[\int_{t=0}^{T_E} M\left(S(t)+R(t)\right)dt\right]$$
$$= \int_0^1\int_0^\infty\int_0^\infty\int_0^1\int_0^1\left(\int_{t=0}^{T_E} M\left(s+r\right)dt\right) f_{S(t),R(t),\Lambda_S,\Lambda_R,\Theta_S}(s,r,\lambda_S,\lambda_R,\theta_S)\,ds\,dr\,d\lambda_S\,d\lambda_R\,d\theta_S, \qquad \text{(A1)}$$

where $f_{S(t),R(t),\Lambda_S,\Lambda_R,\Theta_S}(.)$ is the joint probability density function of $R(t)$, $S(t)$, Λ_S, Λ_R, and Θ_S (t is a deterministic variable between 0 and T_E).

Similarly, I calculate the expected costs until T_E:

$$E\left[Costs\ until\ T_E\right] = E\left[\int_{t=0}^{T_E} C\left(S(t)+R(t)\right)dt\right]$$
$$= \int_0^1\int_0^\infty\int_0^\infty\int_0^1\int_0^1\left(\int_{t=0}^{T_E} C\left(s+r\right)dt\right) f_{S(t),R(t),\Lambda_S,\Lambda_R,\Theta_S}(s,r,\lambda_S,\lambda_R,\theta_S)\,ds\,dr\,d\lambda_S\,d\lambda_R\,d\theta_S. \qquad \text{(A2)}$$

Only those patients who are responding at $t=T_E$ will contribute to future sales and costs of the manufacturer beyond T_E. These patients continue taking the drug until disease progresses. The proportion of patients who are responding at T_E is a random variable

denoted by $R(T_E)$. We can calculate the future costs and sales, as in the following:

$$E\left[\textit{Future sales after } T_E\right] = E\left[E\left[M\int_{t=T_E}^{\infty}\left(R(t)\middle|\left(R(T_E)\middle|S(T_E)\right)\right)dt\right]\right]$$
$$= E\left[M\int_{t=T_E}^{\infty}R(t)dt\right] =$$
$$= \int_0^1\int_0^{\infty}\int_0^{\infty}\int_0^{r(T_E)}\int_0^{s(T_E)}\left(\int_{t=0}^{T_E}M\times r\times dt\right)f_{S(t),R(t),\Lambda_S,\Lambda_R,\Theta_S}(s,r,\lambda_S,\lambda_R,\theta_S)dsdrd\lambda_S d\lambda_R d\theta_S. \quad \text{(A3)}$$

Similarly,

$$E\left[\textit{Future costs after } T_E\right] =$$
$$= \int_0^1\int_0^{\infty}\int_0^{\infty}\int_0^{r(T_E)}\int_0^{s(T_E)}\left(\int_{t=0}^{T_E}C\times r\times dt\right)f_{S(t),R(t),\Lambda_S,\Lambda_R,\Theta_S}(s,r,\lambda_S,\lambda_R,\theta_S)dsdrd\lambda_S d\lambda_R d\theta_S. \quad \text{(A4)}$$

If the manufacturer were to rebate to the payer a proportion α of total sales until the evaluation time T_E, then the total rebate would be calculated as $\alpha M\int_{t=0}^{T_E}\left(S(t)+R(t)\right)dt$. However, in accordance with pay-for-performance, no rebate will be paid for those patients who are responding to the drug at time T_E. If the responders at T_E were supposed to be rebated, then their respective rebate amount would be equal to $\alpha MT_E R(T_E)$. This amount should be deducted from the total rebate in order to calculate the net expected rebate to be paid to the payer:

$$E\left[\textit{Rebates}\right] = E\left[\alpha M\int_{t=0}^{T_E}\left(S(t)+R(t)\right)dt - \alpha MT_E R(T_E)\right]$$
$$= \int_0^1\int_0^{\infty}\int_0^{\infty}\int_0^1\int_0^1\left(\alpha M\int_{t=0}^{T_E}\left(s+r\right)dt - \alpha MT_E r(T_E)dt\right)$$
$$\times f_{S(t),R(t),\Lambda_S,\Lambda_R,\Theta_S}(s,r,\lambda_S,\lambda_R,\theta_S)dsdrd\lambda_S d\lambda_R d\theta_S. \quad \text{(A5)}$$

Calculation of the Expected Profit for a Given Set of Transition Rates

I calculate the expected profit with regard to first-order uncertainty for a given set of CTMC rates, λ_R, λ_S, and θ_S. For this set of given rates, let $R_1(t)$ and $S_1(t)$ be the random

variables for the proportions of patients in state *S* and *R* at time *t*, respectively, and let *s* and *r* denote the realized values. Using similar arguments for the calculation of the profit in the above section leads us to the following expressions for the expected values of the terms in $\Pi_\alpha(T_E)$:

$$E\left[Sales\ until\ T_E\right] = E\left[\int_{t=0}^{T_E} M\left(S_1(t)+R_1(t)\right)dt\right]$$
$$=\int_{s=0}^{1}\left(\int_{t=0}^{T_E} M\times s\times f_{S_1(t)}(s)dt\right)ds+\int_{s=0}^{1}\int_{r=0}^{1-s}\left(\int_{t=0}^{T_E} M\times r\times f_{R_1(t)|S_1(t)}(r|s)dt\right)f_{S_1(t)}(s)drds,$$

where $f_{S(t)}(s)$ is the probability density function of $S_1(t)$ and $f_{R_1(t)|S_1(t)}(r|s)$ is the conditional density function of $R_1(t)$ given $S_1(t)=s$.

Interchanging the order of integration, we obtain:

$$E\left[Sales\ until\ T_E\right] = \int_{t=0}^{T_E} M\left(\int_{s=0}^{1} s\times f_{S_1(t)}(s)ds+\int_{s=0}^{1} f_{S_1(t)}(s)\times\int_{r=0}^{1-s} r\times f_{R_1(t)|S_1(t)}(r|s)drds\right)dt$$
$$= \int_{t=0}^{T_E} M\left(\bar{S}_1(t)+\bar{R}_1(t)\right)dt$$
$$= M\left(\frac{1}{\lambda_S}+\frac{\theta_S}{\lambda_R}\right)\left(1-\bar{S}_1(T_E)\right)-\frac{M}{\lambda_R}\bar{R}_1(T_E). \qquad \text{(A6)}$$

Similarly, we calculate the expected costs until T_E:

$$E\left[Costs\ until\ T_E\right] = C\left(\frac{1}{\lambda_S}+\frac{\theta_S}{\lambda_R}\right)\left(1-\bar{S}_1(T_E)\right)-\frac{C}{\lambda_R}\bar{R}_1(T_E). \qquad \text{(A7)}$$

Only those patients who are responding at $t=T_E$ will contribute to future sales and costs of the manufacturer beyond T_E. These patients continue taking the drug until disease progresses. The proportion of patients who are responding at T_E is a random variable denoted by $R_1(T_E)$ with mean $\bar{R}_1(T_E)=A\times\left(e^{-\lambda_S T_E}-e^{-\lambda_R T_E}\right)$. I define a new CTMC model with only two states, i.e., *R* and *P*, to capture future sales. In this new CTMC model,

those patients who were responding to the drug at time T_E —i.e., $R_1(T_E)$ —begin in state R at $t=T_E$, and then move to state P with transition rate λ_R. We obtain the transition rate matrix G and the corresponding instantaneous transition probability matrix $Q(t)$ of the two-state CTMC disease progression model as in the following: $G = \begin{pmatrix} -\lambda_R & \lambda_R \\ 0 & 0 \end{pmatrix}$, and

$Q(t) = \begin{pmatrix} e^{-\lambda_R (t-T_E)} & 1-e^{-\lambda_R (t-T_E)} \\ 0 & 1 \end{pmatrix}$ for $t \geq T_E$.

Let $\mu(t) = \left(R_1(t)\ P_1(t)\right)$ be the vector of expected values of proportions of patients across states R and P at time $t \geq T_E$ in the two-state CTMC model. Considering the initial condition of $\mu(0) = \left(R_1(T_E)\ 0\right)$, we use the formula $\mu(t) = \mu(0)Q(t)$ to obtain $R_1(t) = R_1(T_E)e^{-\lambda_R (t-T_E)}\ \forall\ t \geq T_E$. Having found $R_1(t)$ for $t \geq T_E$ with the assumed boundary conditions, we can calculate the future costs and sales, as in the following:

$$\begin{aligned} E\left[\textit{Future sales after } T_E\right] &= E\left[E\left[M\int_{t=T_E}^{\infty}\left(R_1(t)\middle|R_1(T_E)\right)dt\right]\right] \\ &= E\left[M\int_{t=T_E}^{\infty}R_1(t)dt\right] = E\left[M\int_{t=T_E}^{\infty}R_1(T_E)e^{-\lambda_R (t-T_E)}dt\right] \\ &= \frac{M}{\lambda_R}\bar{R}_1(T_E). \end{aligned} \tag{A8}$$

Similarly,

$$E\left[\textit{Future costs after } T_E\right] = \frac{C}{\lambda_R}\bar{R}_1(T_E). \tag{A9}$$

If the manufacturer were to rebate to the payer a proportion α of total sales until the evaluation time T_E, then the total rebate would be calculated as $\alpha M\int_{t=0}^{\infty}\left(S_1(t)+R_1(t)\right)dt$. However, in accordance with pay-for-performance, no rebate will be paid for those

patients who are responding to the drug at time T_E. If the responders at T_E were supposed to be rebated, then their respective rebate amount would be equal to $\alpha M T_E R_1(T_E)$. This amount should be deducted from the total rebate in order to calculate the net expected rebate to be paid to the payer:

$$E[Rebates] = E\left[\alpha M \int_{t=0}^{T_E} \left(S_1(t) + R_1(t)\right) dt - \alpha M T_E R_1(T_E)\right]$$

$$= \alpha M \times \left(\left(\frac{1}{\lambda_S} + \frac{\theta_S}{\lambda_R} \right) \left(1 - \bar{S}_1(T_E)\right) - \left(T_E + \frac{1}{\lambda_R} \right) \bar{R}_1(T_E) \right). \qquad \text{(A10)}$$

Lemma A1

Expected profit in Equation (5) is decreasing in the rebate rate α.

Proof of Lemma A1

To prove mathematically that the expected profit in (5) is decreasing in α, it is enough to show that the rebate paid, i.e., (A10), is increasing in α. From (A10) we have :

$$E[Rebates] = E\left[\alpha M \int_{t=0}^{T_E}(S_1(t)+R_1(t))dt - \alpha M T_E R_1(T_E)\right]$$

$$= \alpha M\left(\int_{t=0}^{T_E}(\bar{S}_1(t)+\bar{R}_1(t))dt - T_E\bar{R}_1(T_E)\right)$$

$$\bar{S}_1(T_E)\ \&\ \bar{R}_1(T_E)>0 \ \ \forall t>0 \ \Rightarrow \bar{S}_1(T_E)+\bar{R}_1(T_E)>\bar{R}_1(T_E) \quad \Rightarrow$$

$$T_E\times(\bar{S}_1(T_E)+\bar{R}_1(T_E))>T_E\times\bar{R}_1(T_E)$$

We show that $\bar{S}_1(t)+\bar{R}_1(t)$ is decreasing in *t*. The following differential equations are valid:

$$\frac{\partial\bar{S}_1(t)}{\partial t} = -\lambda_S\bar{S}_1(t) \quad \text{(a)}; \quad \frac{\partial\bar{R}_1(t)}{\partial t} = \lambda_S\theta_S\bar{S}_1(t) - \lambda_R\bar{R}_1(t) \quad \text{(b)}$$

Summing up both sides of equations (a) and (b):

$$\frac{\partial\bar{S}_1(t)}{\partial t} + \frac{\partial\bar{R}_1(t)}{\partial t} = -\lambda_S\bar{S}_1(t) + \lambda_S\theta_S\bar{S}_1(t) - \lambda_R\bar{R}_1(t) \ \Rightarrow$$

$$\frac{\partial(\bar{S}_1(t)+\bar{R}_1(t))}{\partial t} = -\lambda_S(1-\theta_S)\bar{S}_1(t) - \lambda_R\bar{R}_1(t) < 0 \quad \text{for all } t>0 \quad (\text{since } 1-\theta_S>0) \ \Rightarrow$$

$\bar{S}_1(t)+\bar{R}_1(t)$ is decreasing in *t*. $\bar{S}_1(t)+\bar{R}_1(t)$ decreasing in *t* implies that the area under $\bar{S}_1(t)+\bar{R}_1(t)$ from 0 to T_E is greater than the rectangle $T_E\times(\bar{S}_1(T_E)+\bar{R}_1(T_E))$:

$$\int_{t=0}^{T_E}(\bar{S}_1(t)+\bar{R}_1(t))dt > T_E\times(\bar{S}_1(T_E)+\bar{R}_1(T_E)) \ \text{ for all } T_E>0;$$

$$\text{Also } \ T_E\times(\bar{S}_1(T_E)+\bar{R}_1(T_E))>T_E\times\bar{R}_1(T_E) \quad \text{for all } T_E>0 \Rightarrow$$

$$\int_{t=0}^{T_E}(\bar{S}_1(t)+\bar{R}_1(t))dt > T_E\times\bar{R}_1(T_E) \ \text{ for all } T_E>0 \quad \Rightarrow$$

$$\alpha M\left(\int_{t=0}^{T_E}(\bar{S}_1(t)+\bar{R}_1(t))dt - T_E\bar{R}_1(T_E)\right)>0 \quad \text{for all } T_E>0 \Rightarrow$$

$\partial E[Rebates]/\partial\alpha = M\int_{t=0}^{T_E}(\bar{S}_1(t)+\bar{R}_1(t))dt - \alpha M T_E \bar{R}_1(T_E) > 0$ for all $T_E > 0$ $\Rightarrow$

$\partial E[Rebates]/\partial\alpha > 0$ for all $T_E > 0$ $\Rightarrow$

(A10) is increasing in α for all $T_E > 0$ $\Rightarrow$ (5) is decreasing in α for all $T_E > 0$.

Q.E.D.

Lemma A2

For $\lambda_R \neq \lambda_S$, let $t_R = \arg\max_t\{R(t)\}$, and $\hat{t}_R = \arg\min_t\{\partial R(t)/\partial t\}$. Then,

$t_R = \left(\ln(\lambda_R) - \ln(\lambda_S)\right)/(\lambda_R - \lambda_S)$ and $\hat{t}_R = 2t_R$.

Proof of Lemma A2

We show that $t_R = \left(\ln(\lambda_R) - \ln(\lambda_S)\right)/(\lambda_R - \lambda_S)$ for $\lambda_R \neq \lambda_S$ and $\bar{R}_1(t_R)$ is the global maximum.

$\bar{R}_1(t) = 0$ at $t = 0$, $\lim_{t\to\infty}\bar{R}_1(t) = 0$, and $\bar{R}_1(t) > 0$ $\forall t > 0$ imply:

$\exists t_R, 0 < t_R < \infty$, such that $\bar{R}_1(t_R)$ is a global maximum. On the other hand since t_R is an optimal time for $\bar{R}_1(t)$, then accroding to First Order Condition:

$\partial\bar{R}_1(t)/\partial t\big|_{t=t_R} = 0$ for $0 < t_R < \infty$.

$\partial\bar{R}_1(t)/\partial t = 0$ for $0 < t < \infty \Rightarrow t = \left(\ln(\lambda_R) - \ln(\lambda_S)\right)/(\lambda_R - \lambda_S)$ for $\lambda_R \neq \lambda_S$.

Since for $0 < t < \infty$, the solution to $\partial\bar{R}_1(t)/\partial t = 0$ is unique, thus

$t_R = \left(\ln(\lambda_R) - \ln(\lambda_S)\right)/(\lambda_R - \lambda_S)$ for $\lambda_R \neq \lambda_S$ and $\bar{R}_1(t_R)$ is the global maximum.

Similarly, we show that $\hat{t}_R = 2t_R$ for $\lambda_R \neq \lambda_S$ and $\partial\bar{R}_1(t)/\partial t\big|_{t=\hat{t}_R}$ is the global minimum for $t > 0$:

$\partial \bar{R}_1(t)/\partial t = 0$ at $t = t_R$, $\lim_{t\to\infty} \partial \bar{R}_1(t)/\partial t = 0$, and $\partial \bar{R}_1(t)/\partial t < 0 \ \ \forall t > t_R$ imply:

$\exists \hat{t}_R,\ t_R < \hat{t}_R < \infty,$ such that $\partial \bar{R}_1(t)/\partial t\big|_{t=\hat{t}_R}$ is a global minimum. On the other hand since $\hat{t}_R$ is a minimizer for $\partial \bar{R}_1(t)/\partial t,$ then accroding to FOC:

$\partial^2 \bar{R}_1(t)/\partial t^2\big|_{t=\hat{t}_R} = 0$ for $t_R < \hat{t}_R < \infty$.

$\partial^2 \bar{R}_1(t)/\partial t^2 = 0$ for $0 < t < \infty \Rightarrow t = 2\left(\ln(\lambda_R) - \ln\left(\lambda_S\right)\right)/\left(\lambda_R - \lambda_S\right)$ for $\lambda_R \neq \lambda_S$.

Since for $0 < t < \infty$, the solution to $\partial^2 \bar{R}_1(t)/\partial t^2 = 0$ is unique, thus

$\hat{t}_R = 2\left(\ln(\lambda_R) - \ln\left(\lambda_S\right)\right)/\left(\lambda_R - \lambda_S\right) = 2t_R$ for $\lambda_R \neq \lambda_S$ and $\partial \bar{R}_1(t)/\partial t\big|_{t=\hat{t}_R}$ is the global minimum.

Q.E.D.

Lemma A3

Let $\Pi_\alpha(T_E)$ be given by Equation (5). For $\alpha \leq \alpha_L$, $\Pi_\alpha(T_E)$ is concave if $t_R \leq T_E \leq 2t_R$.

Proof of Lemma A3

To investigate the conditions under which $\Pi_\alpha(T_E)$ is concave, we need to calculate the first and second derivatives of $\Pi_\alpha(T_E)$ with regard to T_E :

$$\frac{\partial \Pi_\alpha(T_E)}{\partial T_E} = -\frac{\partial \bar{S}_1(T_E)}{\partial T_E}(M - C - \alpha M)\left(\frac{1}{\lambda_S} + \frac{\theta_S}{\lambda_R}\right)$$

$$+ \alpha M\left(T_E + \frac{1}{\lambda_R}\right)\frac{\partial \bar{R}_1(T_E)}{\partial T_E} + \alpha M \bar{R}_1(T_E).$$

Since $\frac{\partial \bar{S}_1(T_E)}{\partial T_E} = -\lambda_S \bar{S}_1(T_E)$ and $\frac{\partial \bar{R}_1(T_E)}{\partial T_E} = \lambda_S \theta_S \bar{S}_1(T_E) - \lambda_R \bar{R}_1(T_E) \Rightarrow$

$$\frac{\partial \Pi_\alpha(T_E)}{\partial T_E} = \bar{S}_1(T_E)(M - C - \alpha M)(1 + \frac{\lambda_S \theta_S}{\lambda_R})$$

$$+ \alpha M (T_E + \frac{1}{\lambda_R})(\lambda_S \theta_S \bar{S}_1(T_E) - \lambda_R \bar{R}_1(T_E)) + \alpha M \bar{R}_1(T_E) \Rightarrow$$

$$\frac{\partial \Pi_\alpha(T_E)}{\partial T_E} = M\bar{S}_1(T_E)(\alpha_L - \alpha) + \alpha M T_E \frac{\partial \bar{R}_1(T_E)}{\partial T_E}, \text{ where } \alpha_L = \left(1 - \frac{C}{M}\right)(1 + \frac{\lambda_S \theta_S}{\lambda_R}).$$

Now we calculate the second derivative of $\Pi_\alpha(T_E)$:

$$\frac{\partial^2 \Pi_\alpha(T_E)}{\partial T_E^2} = -\lambda_S M\bar{S}_1(T_E)(\alpha_L - \alpha) + \alpha M \frac{\partial \bar{R}_1(T_E)}{\partial T_E} + \alpha M T_E \frac{\partial^2 \bar{R}_1(T_E)}{\partial T_E^2}.$$

$-\lambda_S M\bar{S}_1(T_E)(\alpha_L - \alpha) \le 0 \ \forall \alpha \le \alpha_L$ and $\forall T_E \ge 0$ (since $\bar{S}_1(T_E) \ge 0 \ \ \forall T_E \ge 0$);

$\alpha M \frac{\partial \bar{R}_1(T_E)}{\partial T_E} < 0 \ \ \forall T_E > t_R$ and $\alpha M \frac{\partial \bar{R}_1(T_E)}{\partial T_E} \ge 0 \ \forall T_E \le t_R$,

where $t_R = \frac{Ln(\lambda_R / \lambda_S)}{\lambda_R - \lambda_S}$ (See Lemma 4);

$\alpha M T_E \frac{\partial^2 \bar{R}_1(T_E)}{\partial T_E^2} < 0 \ \forall T_E < 2t_R$, $\alpha M T_E \frac{\partial^2 \bar{R}_1(T_E)}{\partial T_E^2} \ge 0 \ \forall T_E \ge 2t_R$ (See Lemma 4); $\Rightarrow$

$\forall \alpha \le \alpha_L$ and $t_R \le T_E \le 2t_R$, we have $\frac{\partial^2 \Pi_\alpha(T_E)}{\partial T_E^2} < 0 \ \Rightarrow$

$\Pi_\alpha(T_E)$ is concave $\forall \alpha \le \alpha_L$ and $t_R \le T_E \le 2t_R$.

Q.E.D.

Lemma A4

Let $T^*>0$ denote the optimal evaluation time for (OP) given exogenous rebate rate α and marginal production cost C, such that $\partial \Pi_\alpha(T_E) / \partial T_E \big|_{T_E = T^*} = 0$, and

$\partial^2 \Pi_\alpha(T_E) / \partial T_E^2 \big|_{T_E = T^*} < 0$. Then T^* is decreasing in C.

Proof of Lemma A4

According to the implicit function theorem, we have:

$$\left.\frac{\partial T_E}{\partial C}\right|_{T_E=T^*} = -\left.\frac{\partial^2 \Pi_\alpha(T_E)/\partial T_E \partial C}{\partial^2 \Pi_\alpha(T_E)/\partial T_E^2}\right|_{T_E=T^*}$$

$\partial^2 \Pi_\alpha(T_E)/\partial T_E^2\big|_{T_E=T^*} < 0$ and $\partial^2 \Pi_\alpha(T_E)/\partial T_E \partial C\big|_{T_E=T^*} = -(1+\frac{\lambda_S \theta_S}{\lambda_R})S_1(T^*) < 0$

for all $T^* > 0$. $\Rightarrow \left.\frac{\partial T_E}{\partial C}\right|_{T_E=T^*} < 0$ for all $T^* > 0 \Rightarrow$ T^* is decreasing in C.

Q.E.D.

Lemma A5:

Let $T^*>0$ denote the optimal evaluation time for (OP) given an exogenous rebate rate α, such that $\partial \Pi_\alpha(T_E)/\partial T_E\big|_{T_E=T^*} = 0$, and $\partial^2 \Pi_\alpha(T_E)/\partial T_E^2\big|_{T_E=T^*} < 0$.

(a) For λ_R large enough such that $\lambda_R \bar{R}_1(T^*) > \left(\lambda_S \theta_S - 1/T^*\right)\bar{S}_1(T^*)$, T^* is decreasing in rebate rate α.

(b) For $\lambda_R \bar{R}_1(T^*) < \left(\lambda_S \theta_S - 1/T^*\right)\bar{S}_1(T^*)$, T^* is increasing in rebate rate α.

Proof of Lemma A5

According to the implicit function theorem, we have:

$$\left.\frac{\partial T_E}{\partial \alpha}\right|_{T_E=T^*} = -\left.\frac{\partial^2 \Pi_\alpha(T_E)/\partial T_E \partial \alpha}{\partial^2 \Pi_\alpha(T_E)/\partial T_E^2}\right|_{T_E=T^*}$$

Since T^* is the optimal point, $\partial^2 \Pi_\alpha(T_E)/\partial T_E^2\big|_{T_E=T^*} < 0$. On the other hand,

$$\partial^2 \Pi_\alpha(T_E)/\partial T_E \partial \alpha\big|_{T_E=T^*} = M\left(-\left(\frac{1}{\lambda_S}+\frac{\theta_S}{\lambda_R}\right)\lambda_S \bar{S}_1(T^*) + \bar{R}_1(T^*) + \left(T^* + \frac{1}{\lambda_R}\right)\bar{R}_1'(T^*)\right) \Rightarrow$$

Replacing $\bar{R}_1'(T^*)$ with $\lambda_S\theta_S\bar{S}_1(T^*)-\lambda_R\bar{R}_1(T^*)$ yields:

$\partial^2\Pi_\alpha(T_E)/\partial T_E\partial\alpha\big|_{T_E=T^*} = -M\left(\left(1-T^*\lambda_S\theta_S\right)\bar{S}_1(T^*)+T^*\lambda_R\bar{R}_1(T^*)\right)\Rightarrow$

$\partial^2\Pi_\alpha(T_E)/\partial T_E\partial\alpha\big|_{T_E=T^*} < 0$ if $\left(\left(1-T^*\lambda_S\theta_S\right)\bar{S}_1(T^*)+T^*\lambda_R\bar{R}_1(T^*)\right)>0\Rightarrow$

$\partial^2\Pi_\alpha(T_E)/\partial T_E\partial\alpha\big|_{T_E=T^*} < 0$ if $\lambda_R\bar{R}_1(T^*)>\left(\lambda_S\theta_S-1/T^*\right)\bar{S}_1(T^*)$. Thus,

$\left.\dfrac{\partial T_E}{\partial\alpha}\right|_{T_E=T^*} < 0$, i.e., T_E is decreasing in α if $\lambda_R\bar{R}_1(T^*)>\left(\lambda_S\theta_S-1/T^*\right)\bar{S}_1(T^*)$.

Similarly, T_E is increasing in α if $\lambda_R\bar{R}_1(T^*)<\left(\lambda_S\theta_S-1/T^*\right)\bar{S}_1(T^*)$.

Q.E.D.

Corollary 1

The manufacturer's loss in a risk-sharing agreement with rebate rate α=100% is increasing in T_E if $\lambda_R\bar{R}_1(T_E)>\left(\lambda_S\theta_S-1/T_E\right)\bar{S}_1(T_E)$.

Proof of Corollary 1

$$Loss=\alpha M\left(\left(\frac{1}{\lambda_S}+\frac{\theta_S}{\lambda_R}\right)\left(1-\bar{S}_1(T_E)\right)-\left(T_E+\frac{1}{\lambda_R}\right)\bar{R}_1(T_E)\right).$$

$$\partial Loss/\partial T_E=\alpha M\left(\left(\frac{1}{\lambda_S}+\frac{\theta_S}{\lambda_R}\right)\lambda_S\bar{S}_1(T_E)-\bar{R}_1(T_E)-\left(T_E+\frac{1}{\lambda_R}\right)\bar{R}_1'(T_E)\right)\Rightarrow$$

Replacing $\bar{R}_1'(T_E)$ with $\lambda_S\theta_S\bar{S}_1(T_E)-\lambda_R\bar{R}_1(T_E)$ yields:

$\partial Loss/\partial T_E=\alpha M\left(\left(1-T_E\lambda_S\theta_S\right)\bar{S}_1(T_E)+T_E\lambda_R\bar{R}_1(T_E)\right)\Rightarrow$

$\partial Loss/\partial T_E>0$ if $\left(\left(1-T_E\lambda_S\theta_S\right)\bar{S}_1(T_E)+T_E\lambda_R\bar{R}_1(T_E)\right)>0\Rightarrow$

$\partial Loss/\partial T_E>0$ if $\lambda_R\bar{R}_1(T_E)>\left(\lambda_S\theta_S-1/T_E\right)\bar{S}_1(T_E)$.

Q.E.D.

Proof of Part (a) of Proposition 1

$$\Pi_\alpha(T_E) = \big((1-\alpha)M - C\big)\left(\frac{1}{\lambda_S} + \frac{\theta_S}{\lambda_R}\right)\big(1-\bar{S}_1(T_E)\big) + \alpha M\left(T_E + \frac{1}{\lambda_R}\right)\bar{R}_1(T_E),$$

$\Pi_\alpha(T_E) = 0$ at $T_E = 0$. P1-1

$$\frac{\partial \Pi_\alpha(T_E)}{\partial T_E} = M\bar{S}_1(T_E)(\alpha_L - \alpha) + \alpha M T_E \frac{\partial \bar{R}_1(T_E)}{\partial T_E} \Rightarrow$$

$$\left.\frac{\partial \Pi_\alpha(T_E)}{\partial T_E}\right|_{T_E=0} = M(\alpha_L - \alpha) \geq 0 \quad \forall \alpha \leq \alpha_L. \qquad \text{P1-2}$$

P1-2 implies that as long as α is equal or less than α_L, the slope

of $\Pi_\alpha(T_E)$ remains non-negative.

From P1-1 and P1-2: For $\alpha < \alpha_L$, $\exists T^* \in (0,\infty]$ such that $\Pi_\alpha(T^*)$ is the global maximum.

On the other hand for $\alpha = \alpha_L$ we have: $\left.\frac{\partial \Pi_\alpha(T_E)}{\partial T_E}\right|_{T_E=0} = 0;$ and

$\left.\frac{\partial^2 \Pi_\alpha(T_E)}{\partial T_E^2}\right|_{T_E=0} = \alpha_L M \lambda_S \theta_S > 0$ (See Lemma A3 for the second derivative of $\Pi_\alpha(T_E)$),

i.e., $\Pi_{\alpha_L}(0)$ is a local minimum $\Rightarrow$

For $\alpha \leq \alpha_L$, $\exists T^* \in (0,\infty]$ such that $\Pi_\alpha(T^*)$ is the global maximum.

Also from FOC, i.e., $\left.\frac{\partial \Pi_\alpha(T_E)}{\partial T_E}\right|_{T_E=T^*} = 0,$ we have:

$M\bar{S}_1(T^*)(\alpha_L - \alpha) + \alpha M T^* \left.\frac{\partial \bar{R}_1(T_E)}{\partial T_E}\right|_{T_E=T^*} = 0, \Rightarrow$ For $\alpha \leq \alpha_L$, $\bar{S}_1(t)(\alpha_L - \alpha) \geq 0 \ \forall t > 0;$

$\frac{\partial \bar{R}_1(t)}{\partial t} > 0 \ \ \forall t < t_R;$ and $\frac{\partial \bar{R}_1(t)}{\partial t} < 0 \ \ \forall t > t_R, \ \Rightarrow$

In order to get $\left.\frac{\partial \Pi_\alpha(T_E)}{\partial T_E}\right|_{T_E=T^*} = 0,$ we should have $T^* > t_R \ \Rightarrow$

For $\alpha \leq \alpha_L$, $\exists T^* \in (t_R,\infty],$ such that $\Pi_\alpha(T^*)$ is the global maximum.

Q.E.D.

Proof of Part (b) of Proposition 1

For $\alpha \geq \alpha_\infty = 1 - \frac{C}{M} \quad \Rightarrow \quad \left((1-\alpha)M - C\right) \leq 0;$

$\Pi_\alpha(T_E) = 0 \quad$ at $T_E = 0.$ P2-1

$$\lim_{T_E \to +\infty} \Pi_\alpha(T_E) = \left((1-\alpha)M - C\right)\left(\frac{1}{\lambda_S} + \frac{\theta_S}{\lambda_R}\right) \leq 0. \quad \text{P2-2}$$

$$\left.\frac{\partial \Pi_\alpha(T_E)}{\partial T_E}\right|_{T_E=0} = M(\alpha_L - \alpha) \geq 0 \quad \forall \alpha \in [\alpha_\infty, \alpha_L]. \quad \text{P2-3}$$

Considering P2-1, P2-2 and P2-3, for $\alpha \in [\alpha_\infty, \alpha_L]$ the profit goes above zero after T_E=0 and reaches its optimum before changing its direction and reaching its non-positive limit as $T_E \to +\infty$.

This implies that for $\alpha \in [\alpha_\infty, \alpha_L]$, $\exists T^* \in (0, +\infty)$ s.t. $\Pi_\alpha(T^*) > 0$ is the global maximum.

On the other hand similar to part (a) from FOC, i.e., $\left.\frac{\partial \Pi_\alpha(T_E)}{\partial T_E}\right|_{T_E=T^*} = 0,$

we should have $T^* > t_R \Rightarrow$

For $\alpha \in [\alpha_\infty, \alpha_L]$, $\exists T^* \in (t_R, \infty)$ such that $\Pi_\alpha(T^*)$ is the global maximum.

Q.E.D.

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Chapter 2

2 Payer and Manufacturer Perspectives on a Pharmaceutical Health-based Pay-for-performance Risk-sharing Agreement

Development of new pharmaceutical drugs has become increasingly costly, and the incremental benefit or effectiveness is often small and uncertain. One mechanism to offset some of the uncertainties surrounding new and costly drugs is health-based pay-for-performance risk-sharing agreements. In this chapter I extend on the first chapter to examine the performance of a risk-sharing contract between a payer and a pharmaceutical firm from the payer's perspective. The basis of the contract is that the pharmaceutical firm rebates a portion of the sales from patients who do not respond to the drug. The objective of this chapter is to identify the conditions under which the rebate rate and evaluation time are mutually beneficial, i.e. where both the payer and the pharmaceutical firm have incentives to introduce the new drug. I investigate how different classifications of rebates for non-respondent patients affect the two parties. The analysis of the contract performance is based on an underlying patient-level disease progression model. Based on published data from a phase 2 clinical trial of an oncology drug, I empirically estimate disease progression parameters and conduct numerical analyses of the risk-sharing agreement. My results indicate that 1) there are trade-offs in choosing the evaluation time for both parties, such that its optimal value is not easily identifiable; 2) the payer is better off under one specific type of risk-sharing agreement in most practical circumstances; and 3) the evaluation times beneficial to both parties are sensitive to the proportion of the rebate that the payer has missed to invoice and collect.

2.1 Introduction

There are several types of risk-sharing agreements used in practice. Each type of risk-sharing agreement has its unique mechanics including the set of contract parameters, which generate the specific dynamics for that agreement. Zaric et al. (2013) provide a literature review on risk-sharing agreement modeling. They present several examples of different types of risk-sharing schemes illustrating the broad scope of these types of contracts.

A prominent example of a pay-for-performance risk-sharing agreement is the agreement between the UK's National Health Service (NHS) and the drug manufacturer of bortezomib in 2007. In the first chapter, I examined the performance of a risk-sharing agreement similar to the bortezomib agreement in the UK from the perspective of the drug manufacturer in which a rebate rate $\alpha \geq 0$ and an evaluation time $T_E > 0$ were the contract parameters. Patients were evaluated at some evaluation time to determine whether they are responding to the new drug. I analyzed a rebate classification in which the drug manufacturer rebates to the payer a proportion α of the sales from all patients *up to* T_E excluding the sales from those who are responding to the drug *at* T_E.

I refer to the above described rebate classification as RSA1 throughout this chapter. I add the suffix 1 to RSA1 to differentiate this rebate classification from two other classifications that can be derived based on the same contract parameters. Brief descriptions of these two rebate classifications and the motivations for their derivations are as follows. The fact that only responding patients at the evaluation time are not subject to rebate implies that the manufacturer has to pay rebate for responding patients

for whom disease progressed before the evaluation time under RSA1. Some may find this classification unfair and argue that any responding patient up to the evaluation time should be excluded from rebate. Considering this argument, I present another rebate classification denoted by RSA2 in which the drug manufacturer rebates to the payer a proportion of the sales from patients who have not responded to the drug *prior to* and *at* the evaluation time. A more general case for RSA2 would be to assume that a minimum response time is required from any responding patient in order not to be subject to rebate. However in this chapter I assume that such a minimum response time is not required. On the other hand, the payer may decide to ask the manufacturer to pay the rebate only for patients who are *not responding* to the drug *at* the evaluation time (e.g., due to the simplicity of its implementation), which constitutes the third rebate classification RSA3 to be discussed in this chapter. Therefore under RSA3, only patients who are neither responding nor for whom disease has progressed at the evaluation time will be subject to rebate.

In this chapter I extend on the first chapter to examine the performance of RSA1 from the payer's perspective. I further develop the disease progression model by incorporating a fourth health state and use a system of linear differential equations to describe transitions between these health states. The solution to this system of differential equations yields the proportions of patients in each health state at each point in time. I use these proportions to calculate the payer's net monetary benefit (NMB). In calculating the payer's NMB, I incorporate two administrative costs: 1) the administrative cost for monitoring of patients; and 2) the administrative cost for invoicing and collecting the

rebate associated with every non-responding patient. In the rest of this chapter, I refer to this cost as the *administrative cost* of collecting the rebate.

The objective of this chapter is to identify sets of contract parameters (the rebate rate and evaluation time) that are mutually beneficial, i.e. where both the payer and the pharmaceutical firm have incentives to introduce the new drug. I develop the base model by using RSA1 and extend it further to RSA2 and RSA3. I investigate how different rebate classifications affect the two parties. In particular I examine if there is one specific rebate classification under which the payer is better off in most practical circumstances.

The description of the notations used in this chapter is as follows. Lowercase letters are used to denote the *per unit* values of measurable parameters. For instance, "*w*" is used to denote the willingness to pay (WTP) per unit of effectiveness and "c_D" is used to denote the cost of the drug per unit of time. Uppercase letters are used to denote the *total* values of the measureable parameters, e.g., "C_D" is used to denote the total cost of the drug. Lowercase Greek letters are used to denote the rebate rate as well as the transition rates used in the disease progression model.

Table 2-1: Table of model parameters

ITEMS	DESCRIPTIONS
α, T_E	Rebate rate and evaluation time
S,*R*,*P*, and *D*	Disease progression model states: "Sick" (*S*), "Responding to drug" (*R*), "Progression of disease" (*P*), and "Death" (*D*)
$\lambda_S, \lambda_R, \lambda_P$	Transition rates from states *S*, *R*, and *P* respectively
θ_S	Proportion of patients transitioning from state *S* to state *R*
$\hat{\lambda}_S$	Transition rates from state *S* to state *P* after evaluation time T_E
$S(t)$, $R(t)$, $P(t)$, $D(t)$	Proportions of patients in *S*, *R*, *P*, and *D* respectively for $t>0$
H_N, H_O	Total effectiveness of the new and existing treatments
C_N, C_O	Total cost of the new and existing treatments
C_D, c_D	Total and per unit of time price of the new drug
C_M, c_M	Total and per unit of time production cost of the new drug
C_B, C_A	Total cost of care for the new treatment before and after T_E
q_S, q_R, q_P	Weights of quality of life in health states *S*, *R*, and *P*
$\hat{q}_S$	Weight of quality of life in health state *S* after T_E
C_V, c_V	Total and per unit of time administrative cost of monitoring
C_I, c_I	Total and per non-responding patient administrative cost of collecting rebate
c_S, c_R, c_P	Unit cost of care in health states *S*, *R*, and *P* respectively
$\hat{c}_S$	Unit cost of care in health state *S* after T_E
w	Willingness to pay for one unit of effectiveness
B, π	Payer's net monetary benefit and drug manufacturer's profit

2.2 The Model

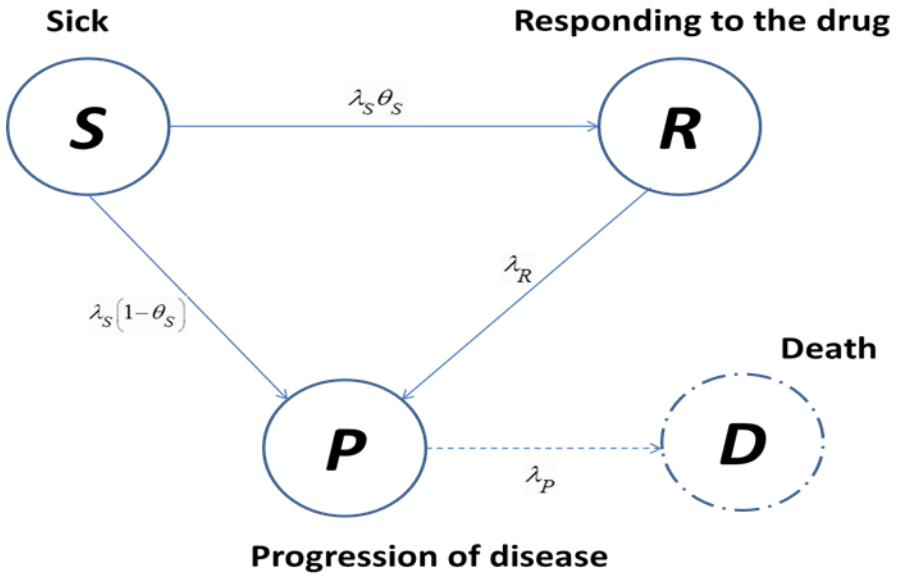
2.2.1 Disease Progression Model

To describe patient response to the new drug, I extend the disease progression model developed in the first chapter by adding a new state "Death", which results in a disease progression model with the following four health states: "Sick" (*S*), "Responding to the new drug" (*R*), "Progression of disease" (*P*), and "Death" (*D*) (Figure 2-1). Adding the

fourth state "Death" enables us to calculate the NMB of patients for whom the disease has progressed (i.e., patients in state *P*).

All patients begin in state *S* at time *t*=0 and start taking the drug. Patients who respond to the drug make a transition from *S* to *R*. Patients who do not respond to the drug and whose health status does not worsen remain in *S*. Patients who do not respond to the drug, and whose health status worsens make a transition from *S* to *P*. The disease will eventually progress for responding patients, implying that those patients make a transition from *R* to *P*. I assume that patients stop receiving the drug as soon as the disease progresses (i.e., as soon as they enter state *P*, from either state *S* or *R*). We also assume that all patients experience disease progression before entering the "Death" state.

Figure 2-1: Disease progression model



Let λ_S be the transition rate from *S* and let θ_S be the proportion of patients who move from *S* to *R*. Thus, the transition rates from *S* to *R* and from *S* to *P* are $\lambda_S\theta_S$ and

$\lambda_S(1-\theta_S)$. Let λ_R be the transition rate from *R* to *P* and λ_P be the transition rate from *P* to *D*. Let *S*(*t*), *R*(*t*), *P*(*t*), and *D*(*t*) be the proportions of patients in states *S*, *R*, *P*, and *D* at time *t*, respectively. Figure 2-1 shows the disease progression model and its respective system of linear differential equations. I use the following system of linear differential equations to represent the disease progression model of Figure 2-1:

$$\frac{\partial S(t)}{\partial (t)} = -\lambda_S S(t),$$

$$\frac{\partial R(t)}{\partial t} = \lambda_S \theta_S S(t) - \lambda_R R(t),$$

$$\frac{\partial P(t)}{\partial t} = \lambda_S (1-\theta_S) S(t) + \lambda_R R(t) - \lambda_P P(t),$$

$$\frac{\partial D(t)}{\partial t} = \lambda_P P(t).$$

Since all patients start in state *S*, we have the following initial conditions: *S*(0)=1 and *R*(0)=*P*(0)=*D*(0)=0. We solve this system of linear differential equations using standard techniques (Boyce and Diprima, 2009) and obtain the following solutions:

$$S(t) = e^{-\lambda_S t}, \quad (1)$$

$$R(t) = \lambda_S \theta_S (e^{-\lambda_S t} - e^{-\lambda_R t}) / (\lambda_R - \lambda_S), \quad (2)$$

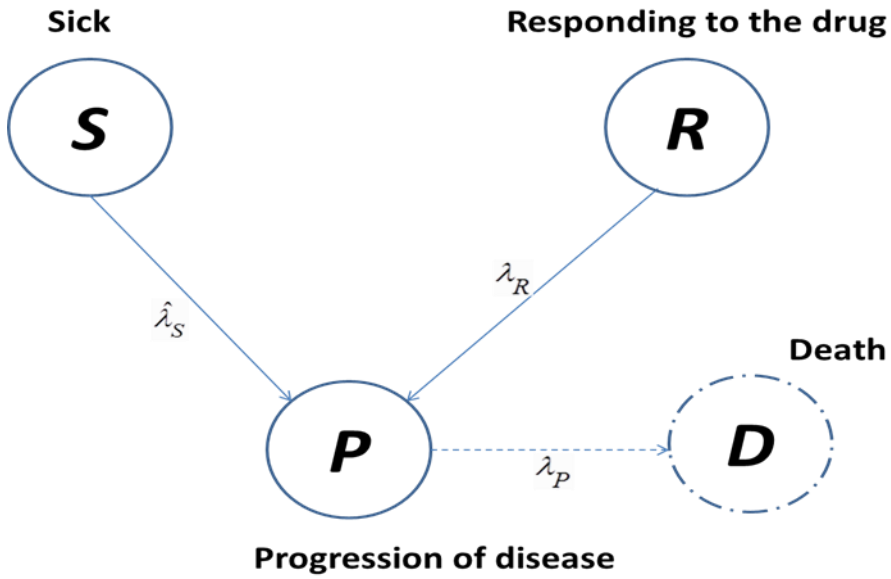
$$P(t) = K_1 e^{-\lambda_S t} - K_2 e^{-\lambda_R t} + (K_2 - K_1) e^{-\lambda_P t}, \quad (3)$$

where $t \le T_E$, $K_1 = \lambda_S(\lambda_R - \lambda_S + \lambda_S \theta_S) / \left((\lambda_P - \lambda_S)(\lambda_R - \lambda_S)\right)$, and $K_2 = \lambda_R \lambda_S \theta_S / \left((\lambda_P - \lambda_R)(\lambda_R - \lambda_S)\right)$. The proportion of patients in state *D* is calculated by: $D(t) = 1 - S(t) - R(t) - P(t)$.

2.2.2 Disease Progression Model after Evaluation Time

Patients are evaluated at some evaluation time $T_E > 0$ to determine whether they are responding to the new drug (and hence whether the new treatment has been successful). Patients who are not responding at T_E and are still in *S* stop receiving the drug. These patients may switch back to the old treatment or be administered an alternative treatment while they continue to receive necessary care. In the context of this chapter we assume that after the evaluation time T_E, the proportion of transitions from *S* to *R* will become zero, i.e., $\theta_S = 0$, and the new transition rate from *S* to *P* will be $\hat{\lambda}_S$ (Figure 2-2).

Figure 2-2: Disease progression model for $t>T_E$



Patients who are responding at T_E, i.e., those who are in *R*, continue to take the drug as long as they respond to the drug. Thus, the transition rates λ_R and λ_P will remain the same after T_E. We solve the new system of differential equations for $t > T_E$ with $S(T_E)$,

$R(T_E)$, and $P(T_E)$ as its initial conditions calculated by substituting T_E for *t* in equations (1) to (3) respectively and obtain the following result:

$$S(t) = S(T_E)e^{-\hat{\lambda}_S(t-T_E)}, \quad (4)$$

$$R(t) = R(T_E)e^{-\lambda_R(t-T_E)}, \quad (5)$$

$$P(t) = K_3 S(T_E)e^{-\hat{\lambda}_S(t-T_E)} + K_4 R(T_E)e^{-\lambda_R(t-T_E)} + \left(P(T_E) - K_3 S(T_E) - K_4 R(T_E)\right)e^{-\lambda_P(t-T_E)}, \quad (6)$$

where $t > T_E$, $K_3 = \hat{\lambda}_S / (\lambda_P - \hat{\lambda}_S)$, $K_4 = \lambda_R / (\lambda_P - \lambda_R)$, and $S(T_E)$, $R(T_E)$ and $P(T_E)$ are obtained by substituting T_E for *t* in equation (1) to (3), respectively. Similarly, the proportion of patients in state *D* is calculated by: $D(t) = 1 - S(t) - R(t) - P(t)$.

2.2.3 Calculation of Payer's Net Monetary Benefit

According to the economic evaluation method used in this chapter, a new drug is deemed cost-effective if its NMB is positive (NMB>0). Let $B(T_E,\alpha)$ be the NMB of the payer resulting from the administration of the new treatment to a cohort of patients. We use the following formula to calculate the NMB (Drummond et al., 2005):

$$B(T_E,\alpha) = w \times (H_N - H_O) - (C_N - C_O), \quad (7)$$

where H_N and C_N are the total effectiveness and the total cost of the new treatment, H_O and C_O are the total effectiveness and the total cost of the existing treatment, and *w* is the payer's WTP per unit of benefit (which we operationalize as quality-adjusted life years [QALYs] gained). Thus, H_N in (7) will consist of the effectiveness of the new treatment before and after T_E, denoted by H_B and H_A (i.e., $H_N = H_B + H_A$).

The total cost of new treatment C_N in (7) consists of the following cost components: C_B and C_A for the cost of care for the new treatment before and after T_E, C_D for the total cost of the drug for the new treatment, C_V for the administrative cost of monitoring of patients, and C_{Ij} for the administrative cost of collecting the rebate for non-respondent patients, where j=1, 2, and 3 ($C_{Nj} = C_B + C_A + C_D + C_V + C_{Ij}$). Cost of care refers to the cost of care services needed to manage illness throughout the treatment. Some examples of care services are pain management and management of the adverse effects of drugs. The subscript j=1, 2, and 3 in C_{Ij} refers to RSA1-3 since, as it will be shown, this cost is a function of the rebate classification used in the agreement. Let $R_{\alpha j}$ be the rebate to be paid to the payer under risk-sharing, where j=1, 2, and 3 refers to the rebate classifications RSA1-3.

We incorporate the above described cost and effectiveness components in (7) and obtain the following equation for the payer's NMB under risk-sharing:

$$B_j(T_E, \alpha) = w \times (H_B + H_A) - (C_B + C_A + C_D + C_V + C_{Ij}) + R_{\alpha j} - w \times H_O + C_O, \quad (8)$$

where j=1, 2, and 3 refers to RSA1-3. Next we calculate the components of equation (8). In calculating these components, $S(t)$, $R(t)$, and $P(t)$ are given by equations (1) to (3) for $t \le T_E$ and by equations (4) to (6) for $t > T_E$, respectively.

Let $0 \le q_i \le 1$ be the quality of life (QoL) weight of the drug effectiveness in state i=S, R, and P, and $0 \le \hat{q}_S \le 1$ be the respective QoL weight in S after T_E. I have assumed a

different QoL weight in *S* after the evaluation time because non-responding patients stop receiving the drug after that time. The quality-adjusted effectiveness of the new treatment until T_E and after T_E are given by:

$$H_B = \int_{t=0}^{T_E} \left(q_S \times S(t) + q_R \times R(t) + q_P \times P(t)\right) dt, \quad (9)$$

$$H_A = \int_{t=T_E}^{\infty} \left(\hat{q}_S \times S(t) + q_R \times R(t) + q_P \times P(t)\right) dt. \quad (10)$$

To calculate the cost of care for the new treatment before and after T_E, i.e., C_B and C_A, we replace q_S, $\hat{q}_S$, q_R, and q_P with the respective costs of care per unit of time, i.e., c_S, $\hat{c}_S$, c_R, and c_P, in H_B and H_A, respectively. For the same reason presented above for QoL weight, I have assumed a different unit cost of care in *S* after the evaluation time. Thus:

$$C_B = \int_{t=0}^{T_E} \left(c_S \times S(t) + c_R \times R(t) + c_P \times P(t)\right) dt, \quad (11)$$

$$C_A = \int_{t=T_E}^{\infty} \left(\hat{c}_S \times S(t) + c_R \times R(t) + c_P \times P(t)\right) dt. \quad (12)$$

Let c_D be the payment for the new drug per unit of time. The total payment for the new drug by the payer to the drug manufacturer C_D is calculated using the following equation:

$$C_D = c_D \times \left(\int_{t=0}^{T_E} \left(S(t) + R(t)\right) dt + \int_{t=T_E}^{\infty} R(t) dt \right). \quad (13)$$

In this chapter, I incorporate two types of administrative costs including the cost for monitoring of patients and the cost for collecting and invoicing the rebate. I assume that both administrative costs are incurred by the payer. Next I describe these costs in more detail and show how to calculate them.

Administrative Cost for Monitoring of Patients

Patients need to be monitored on a regular basis (e.g. monthly) to keep track of the number of cycles of the drug and to ensure that they stop taking the drug as soon as the disease progresses. Monitoring of patients is also needed in order to ensure that no rebate for non-responding patients will be missed to be invoiced and collected. Let c_V be the administrative cost of monitoring each patient per unit of time. The total monitoring cost C_V is given by:

$$C_V = c_V \times \left(\int_{t=0}^{T_E} \big(S(t) + R(t)\big)\, dt + \int_{t=T_E}^{\infty} R(t) dt \right). \qquad (14)$$

Administrative Cost for Collecting the Rebate

According to a report on the uptake of the patient access scheme for bortezomib in the UK, the bortezomib risk-sharing scheme was considered as being a "time consuming process" and "very labour intensive" ((Williamson, 2009), page 28). Considering the above statement, I assume that the payer incurs an administrative cost for collecting the rebate associated with a non-responding patient denoted by c_I. Table 2-2 shows the health state transition scenarios for a patient until T_E, their respective rebate or no rebate

status at T_E, and the respective proportion of patients resulting after each health state transition up to T_E. As can be seen from Table 2-2, the total administrative cost of collecting the rebate is a function of the respective rebate classification. Thus, we let C_{Ij} denote the total one-time cost of collecting the rebate, where j=1, 2, and 3 refers to RSA1-3.

Table 2-2: Health state transition scenarios until T_E under RSA1, RSA2, and RSA3

Heath State Transition	**RSA1**	**RSA2**	**RSA3**	**Proportions up to T_E**
Respond and remain in *R*	No Rebate	No Rebate	No Rebate	$R(T_E)$
Respond and progress	Rebate	No Rebate	No Rebate	$\theta_S(1-S(T_E))-R(T_E)$
Direct progress from *S*	Rebate	Rebate	No Rebate	$(1-\theta_S)(1-S(T_E))$
Remain in *S*	Rebate	Rebate	Rebate	$S(T_E)$

We substitute equations (9) to (14) for H_B, H_A, C_B, C_A, C_D, and C_V, respectively, in (8) and obtain the following equation for NMB:

$$\begin{aligned} B_{\mathrm{j}}(T_E,\alpha) = & \int_{t=0}^{T_E}\left(k_S\times S(t)+k_R\times R(t)+k_P\times P(t)\right)dt \\ & +\int_{t=T_E}^{\infty}\left(\hat{k}_S\times S(t)+k_R\times R(t)+k_P\times P(t)\right)dt \\ & -C_{I\mathrm{j}}+R_{\alpha\mathrm{j}}-w\times H_O+C_O, \end{aligned} \tag{15}$$

where j=1, 2, and 3 refers to RSA1-3, $S(t)$, $R(t)$, and $P(t)$ are given by equations (1) to (3) for $t\le T_E$, and by equations (4) to (6) for $t>T_E$, respectively, and

$k_S = w \times q_S - (c_D + c_S + c_V)$, $\hat{k}_S = w \times \hat{q}_S - \hat{c}_S$, $k_R = w \times q_R - (c_D + c_R + c_V)$, and $k_P = w \times q_P - c_P$.

By assuming that patients are monitored even without any risk-sharing scheme in place (i.e., $c_V \geq 0$ for α=0), the coefficients in (15) can have the following interpretations: k_S and $\hat{k}_S$ are the monetary benefit minus the cost per patient in health state *S* per unit of time before and after the evaluation time T_E, respectively. Similarly, k_R and k_P are the monetary benefit minus cost per unit of time per patient in health state *R* and *P*, respectively.

We substitute equations (1) to (3) and (4) to (6) for to the proportions of patients in state *S*, *R*, and *P* before and after T_E in (15) to obtain the following equation for the NMB of the payer:

$$B_j(T_E, \alpha) = \left(\frac{\hat{k}_S}{\hat{\lambda}_S} - \frac{k_S}{\lambda_S} - \frac{k_R \theta_S}{\lambda_R} \right) S(T_E) + \left(\frac{k_S}{\lambda_S} + \frac{k_R \theta_S}{\lambda_R} + \frac{k_P}{\lambda_P} \right) - C_{I_j} + R_{\alpha j} - w \times H_O + C_O. \quad (16)$$

The coefficients k_S / λ_S and $\hat{k}_S / \hat{\lambda}_S$ in (16) represent the mean monetary benefit minus the mean cost per patient in state *S* under no risk-sharing before and after the evaluation time T_E, respectively. Since $S(T_E) < 1$ for all T_E, a positive k_S in (16) indicates that the payer's NMB is increasing in $1/\lambda_S$ (mean time spent in state *S*). Similarly, the coefficients $k_R \theta_S / \lambda_R$ and k_P / λ_P in (16) represent the mean monetary benefit minus the mean cost generated by a patient in state *R* and *P*, respectively. Also, a positive k_R in (16)

indicates that the payer's NMB is increasing in θ_S (proportion of patients responding to the drug) and $1/\lambda_R$ (mean response time).

Estimating Parameters of the Existing Treatment H_O and C_O

The components $w \times H_O$ and C_O in (16) represent the estimated means of the monetary health benefit and cost of the existing treatment, respectively. To estimate these components as functions of the other model parameters, I envision a hypothetical case where patients are administered the new drugs at $T_E = 0$ and evaluated at the same time. This implies that for $T_E = 0,$ nobody is using the new drug effectively and, therefore, the NMB of the payer resulting from the new treatment under this hypothetical situation is null. Thus, by incorporating $T_E = 0$ in equation (16) we obtain the following result (note that $R_{\alpha \mathrm{j}} = 0$ and $C_{I\mathrm{j}} = 0$ at $T_E = 0$ since the administration of the new treatment has not started yet):

$$\begin{aligned} B_{\mathrm{j}}(T_E = 0, \alpha) &= \frac{\hat{k}_S}{\hat{\lambda}_S} + \frac{k_P}{\lambda_P} - w \times H_O + C_O \\ &= 0. \end{aligned} \tag{17}$$

It follows from (17) that $w \times H_O - C_O$ is equal to $\hat{k}_S / \hat{\lambda}_S + k_P / \lambda_P.$ The component $\hat{k}_S / \hat{\lambda}_S + k_P / \lambda_P$ in (17) can be interpreted as the NMB that would result from the new treatment (i.e., monetary benefit minus cost of the new treatment) if patients were evaluated at $T_E = 0.$ Under this condition, the benefit of the payer would consist of the QALYs gained in states *S* and *P*, where the QoL weight in state *S* is $\hat{q}_S$ and the transition

rate to state *P* is $\hat{\lambda}_S$. Similarly, the cost of the payer would consist of the costs of care in states *P* and *S*, where the unit cost of care in state *S* is $\hat{c}_S$.

Substituting $-(\hat{k}_S / \hat{\lambda}_S + k_P / \lambda_P)$ for $-W \times H_O + C_O$ in (16) yields the following equation for the payer's NMB:

$$B_j(T_E, \alpha) = k_B\left(1 - S(T_E)\right) + R_{\alpha j} - C_{Ij}, \tag{18}$$

where j=1, 2, and 3 refers RSA1-3 and $k_B = k_S / \lambda_S + k_R \theta_S / \lambda_R - \hat{k}_S / \hat{\lambda}_S$. In equation (18) the component $1 - S(T_E)$ represents the proportion of patients who are not in state S at time T_E and the coefficient k_B represents the mean NMB resulting from a patient as long as that patient is taking the drug.

2.2.4 Payer's Net Monetary Benefit Under RSA1

It follows from equation (18) that for calculating the NMB of the payer under RSA1, $B_1(T_E, \alpha)$, we need to calculate C_{I1} and $R_{\alpha 1}$. Table 2-2 shows that under RSA1, the proportion of patients who are subject to rebate is equal to $1 - R(T_E)$. Thus, we obtain the following equation for the administrative cost of collecting the rebate for $T_E > 0$:

$$C_{I1} = c_I \times \left(1 - R\left(T_E\right)\right). \tag{19}$$

Note that $C_{I1} = 0$ at $T_E = 0$ since the treatment with the new drug has not started yet.

Calculation of Rebate Under RSA1

According to the technology appraisal guidance for the use of bortezomib in the UK patients are evaluated after four cycles of treatment. The treatment needs to be discontinued and rebated in patients who had responded less than partially and should continue in those who had responded at least partially (NICE, 2007). RSA1 is based on the following interpretation from the above guidance: The drug manufacturer rebates to the payer a proportion α of the sales from all patients *up to* the evaluation time T_E (i.e., after four cycles) excluding the sales from those who are responding to the drug *at* T_E.

The rebate under RSA1 (i.e., $R_{\alpha 1}$) can be calculated from the information shown in Table 2-2 (i.e., health state transition scenarios for a patient until T_E and their respective rebate or no rebate status at T_E under RSA1). I use equation (A10) from the first chapter to calculate the rebate under RSA1 as given below:

$$R_{\alpha 1} = \alpha c_D \left(\left(\frac{1}{\lambda_S} + \frac{\theta_S}{\lambda_R} \right) (1 - S(T_E)) - \left(T_E + \frac{1}{\lambda_R} \right) R(T_E) \right). \quad (20)$$

2.2.5 Manufacturer's Profit Under RSA1

Let c_M be the marginal production and distribution cost of the drug for the manufacturer per unit of time. From the first chapter, the manufacturer's profit under RSA1 denoted by $\pi_1(T_E, \alpha)$ is given by the following equation:

$$\pi_1(T_E, \alpha) = (c_D - c_M)(1/\lambda_S + \theta_S/\lambda_R)(1 - S(T_E)) - R_{\alpha 1}. \quad (21)$$

2.3 Payer's Decision Under RSA1

The payer solves the following single-variable, non-linear constrained optimization problem to maximize its NMB:

$$(\text{OP1}): \max_{T_E} \; B_1(T_E, \alpha)$$

$$\text{s.t.:} \quad \pi_1(T_E, \alpha) \geq 0,$$

$$T_E \geq 0,$$

where $B_1(T_E, \alpha)$ is given by equation (18) for j=1, and C_{I1}, $R_{\alpha 1}$, and $\pi_1(T_E, \alpha)$ are given by equations (19) - (21), respectively.

For both the payer and the manufacturer, there are trade-offs in choosing T_E under RSA1: if T_E is too short, the payer does not have time to generate much benefit, nor the manufacturer to generate much sales revenue. On the other hand, if T_E is too long, the manufacturer will have to pay a rebate to the payer for a high percentage of patients because all patients will eventually experience disease progression after responding to the drug (i.e., few patients remain in state *R*). Thus, for the base case RSA1, a too long T_E could be beneficial to the payer, but not to the manufacturer. This implies that the optimal value of T_E for the optimization problem of (OP1) is not obvious, and in finding the optimal T_E, the cost of evaluating too early should be balanced with the cost of evaluating too late. There is no closed-form solution for the optimization problem of (OP1). I investigate the properties of (OP1) in the next section.

2.3.1 Properties of Net Monetary Benefit and Profit Functions under RSA1

When T_E approaches infinity, all patients are entitled to receive a rebate and, thus, the payer collects the largest rebate. From equation (18), the asymptotic NMB of the payer is given by:

$$\lim_{T_E \to \infty} B_1(T_E, \alpha) = k_B - c_I + \alpha \times c_D \times \left(\frac{1}{\lambda_S} + \frac{\theta_S}{\lambda_R} \right). \quad (22)$$

In equation (22) the first term represents the loss incurred (i.e., $k_B - c_I < 0$) and the second term represents the rebate collected at infinity. It follows from (22) that $\lim_{T_E \to \infty} B_1(\alpha, T_E) > 0$ for $\alpha > \alpha_\infty^p$, where $\alpha_\infty^p = \frac{\lambda_S \lambda_R (c_I - k_B)}{c_D \times (\lambda_R + \lambda_S \theta_S)}$ (See the derivation in the Appendix). Thus, α_p^∞ is a threshold for the rebate rate, above which the NMB>0 (i.e., the rebate would exceed the loss incurred) as T_E approaches infinity. For $\alpha > \alpha_\infty^p$, the payer's NMB can still be negative for some $0<T_E<\infty$, namely if the number of non-responding patients at T_E is not high enough to compensate for the respective loss through the collected rebate at T_E.

Similarly, in the first chapter I defined α_∞^m as a threshold for the rebate rate, above which the profit becomes negative as T_E approaches infinity, i.e., $\lim_{T_E \to \infty} \pi_1(\alpha, T_E) > 0$ for $\alpha < \alpha_\infty^m$, where $\alpha_\infty^m = 1 - \frac{c_M}{c_D}$.

Next, I describe the conditions under which the rebate rate and evaluation time are mutually beneficial, i.e. where both the payer and the drug manufacture have incentives to introduce the new drug.

Proposition 1: *Let* $\alpha_{\infty}^{m} = 1 - \frac{c_M}{c_D}$ *and* $\alpha_{\infty}^{p} = \frac{(c_I - k_B)\lambda_S\lambda_R}{c_D \times (\lambda_R + \lambda_S\theta_S)}$. *If* $\alpha_{\infty}^{p} < \alpha < \alpha_{\infty}^{m}$, *then there are feasible solutions for the optimization problem* (*OP1*).

Note that $\alpha_{\infty}^{p} < \alpha_{\infty}^{m}$ is satisfied when $\frac{c_I - k_B}{c_D - c_M} < \frac{\lambda_R + \lambda_S\theta_S}{\lambda_S\lambda_R}$. This is equivalent to $c_I - k_B < (c_D - c_M)\frac{\lambda_R + \lambda_S\theta_S}{\lambda_S\lambda_R}$ as $c_D > c_M$. The right-hand side of this inequality represents the mean net profit from the sales of the drug in state *S* and *R*, i.e., $(c_D - c_M)/\lambda_S$ and $(c_D - c_M)\theta_S/\lambda_R$, respectively. Therefore, $\alpha_{\infty}^{p} < \alpha_{\infty}^{m}$ when the mean net profit of the manufacturer becomes greater than a certain value resulting from the payer's cost and monetary benefit parameters, i.e., $c_I - k_B$.

Proposition 1 guaranty the existence of feasible solutions for both the payer and the manufacturer when $\alpha_{\infty}^{p} < \alpha < \alpha_{\infty}^{m}$. However, the existence of feasible solutions under other scenarios for α, such as $\alpha < \alpha_{\infty}^{p}$, $\alpha > \alpha_{\infty}^{m}$, or $\alpha_{\infty}^{m} < \alpha < \alpha_{\infty}^{p}$, need to be examined separately. In the next section the existence of feasible solutions for both players are investigated in a number of examples.

2.4 Examples

I calculate the payer's NMB and the drug manufacturer's profit under RSA1 for a numerical example. I use the following values for the transition rates estimated in the first chapter by using data from a phase 2 clinical trial for bortezomib (Richardson et al., 2003): $\lambda_S = 0.15$, $\lambda_R = 0.11$, and $\theta_S = 0.4$. I also assume $\hat{\lambda}_S = 0.3$ and $\lambda_P = 0.8$.

I assume that the treatment cycle of bortezomib is 3 weeks (Richardson et al., 2003) and its average cost per treatment cycle is £3,000 (NICE, 2011). Thus, we obtain the following monthly payment for the drug: $c_D = £4{,}000$. The NHS WTP threshold for an intervention is between £20,000 and £30,000 per QALY (NICE, 2010; McCabe et al., 2008). Thus, considering the upper limit of £30,000 per QALY in our examples, we obtain *w*=£2,500 as the WTP per one quality-adjusted life month. The values for other parameters used in this example, including the unit administrative costs, the unit costs of care, as well as the weights of QoL in different health states, are given in Table 2-3.

Table 2-3: Baseline values and costs used in the model

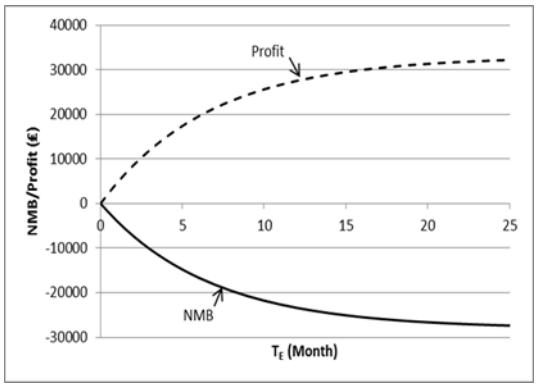
Parameter	**Amount**	**Reference**
λ_S, λ_R, θ_S	0.15, 0.11, 0.4	Chapter 1
$\hat{\lambda}_S$, λ_P	0.3, 0.8	Assumed
w	£2,500	(NICE, 2010; McCabe et al., 2008)
c_D	£4,000	(NICE, 2011; Richardson et al., 2003)
c_V, c_I	£100, £1,000	Assumed
c_S, c_R	£400	Assumed
c_P, $\hat{c}_S$	£2,000	Assumed
q_S, q_R	0.58, 0.68	(NICE, 2011)
q_P, $\hat{q}_S$	0.1, 0.5	Assumed

In panel (a) and (b) of Figure 2-3, the solid lines and the dashed lines show the NMB of the payer and the profit of the manufacturer, respectively. The solid circles in panels (a) and (b) show that the NMB of the payer is equal to zero right at the start of the treatment (i.e., at $T_E = 0$). Panel (a) in Figure 2-3 shows that under no risk-sharing, i.e., α=0, no agreement is possible between both parties because the payer's NMB is always negative. For $c_M = 0.2c_D$, we obtain the following thresholds for the rebate rate: $\alpha_\infty^p = 0.7$ and $\alpha_\infty^m = 0.8$. Thus, according to Proposition 1, for α, $0.7 < \alpha < 0.8$, there are feasible solutions for both the payer and the drug manufacturer. For example, for $\alpha = 0.79$, the NMB of the payer and the profit of the manufacturer are both positive when $T_E \geq 35$ months. However, such large evaluation times might not be practical when the life expectancy is small (e.g., less than 24 months). Under this circumstance, it needs to be examined whether there are feasible solutions with shorter evaluation time for the rebate rates outside of the above mentioned range (e.g., for $\alpha > 0.8$).

Panel (b) of Figure 2-3 shows that for α=100% and $c_M = 0.2c_D$, a feasible agreement is possible for $17 < T_E < 25$ months (because NMB and π are both positive), whereas for $c_M = 0.35c_D$, no agreement is possible. On the other hand, Figure 2-4 shows that for α=120% and $c_M = 0.2c_D$, a feasible agreement is possible for $6 < T_E < 16$ months (i.e., as α increases the agreement becomes feasible for shorter evaluation times).

Figure 2-3: Payer's NMB (solid line) and manufacturer's profit (dashed line) under RSA1

(a): α=0 and $c_M = 0.2c_D$ **(b): α=100%, $c_M = 0.2c_D$ and $0.35c_D$**



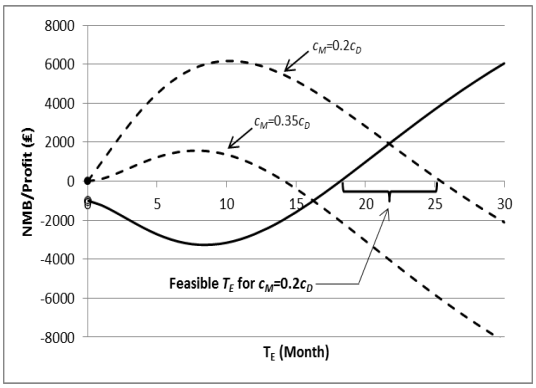
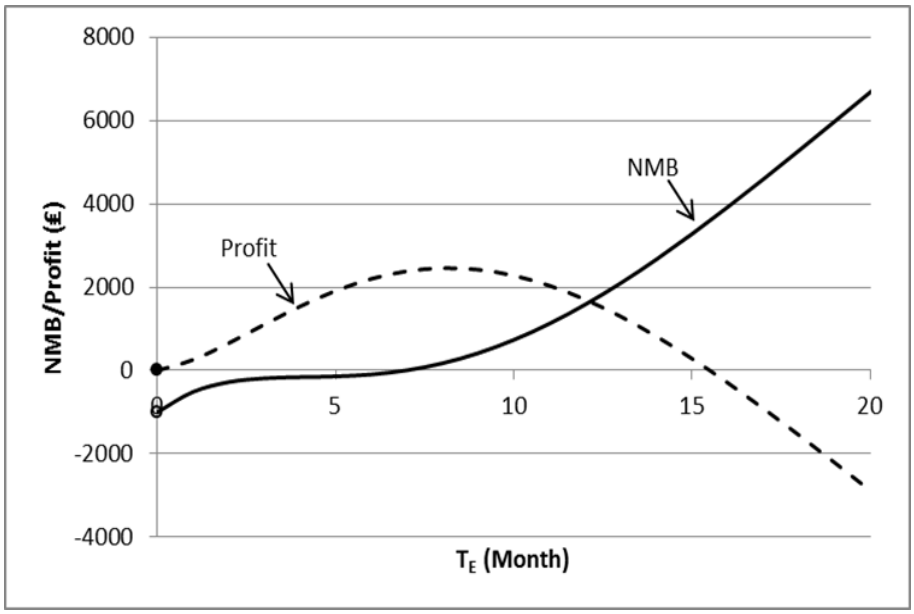


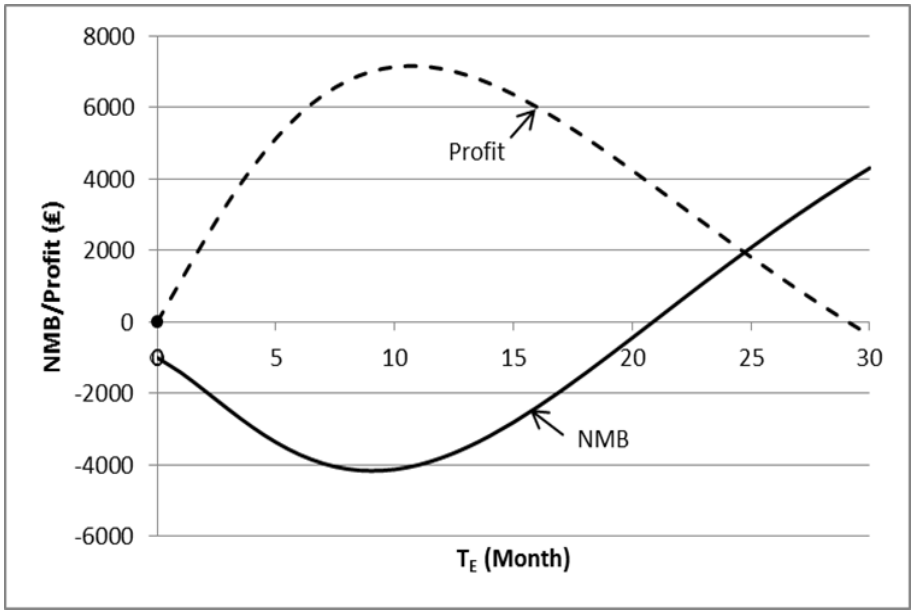
Figure 2-4: Payer's NMB (solid line) and manufacturer's profit (dashed line) under RSA1 for α=120% and $c_M = 0.2c_D$



A report on the uptake of patient access schemes in the NHS notes that a major rebate was lost because the respective departments had missed multiple claims for bortezomib. The same report concludes that the NHS could lose significant revenue if the risk-sharing

scheme is not managed effectively and claims are missed ((Williamson, 2009), page 28). In order to account for the missed rebate, we assume that ω, $0 \leq \omega \leq 1$, is the proportion of the rebate collected (i.e., the collected rebate is equal to $\omega \times R_\alpha$) while the administrative cost of collecting the rebate is incurred for the whole R_α. Figure 2-5 shows that for α=100%, $c_M = 0.2c_D$, and $\omega = 95\%$, a feasible agreement is possible for $21 < T_E < 29$ months (i.e., as the proportion of the collected rebate decreases the agreement becomes feasible for larger T_E).

Figure 2-5: Payer's NMB (solid line) and manufacturer's profit (dashed line) under RSA1 for α=100%, $c_M = 0.2c_D$, and ω=95%



2.5 Other Rebate Classifications

In this section I describe the rebate classifications RSA2 and RSA3 in more detail and derive the equations for the calculation of rebate and administrative cost of collecting the rebate under those classifications. Then, I compare all three different rebate

classifications and show that as the rebate increases so does the administrative cost of collecting the rebate. Therefore, it is not obvious under which rebate classification the payer generates the highest NMB.

Rebate Under RSA2 and RSA3

The second rebate classification (RSA2) is derived from a slight modification in the interpretation for the base case RSA1. According to this modified interpretation, the drug manufacturer rebates to the payer a proportion α of the sales from patients who have *not* responded to the drug *prior to* and *at* T_E. The difference between RSA1 and RSA2 is with respect to patients who responded to the drug but whose disease progressed prior to T_E (and they switched to a different drug). Under RSA1, the sales from this group are subject to rebate, while they are not subject to rebate under RSA2 (Table 2-2). From Table 2-2 the health state transition scenarios that are subject to rebate under RSA2 are: "Direct progress from *S*" and "Remain in *S*" by T_E. By calculating the total time spent by patients in these health state transition scenarios, we obtain the following equation for the calculation of rebate under RSA2:

$$\begin{aligned} R_{\alpha 2} &= \alpha c_D \left((1-\theta_S) \left(\int_0^{T_E} S(t)dt - T_E S(T_E) \right) + T_E S(T_E) \right) \\ &= \alpha c_D \left((1-\theta_S) \int_0^{T_E} S(t)dt + T_E \theta_S S(T_E) \right), \end{aligned} \tag{23}$$

where $(1-\theta_S)\left(\int_0^{T_E} S(t)dt - T_E S(T_E)\right)$ is the total time spent in state *S* by non-respondents who progressed by T_E and $T_E S(T_E)$ is the total time spent in state *S* by non-respondents at T_E. Substituting (1) for *S*(*t*) yields:

$$R_{\alpha 2} = \alpha c_D \left(\frac{(1-\theta_S)}{\lambda_S}\left(1 - S\left(T_E\right)\right) + T_E \theta_S S\left(T_E\right) \right). \quad (24)$$

I derive the third rebate classification (RSA3) from the report into the uptake of the patient access scheme for bortezomib in the NHS, which implies that the rebate is potentially missed to be invoiced for patients who do not get as far as 4 cycles of treatment ((Williamson, 2009), page 17). This statement implies that those patients, for whom the disease progresses before the evaluation time (i.e., 4 cycles), are not rebated. According to this interpretation, the drug manufacturer rebates to the payer a proportion α of the sales from patients who are *not* responding to the drug *at* T_E (i.e., only patients who are neither responding nor for whom disease has progressed at the evaluation time will be subject to rebate).The difference between RSA2 and RSA3 is with respect to non-responding patients whose disease progressed prior to T_E. Under RSA2, the sales from this group are subject to rebate, while the manufacturer does not need to pay rebate for this group under RSA3 (Table 2-2).

The proportion of patients who are not responding to the drug at time T_E is equal to $S(T_E)$. Therefore, we calculate the rebate under RSA3 according to the following equation:

$$R_{\alpha 3} = \alpha c_D \times T_E \times S(T_E). \quad (25)$$

It is intuitive from Table 2-2 and the descriptions of rebates under the base case RSA1 and two other classifications that $R_{\alpha 1} > R_{\alpha 2} > R_{\alpha 3}$ for all T_E. The formal mathematical proof is also given in Lemma A1 in the Appendix.

Administrative Costs of Collecting Rebates Under RSA2 and RSA3

With reference to Table 2-2, we obtain the administrative costs of collecting the rebate under RSA2 and RSA3 by the following equations for $T_E > 0$:

$$C_{I2} = c_I \times \left(1 - \theta_S \left(1 - S\left(T_E\right)\right)\right), \tag{26}$$

$$C_{I3} = c_I \times S\left(T_E\right). \tag{27}$$

Note that C_{I2} and $C_{I3} = 0$ at $T_E = 0$ since the treatment with the new drug has not started yet. It is intuitive from Table 2-2 that $C_{I1} > C_{I2} > C_{I3}$ for all T_E. The formal mathematical proof is also given in Lemma A2 in the Appendix.

To calculate the NMB of the payer under RSA2 and RSA3 we use equation (18) in which for j=2, $R_{\alpha 2}$ and C_{I2} are given by equations (24) and (26) for RSA2, and for j=3, $R_{\alpha 3}$ and C_{I3} are given by equations (25) and (27) for RSA3. To calculate the manufacturer's profit under RSA2 and RSA3, I generalize on equation (21) by replacing $R_{\alpha 1}$ with $R_{\alpha \mathrm{j}}$:

$$\pi_{\mathrm{j}}(T_E, \alpha) = (c_D - c_M)\left(\frac{1}{\lambda_S} + \frac{\theta_S}{\lambda_R}\right)\left(1 - S(T_E)\right) - R_{\alpha \mathrm{j}}, \tag{28}$$

where j=2, 3 is the subscript referring to RSA2 and RSA3, and $R_{\alpha 2}$ and $R_{\alpha 3}$ are given by (24) and (25), respectively.

As it was shown for RSA1, the following single-variable, non-linear constrained optimization problem needs to be solved in order to find the optimal evaluation time for the payer to maximize its NMB under RSA2 and RSA3:

$$(\text{OPj}): \max_{T_E} \; B_{\text{j}}(T_E, \alpha)$$
$$\pi_{\text{j}}(T_E, \alpha) \geq 0$$
$$T_E \geq 0,$$

where for j=2, 3, $B_{\text{j}}(T_E,\alpha)$ is given by (18), and $\pi_{\text{j}}(T_E,\alpha)$ is given by (28).

Similar to RSA1, there are trade-offs in choosing T_E for both the payer and the manufacturer under RSA2 and RSA3. However, contrary to RSA1, a too long T_E could be beneficial only to the manufacturer (and not to the payer) under both RSA2 and RSA3. This is because all patients will eventually experience disease progression either directly or after responding to the drug (i.e., few patients remain in state *S*). Thus, if T_E is too long, the payer will claim a rebate for a lower percentage of patients under RSA2 and RSA3. This also implies that the optimal values of T_E for the optimization problems of (OP2) and (OP3) are not obvious, and in finding the optimal T_E, the cost of evaluating too early should be balanced with the cost of evaluating too late.

As in the case of (OP1), there are not any closed-form solutions for the optimization problems of (OP2) and (OP3) either. Since $R_{\alpha 1} > R_{\alpha 2} > R_{\alpha 3}$ and at the same time $C_{I1} > C_{I2} > C_{I3}$, it is not obvious which rebate classification generates the largest NMB for a given T_E (i.e., it is not obvious if $B_1 > B_2 > B_3$). Figure 2-6 shows the NMB of the payer under RSA1 (solid line), RSA2 (dashed line), and RSA3 (dotted-dashed line) for α=100% (the rest of the model parameters used in these figures are taken from Table 2-3). This example illustrates a case in which the price of the drug is high while the rebate rate is not large enough. Under this circumstance, as shown in Figure 2-6, RSA1 would

be the only rebate classification that could compensate for the loss and generate some positive NMB. This is achieved by demanding the manufacturer pay the rebate for those responding patients who are not responding at T_E (see panel [b] of Figure 2-3 for the conditions on T_E for a feasible agreement under RSA1 when $c_M = 0.2c_D$).

Figure 2-6: Payer's NMB under RSA1 (solid line), RSA2 (dashed line), and RSA3 (dotted-dashed line) for α=100% and c_D = £4,000; solid circle shows NMB at $T_E = 0$

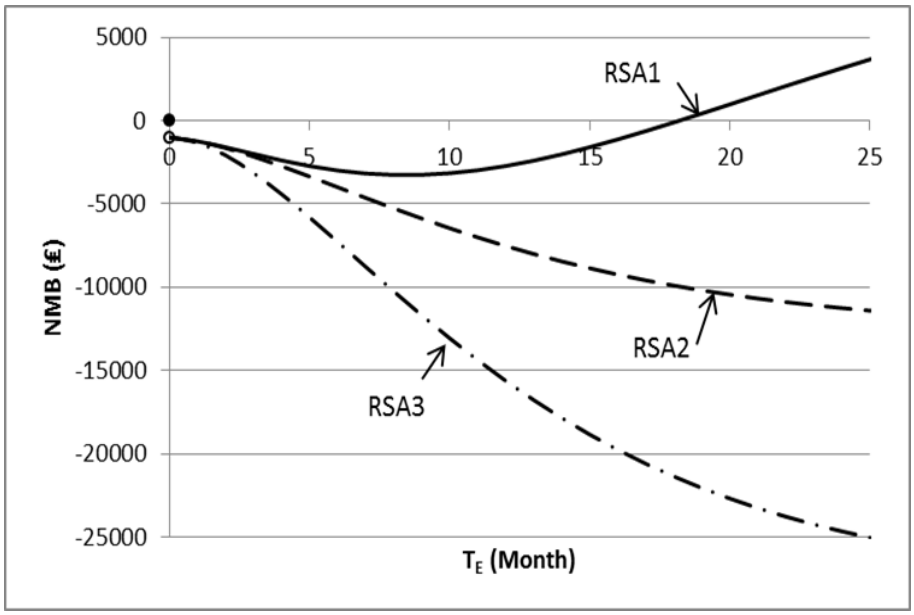
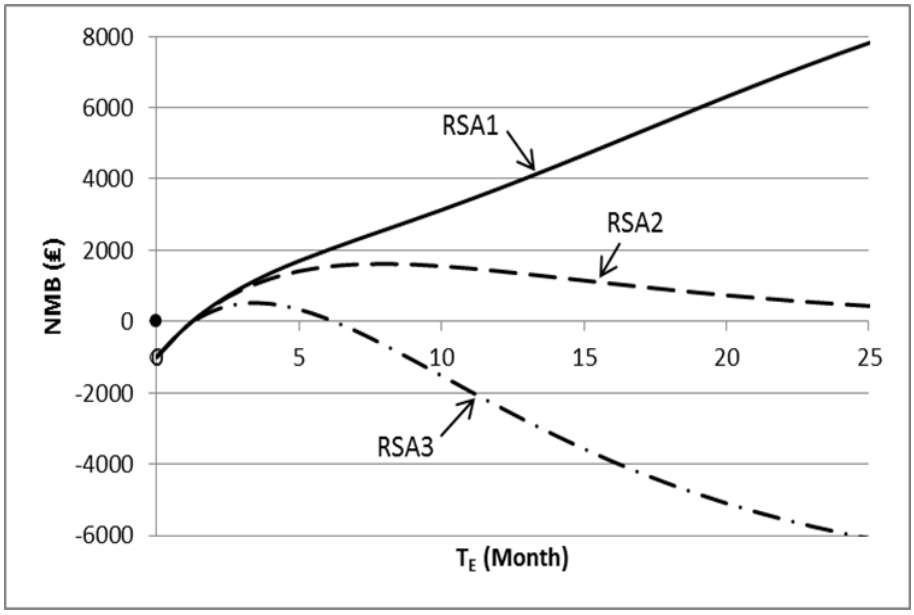


Figure 2-7 shows the NMB of the payer under RSA1-3 when the price of the drug is halved compared to example 2-6, i.e., c_D = £2,000 per unit month. As a result of reducing the price of the drug, the NMB of the payer has become positive under RSA2 and RSA3 for certain ranges of T_E.

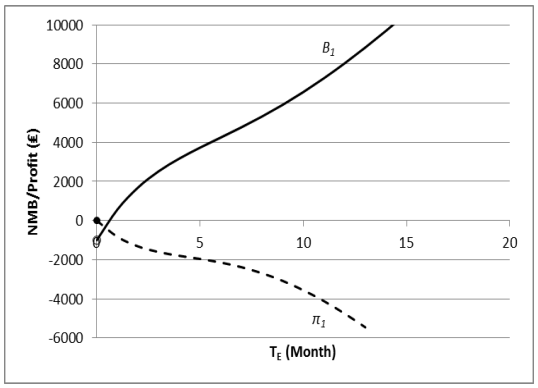
Figure 2-7: Payer's NMB under RSA1 (solid line), RSA2 (dashed line), and RSA3 (dotted-dashed line) for α=100% and c_D = £2,000; solid circle shows NMB at $T_E = 0$



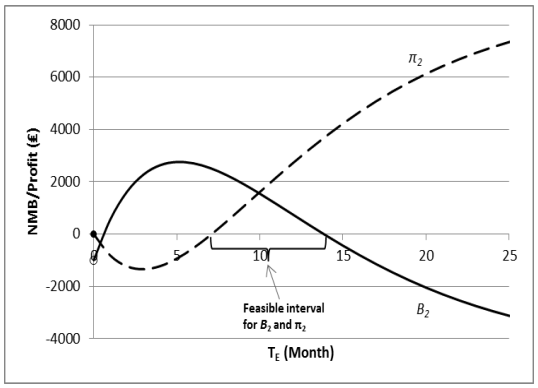
On the other hand, Figure 2-8 illustrates the case where the rebate rate is increased to 150% while the price of the drug is high (i.e., c_D = £4,000 per unit month). Under this circumstance, as depicted in Panel (a) of Figure 2-8, RSA1 has become infeasible because of generating loss for the manufacturer for $T_E > 0$ resulting from the large rebate rate. However, Panel (b) and (c) of Figure 2-8 show that RSA2 and RSA3 are feasible for $7 < T_E < 14$ months and $2 < T_E < 4$ months, respectively. Figures 2-6 to 2-8 also illustrate that $B_1(\alpha, T_E) > B_2(\alpha, T_E) > B_3(\alpha, T_E)$ for $T_E > 0$. These examples show that for small administrative costs of collecting the rebate c_I, the payer is better off with RSA1 subject to the existence of feasible solutions for the drug manufacturer.

Figure 2-8: Payer's NMB (solid line) and manufacturer's profit (dashed line) for α=150%, c_D =£4,000, and $c_M = 0.2c_D$

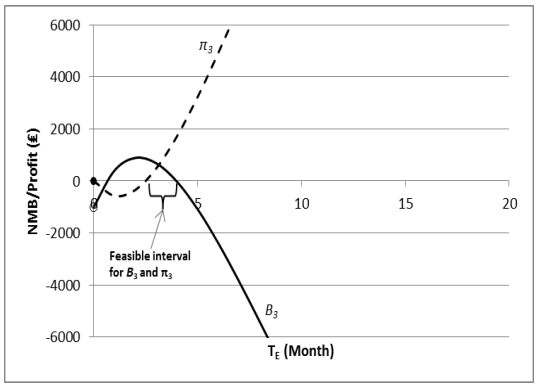
(a) Under RSA1



(b) Under RSA2



(c) Under RSA3



2.6 Conclusions and Future Research

I examined the performance of a pay-for-performance risk-sharing agreement similar to the agreement for bortezomib in the UK from the perspective of a payer. The parameters used in this analysis can be categorized into three groups. The first group consists of the rebate rate α, the unit price of the drug c_D, the WTP per unit of effectiveness *w*, and the evaluation time T_E. The parameters in this group are usually used to define the terms and

conditions in the contract. The second group consists of the drug response rate $\lambda_S\theta_S$, the disease progression rate λ_R, the unit production and distribution cost of the drug c_M, and the quality weights of the drug effectiveness q_S, $\hat{q}_S$, q_R, and q_P. The parameters in this group are related to the characteristics of the drug. The parameters in the third group include all costs incurred during the course of treatment (excluding the cost of the drug) consisting of the costs of care per unit of time c_S, $\hat{c}_S$, c_R, and c_P, and the administrative unit costs c_V and c_I.

My analysis in this chapter reveals how different settings among the parameters of these three groups affect the NMB of the payer and the existence of a feasible contract with a drug manufacturer. Specifically, my analysis of the coefficient k_B, which is a function of several model parameters, including the payer's WTP, disease progression rates, QoL and unit cost of care in certain health states, and unit costs of the drug and monitoring of patients, revealed the following. When $k_B > 0$, the payer's NMB is positive without any risk-sharing scheme in place, i.e., when α=0. Also when $k_B > 0$ and α=0, the optimal evaluation time for both the payer and the drug manufacturer would approach infinity. In practice, this means that an evaluation time in the later stages of the treatment would be beneficial for both the payer and the manufacturer.

However, the payer might still want to consider a risk-sharing agreement with the manufacturer when $k_B > 0$ for the following reason. I have not incorporated uncertainty in my model. Uncertainty in the parameters such as transition rates, cost of care, or QoL can

lead to uncertainty in k_B. As a result of an uncertain k_B, it is no longer guaranteed that the payer's NMB would be positive for $T_E > 0$. Thus the payer may consider a risk-sharing agreement with the drug manufacture to manage this uncertainty.

If $k_B < 0$ and α=0, the payer's NMB will be negative. To compensate for this loss, I applied a risk-sharing agreement similar to the bortezomib agreement in the UK and analysed the NMB of the payer under the base case rebate classification RSA1 and two other rebate classifications RSA2 and RSA3. My analysis showed that there are trade-offs in choosing the evaluation time for both the payer and the manufacturer, such that its optimal value is not obvious. The results from the examples also show that the set of evaluation time at which both the payer and the drug manufacturer benefit is sensitive to the proportion of collected rebates. This implies that by failing to collect a proportion of the rebate, the risk-sharing agreement might not be beneficial to the payer anymore.

The examples illustrate that for a high price of the drug and a rebate rate that is not large enough, RSA1 could possibly be the only feasible contract. By reducing the price of the drug, RSA2 and RSA3 could also become feasible. For a high price of the drug and a large rebate rate, RSA2 could become the only feasible rebate classification for both parties. I also showed that it is not obvious under which rebate classification the payer generates the highest NMB, as a higher rebate incurs a higher administrative cost for collecting it. Nonetheless, the examples in this chapter demonstrate that when the administrative cost of collecting the rebate per non-responding patient is relatively small (e.g., $c_I = £1{,}000$ used in this chapter), the payer is better off with respect to NMB under RSA1. However, when both RSA1 and RSA2 are feasible options, RSA2 could be a

more reasonable option for both parties to compromise during negotiation. This is because RSA2 does not penalize the manufacturer for non-responding patients who had responded to the drug before the evaluation time.

The National Institute for Health and Care Excellence appraisal guidance for the use of bortezomib in the UK found that the incremental cost per QALY gained among patients with minimal response (i.e., a reduction of 25% to 49% in serum M protein) would be very high (NICE, 2007). Thus, a potential extension to the model would be to assume the payer (NHS) pays a discounted price when the observed effectiveness is less than expected (i.e., minimal response) and then investigate the optimal solution under the new contract structure. In this chapter, I have assumed that the monitoring cost is fixed throughout the treatment. As an extension to the model, it is possible to assume that establishing an optimal patient monitoring scheme is a sub-problem that needs to be considered for establishing the optimal evaluation time.

A potential area of future research would be to investigate the payer's adverse selection under risk-sharing by assuming that there are two drugs for the treatment of the same disease (for instance bortezomib and thalidomide used for the first-line treatment of multiple myeloma (NICE, 2011)). However, the effectiveness of these drugs is not completely the same (i.e., θ_S, λ_S, or λ_R or any combination of these parameters are different in these drugs), and they also have different prices.

Appendix to Chapter 2

Derivation of α_∞^p

According to the first chapter, $\alpha_\infty^m = 1 - \frac{c_M}{c_D}$ is a threshold for rebate rate, above which the manufacturer's profit becomes negative as T_E approaches infinity. In other words, $\lim_{T_E \to \infty} \pi_1(\alpha, T_E) > 0$ for $\alpha < \alpha_\infty^m$. Now we show in the following that $\alpha_\infty^p = \frac{(c_I - k_B)\lambda_S \lambda_R}{c_D \times (\lambda_R + \lambda_S \theta_S)}$ is a threshold for the rebate rate, below which the payer's NMB becomes negative as T_E approaches infinity, i.e., $\lim_{T_E \to \infty} B_1(\alpha, T_E) < 0$ for $\alpha < \alpha_\infty^p$, or alternatively, $\lim_{T_E \to \infty} B_1(\alpha, T_E) > 0$ for $\alpha > \alpha_\infty^p$:

From equation (18) for j=1: $\lim_{T_E \to \infty} B_1(\alpha, T_E) = \lim_{T_E \to \infty} (k_B(1 - S(T_E)) + R_{\alpha 1} - C_{I1})$.

Since $\lim_{T_E \to \infty} S(T_E) = \lim_{T_E \to \infty} R(T_E) = 0$, it follows from equation (20) that $\lim_{T_E \to \infty} R_{\alpha 1} = \alpha c_D \left(\frac{1}{\lambda_S} + \frac{\theta_S}{\lambda_R} \right)$. Also from equation (19) $\lim_{T_E \to \infty} C_{I1} = c_I$.

Thus: $\lim_{T_E \to \infty} B_1(\alpha, T_E) = k_B + \alpha c_D \left(\frac{1}{\lambda_S} + \frac{\theta_S}{\lambda_R} \right) - c_I$, where $k_B = k_S / \lambda_S + k_R \theta_S / \lambda_R - \hat{k}_S / \hat{\lambda}_S$.

Incorporating k_B in the above equation for $\lim_{T_E \to \infty} B_1(\alpha, T_E)$ yields:

$\lim_{T_E \to \infty} B_1(\alpha, T_E) = \frac{\lambda_S \lambda_R (k_B - c_I) + \alpha c_D (\lambda_R + \lambda_S \theta_S)}{\lambda_S \lambda_R}$. It follows from this equation that $\lim_{T_E \to \infty} B_1(\alpha, T_E) > 0$ for $\lambda_S \lambda_R (k_B - c_I) + \alpha c_D (\lambda_R + \lambda_S \theta_S) > 0$ or alternatively for $\alpha c_D (\lambda_R + \lambda_S \theta_S) > \lambda_S \lambda_R (c_I - k_B)$. This in turn yields

$\lim_{T_E \to \infty} B_1(\alpha, T_E) > 0$ for $\alpha > \alpha_\infty^p$, where $\alpha_\infty^p = \frac{\lambda_S \lambda_R (c_I - k_B)}{c_D (\lambda_R + \lambda_S \theta_S)}$.

Proof of Proposition 1

It follows from $\lim_{T_E \to \infty} B_1(\alpha, T_E) > 0$ for $\alpha > \alpha_\infty^p$ that for $\alpha > \alpha_\infty^p \ \exists T_1 \in [0,\infty)$ such that $B_1(\alpha, T_E) > 0$ for $T_E > T_1$. On the other hand, it follows from $\lim_{T_E \to \infty} \pi_1(\alpha, T_E) > 0$ for $\alpha < \alpha_\infty^m$ that for $\alpha < \alpha_\infty^m \ \exists T_2 \in [0,\infty)$ such that $\pi_1(\alpha, T_E) > 0$ for $T_E > T_2$; Thus, for $\alpha_\infty^p < \alpha < \alpha_\infty^m$, $\pi_1(\alpha, T_E) > 0$ and $B_1(\alpha, T_E) > 0$ for $T_E > \max(T_1, T_2)$. This in turn implies that for $\alpha_\infty^p < \alpha < \alpha_\infty^m$, there are feasible solutions for both players.

Q.E.D.

Lemma A1

$R_{\alpha 1} > R_{\alpha 2} > R_{\alpha 3}$ for $T_E > 0$.

Proof of Lemma A1

$R_{\alpha 1} > R_{\alpha 2}$ for $T_E > 0$, since from (23-b) $R_{\alpha 2}$ can be written as:

$$R_{\alpha 2} = \alpha c_D \int_{t=0}^{T_E} \big(S(t) + R(t)\big)dt - \alpha c_D \int_{t=0}^{T_E} \big(\theta_S S(t) + R(t)\big)dt + \alpha c_D T_E \theta_S S\big(T_E\big).$$

Also from the first chapter, $R_{\alpha 1}$ can also be written as:

$R_{\alpha 1} = \alpha c_D \int_{t=0}^{T_E} \big(S(t) + R(t)\big)dt - \alpha c_D \times T_E R\big(T_E\big)$. It follows from the above statements for $R_{\alpha 1}$ and $R_{\alpha 2}$ that in order to show $R_{\alpha 1} > R_{\alpha 2}$ for $T_E > 0$, we need to prove:

$T_E\big(\theta_S S\big(T_E\big) + R\big(T_E\big)\big) < \int_{t=0}^{T_E} \big(\theta_S S(t) + R(t)\big)dt \ \ \forall T_E > 0$. This is true since:

$$\frac{dS(t)}{d(t)} = -\lambda_S S(t) \Rightarrow \theta_S \frac{dS(t)}{d(t)} = -\lambda_S \theta_S S(t)$$

$$\frac{dR(t)}{dt} = \lambda_S \theta_S S(t) - \lambda_R R(t) \Rightarrow$$

$$\frac{d\left(\theta_S S(t) + R(t)\right)}{d(t)} = -\lambda_S \theta_S S(t) + \lambda_S \theta_S S(t) - \lambda_R R(t) = -\lambda_R R(t) < 0 \quad \forall t > 0 \Rightarrow$$

$\theta_S S(t) + R(t)$ is decreasing in $t > 0$.

$$\text{Thus}: \int_{t=0}^{T_E} \left(\theta_S S(t) + R(t)\right) dt > T_E \times \left(\theta_S S(T_E) + R(T_E)\right) \quad \forall T_E > 0 \Rightarrow$$

$R_{\alpha 1} > R_{\alpha 2} \quad \forall T_E > 0.$

Since $\int_0^{T_E} S(t)dt - T_E S(T_E) > 0$ for $T_E > 0,$ it follows from (23), i.e.,

$R_{\alpha 2} = \alpha c_D \left(\left(1-\theta_S\right)\left(\int_0^{T_E} S(t)dt - T_E S\left(T_E\right)\right) + T_E S\left(T_E\right)\right),$ and $R_{\alpha 3} = \alpha c_D \times T_E \times S(T_E)$ that

$R_{\alpha 2} > R_{\alpha 3}$ for $T_E > 0.$ Thus, $R_{\alpha 1} > R_{\alpha 2} > R_{\alpha 3}$ for $T_E > 0.$

Q.E.D.

Lemma A2

$C_{I1} > C_{I2} > C_{I3}$ for $T_E > 0.$

Proof of Lemma A2

To show that $C_{I2} > C_{I3}$ for $T_E > 0,$ we use the principle of "proof by contradiction". Let us assume that $C_{I2} < C_{I3}$ for $T_E > 0.$ Thus from equations (26) and (27) we have:

$$c_I \times \left(1 - \theta_S \left(1 - S\left(T_E\right)\right)\right) < c_I \times S\left(T_E\right) \Rightarrow$$
$$1 - \theta_S \left(1 - S\left(T_E\right)\right) < S\left(T_E\right) \Rightarrow$$
$$\left(1 - S\left(T_E\right)\right)\left(1 - \theta_S\right) < 0.$$

This is not a true inequality since $S(T_E) < 1$ for $T_E > 0$ and also $0 \le \theta_S \le 1$, resulting in $(1 - S(T_E))(1 - \theta_S) \ge 0$ for $T_E > 0$. Thus, $C_{I2} > C_{I3}$ for $T_E > 0$.

To show that $C_{I1} > C_{I2}$, we calculate the slopes of C_{I1} and C_{I2} as shown in the following:

$\partial C_{I1} / \partial T_E = -\partial R(T_E) / \partial T_E = -\lambda_S \theta_S S(T_E) + \lambda_R R(T_E)$,

$\partial C_{I2} / \partial T_E = -\theta_S \partial S(T_E) / \partial T_E = -\lambda_S \theta_S S(T_E) < 0. \Rightarrow$

$\partial C_{I1} / \partial T_E > \partial C_{I2} / \partial T_E \quad \forall T_E \in (0, \infty)$ since $\lambda_R R(T_E) > 0 \ \forall T_E \in (0, \infty)$.

It results from the above statements that C_{I2} is decreasing in T_E and C_{I1} is either decreasing less than C_{I2} or is increasing in T_E.

Since the treatment has not started yet at $T_E = 0$, we assumed that

$C_{I1} = C_{I2} = 0$ at $T_E = 0$, i.e., C_{I1} and C_{I2} are discontinuous at $T_E = 0$.

Ignoring the above assumption on discontinuity at $T_E = 0$ results in:

$C_{I1} = C_{I2} = 1$ at $T_E = 0$; That is C_{I1} and C_{I2} start at the same point at $T_E = 0$.

On the other hand, $\lim_{T_E \to \infty} C_{I1} = 1$ and $\lim_{T_E \to \infty} C_{I2} = 1 - \theta_S < 1$, i.e., $\lim_{T_E \to \infty} C_{I1} > \lim_{T_E \to \infty} C_{I2}$.

Thus, from $C_{I1} = C_{I2} = 1$ at $T_E = 0$, $\lim_{T_E \to \infty} C_{I1} > \lim_{T_E \to \infty} C_{I2}$, and the fact that C_{I1} is less decreasing than C_{I2} it follows that $C_{I1} > C_{I2} \quad \forall T_E > 0$.

$C_{I1} > C_{I2}$ and $C_{I2} > C_{I3} \ \forall T_E > 0 \Rightarrow C_{I1} > C_{I2} > C_{I3} \ \forall T_E > 0$.

Q.E.D.

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Chapter 3

3 Revisiting the Economics of a Pay-for-performance Risk-sharing Agreement

In this chapter I analyse a risk-sharing agreement between a third-party payer and a pharmaceutical firm. According to this agreement, patients are prescribed the drug in question only if their probability of response to the drug lies within a range of probabilities of success. The payer determines this range such that the use of the drug becomes cost-effective. The pharmaceutical firm provides the payer with a rebate for patients who do not respond to the drug. I generalize on Barros (2011), allowing the rebate to be different from the price of the drug, as well as incorporating two types of administrative costs. I find a threshold for the rebate rate at which the payoff of the payer and the profit of the manufacturer become non-monotonic. I demonstrate that the implications of choosing a large rebate rate for the payer will be the unusual policy of treating patients with lower probability of response. I also derive the conditions under which the payer can choose not to follow the unusual policy while still achieving a positive payoff. I show that as administrative costs are reduced and/or the variability in the probability of response increases, the risk-sharing agreement becomes welfare-improving for a wider range of rebate rates compared with no risk-sharing. I also show that for a given variability in the probability of response, the risk-sharing agreement becomes welfare-improving at a larger rebate rate when the density of patients with lower probability of response is higher. I investigate how to eliminate the welfare loss either by imposing taxes, by paying subsidies, or through contract by deriving the proper transfer payment scheme.

3.1 Introduction

Several expensive drugs have been introduced in the past 10 years. Some examples include carfilzomib for relapsed and refractory multiple myeloma, costing $10,000 (USD) per 28-day cycle (Stenger, 2012); pralatrexate for patients with relapsed or refractory peripheral T-cell lymphoma, costing $67,500 (USD) per each 7-week cycle (Hui et al., 2012); and bevacizumab for the treatment of breast, colon, lung, and brain cancer, costing up to $100,000 (USD) a year (Jirillo et al., 2008).

At the time of introduction, the effectiveness of these drugs is often unproven outside of clinical trials. This creates a risk to third-party payers, as the outcomes of these drugs in real-world practice is highly uncertain ex-ante. As a result, payers may be reluctant to cover them.

These issues have prompted many payers to consider pay-for-performance risk-sharing agreements as an innovative approach that enables the risk associated with inclusion of these drugs in the formulary to be shared between the payer and the drug manufacturer. As the implementation of pharmaceutical pay-for-performance risk-sharing agreements grows (Adamski et al., 2010; Carlson et al., 2010), so does the need for detailed analysis on the economics of these agreements. Two important considerations of any economic analysis are when an agreement (in this case, a pay-for-performance risk-sharing agreement) is beneficial to both parties (in this case, the payer and the manufacturer) and when it becomes welfare-improving.

Barros (2011) studied the economics of a pay-for-performance risk-sharing agreement in which a new treatment is prescribed to a patient whose probability of response is higher

than a cut-off probability. The drug manufacturer then provides a rebate to the payer for all sales for patients who did not respond. He assumed that the drug manufacturer is a monopolist who sets the price of the drug and compared the utility for the payer and the profit for the drug manufacturer in two scenarios: risk-sharing and no risk-sharing. He showed that, depending on when a risk-sharing agreement is negotiated (i.e., before or after the price has been set for the drug), the agreement may increase or decrease social welfare. Using a similar model, Antonanzas et al. (2011) assumed that the price of the new drug is determined through a negotiation between the payer and the drug manufacturer and showed that the optimal contract depends on the trade-off among the monitoring costs, the marginal production cost, and the utility derived from treatment.

In this chapter I generalize on Barros (2011) in two ways. First I allow the rebate rate to be any value, whereas Barros (2011) assumed it was 100%. The payer might choose a rebate rate greater than 100% when there is a possibility that the payer also incurs some extra costs arising from treating a non-responding patient with the drug (e.g., costs related to hospital care, pharmacy dispensing, or side effects of the drug). Second, in addition to the administrative cost of verifying whether each patient receiving the drug is responding (which was included in Barros (2011)), I assume that there is an administrative cost for collecting (invoicing) the rebate for every non-responding patient.

This chapter makes the following contributions. First, I find a threshold for the rebate rate at which the payoff of the payer and the profit of the manufacturer become non-monotonic. Second, I show that the implications of choosing a large rebate rate for the payer will be the perverse incentive policy of treating patients with lower probability of response. Third, I derive the conditions where the payer can choose not to follow the

respective perverse incentive policy while still achieving a positive payoff. Fourth, I show that as administrative costs are reduced and/or the variability in the probability of response increases, the risk-sharing agreement becomes welfare-improving for a wider range of rebate rates compared with no risk-sharing. Fifth, I also show that for a given variability in the probability of response, the risk-sharing agreement becomes welfare-improving at a larger rebate rate when the density of patients with lower probability of response is higher. And sixth, I show how to eliminate the welfare loss by imposing taxes, by paying subsidies, or through contract by deriving the proper transfer payment scheme.

In section 2 of this chapter, I derive the optimal solutions for the payer and the drug manufacturer. In section 3, I examine a number of examples to evaluate the performance of risk-sharing at optimal points. In section 4, I analyse the situation in which the price is fixed. In section 5, I calculate the optimal social welfare from the perspective of a social planner and explore some of the transfer payment methods to achieve that optimal solution. In section 6, I make my concluding remarks.

3.2 The Model

I use Barros (2011) approach to model patients' response to a new drug. Let π be the probability of success per patient, $0 \leq \pi \leq 1$, which can be observed by physicians prior to treatment. Because of heterogeneity in response to the drug throughout the patient population, I allow π to be randomly distributed between 0 and 1. For mathematical convenience I assume that π is continuous with probability density function $f(.)$ and cumulative distribution function $F(.)$. As in Barros (2011), I assume that physicians are

perfect agents of the payer, and thus the interactions between the three parties—physicians, the manufacturer, and the payer—can be simplified to interactions between the payer and the manufacturer. Let *b* be the monetary benefit to the payer from the successful response of a patient to the new drug, $b > 0$. For example, *b* could be the quality-adjusted life years gained by a patient multiplied by the payer's willingness-to-pay (WTP) per unit gained. Let c_V be the administrative cost for verifying whether or not each patient receiving the drug is responding, $c_V \geq 0$. I assume c_V is incurred by the payer. Let *w* be the marginal production and distribution cost of the drug incurred by the manufacturer, $w \geq 0$.

Table 3-1: Table of model parameters

ITEMS	DESCRIPTIONS
π	Probability of response to the drug
L, U	Lower and upper cut-off probabilities
L^*, U^*	Optimal lower and upper cut-off probabilities
L^C, U^C	Optimal cut-off probabilities from social planner perspective
$f(\pi)$, $F(\pi)$	Probability density and probability distribution functions for π
μ_π	Expected value of π
V_P, V_M	Expected payoff of the payer and the profit of the manufacturer
V_P^*, V_M^*	Optimal expected payoff and optimal expected profit
$V_M^{\sim}$	Reservation profit for the manufacturer
$\hat{V}_P, \hat{V}_M$	Payoff of the payer and the profit of the manufacturer after the payment transfer
p, p^*	Price of the drug, optimal price
c_V	Verification cost (all patients are subjected to)
c_I	Rebate invoicing cost (only non-respondents are subjected to)
w	Manufacturing and distribution cost of the drug
α	Rebate rate

As in Barros (2011), I assume that the manufacturer is a monopolist and thus sets the price *p* of the drug, $p \geq 0$. Under the risk-sharing agreement discussed in this chapter, the drug manufacturer rebates to the payer a proportion α of the sales of the drug from a non-responding patient, $\alpha \geq 0$. I assume that α is fixed by the payer exogenously and that α could be larger than 1. Let c_I be the administrative cost for collecting (invoicing) the rebate for every non-responding patient, $c_I \geq 0$. I assume c_I is also incurred by the payer. The timeline of the decisions is such that first the manufacturer sets the price *p*. Then similar to Zaric (2008), I assume that the payer decides on a lower and an upper cut-off probability, *L* and *U*, such that patients whose probability of response lies between these two cut-off probabilities will be prescribed the drug (i.e., the drug is only available if $L \leq \pi \leq U$). Under normal circumstances we would expect $U = 1$. However, we allow an upper bound *U*, $0 \leq U \leq 1$, because for large α, treatment by the drug becomes cost-effective for patients with lower probability of response. I have included the unusual case of $U < 1$ in my analysis to explore the implications of having a large exogenous rebate rate.

Let V_P be the expected payer's payoff and V_M be the expected manufacturer's profit:

$$\begin{aligned} V_P &= \int_L^U \left(b - (p + c_V)\pi + \left((\alpha p - c_I) - (p + c_V)\right)(1 - \pi)\right) f(\pi) d\pi, \\ &= \int_L^U \left(d \times \pi - n\right) f(\pi) d\pi, \end{aligned} \tag{1}$$

where $d = b - (\alpha p - c_I)$ and $n = p + c_V - (\alpha p - c_I)$.

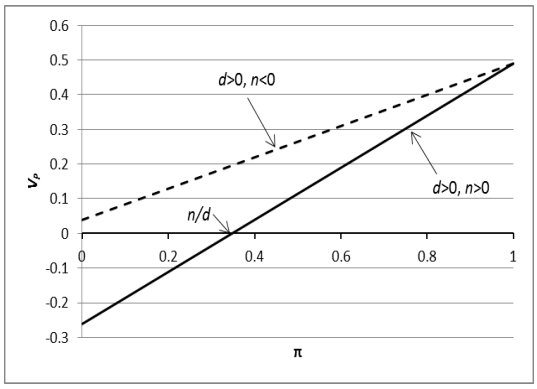
In (1) d is the difference to the payer between the benefit of a *responding patient, b*, and the net benefit of a *non-responding patient* $(\alpha p - c_I)$; and *n* is the difference between the cost of a *responding patient* $(p + c_V)$ and the benefit of a *non-responding patient* $(\alpha p - c_I)$. Positive *d* implies that the benefit of a respondent is higher than the net benefit of a non-respondent $(b > \alpha p - c_I)$, whereas negative *d* implies that the net benefit of a non-respondent is higher than the benefit of a respondent to the payer $(b < \alpha p - c_I)$. Positive *n* implies that the cost of a respondent is higher than the benefit of a non-responding patient $(p + c_V > \alpha p - c_I)$, whereas negative *n* implies that the benefit of a non-responding patient is higher than the cost of a respondent to the payer $(p + c_V < \alpha p - c_I)$.

To analyse the payoff of the payer as a function of the probability of response, I use equation (1) to obtain the following equation for the payoff of the payer for a given π: $V_P = d \times \pi - n$. In Figure 3-1, the payoff of the payer is depicted as a function of π for four different combinations of the parameters *d* and *n*. For all these cases I have assumed that *b*=1. Panel (a) of Figure 3-1 shows the payoff when model parameters (i.e., α, p, c_V, and c_I) are chosen such that they result in the following two cases: 1. *d*>0 and *n*>0, and 2. *d>0* and *n*<0. As shown in this panel, for *d*>0 and *n*>0, the payoff of the payer is non-negative if $\pi \geq n/d$, and for *d*>0 and *n*<0, the payoff is always non-negative (i.e., all patients will be treated).

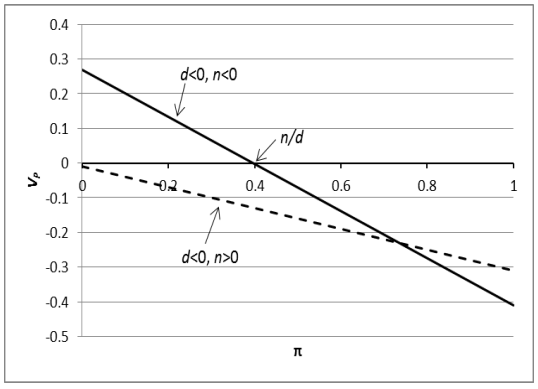
Panel (b) of Figure 3-1 shows the payoff for $d<0$ and $n<0$, as well as for $d<0$ and $n>0$. This panel illustrates that for $d>0$ and $n<0$, the payoff is always negative (i.e., no patient will be treated) while for $d<0$ and $n<0$, the payoff of the payer becomes non-negative if $\pi \le n/d$. The latter case results in an unusual case in which patients who are less likely to respond will be treated. However, the payer can decide to treat all patients and still make a positive payoff if the area under the line depicting the payoff of the payer for π, $0 \le \pi \le 1$, is positive.

Figure 3-1: $V_P = d \times \pi - n$ **as a function of π**

(a) *d*>0 and *n*>0 (solid line) and *d*>0 and *n*<0 (dashed line)



(b) *d*<0 and *n*<0 (solid line) and d<0 and n>0 (dashed line)



Let V_M be the expected manufacturer's profit:

$$V_M = \int_L^U \left((p-w)\pi + (p-\alpha p - w)(1-\pi)\right) f(\pi) d\pi,$$
$$= \int_L^U \left(\alpha p \times \pi + p(1-\alpha) - w\right) f(\pi) d\pi, \qquad (2)$$

The setup of the problem is based on a Stackelberg game, in which the manufacturer acts as the leader and determines the optimal price p^* for the drug to maximize its expected

profit. Then the payer chooses the optimal cut-off probabilities, L^* and U^*, which maximize its expected payoff. The problem is solved in reverse time sequence. Thus in the first step of the analysis, we find the optimal decisions by the payer for a given *p*, i.e., L^* and U^*, by solving the following optimization problem:

$$\begin{aligned} &\text{(OP1)} \quad \max_{L,U} V_P \\ &\text{s.t.} \quad 0 \le L \le 1, \\ &\qquad 0 \le U \le 1, \end{aligned}$$

where V_P is given according to equation (1).

In the second step of the analysis, we find the drug manufacturer's optimal price p^* for given L^* and U^* by solving the following optimization problem:

$$\begin{aligned} &\text{(OP2)} \quad \max_{p} V_M \\ &\text{s.t.} \quad p \ge 0, \\ &\qquad V_P\big|_{L=L^*,U=U^*} \ge 0, \end{aligned}$$

where V_P and V_M are given according to equations (1) and (2), respectively.

As in Barros (2011), there is no closed-form solution for p^* in general. However, when π is uniformly distributed p^* will be the roots of a cubic equation resulting from the first order condition (see Appendix). Also for a given π, there is a closed form solution for p^* (see Appendix). Let $\alpha_T = (b + c_I)/(b - c_V)$ be a threshold value for the rebate rate. The optimum decisions by the payer for a given *p* (i.e., L^* and U^*) are summarized in Table 3-2.

Table 3-2: Scenarios for optimal cut-off probabilities for a given price

		$d>0$ $(b>\alpha p-c_I)$	$d<0$ $(b<\alpha p-c_I)$	$d=0$ $(b=\alpha p-c_I)$
$n>0$ $(p+c_V>\alpha p-c_I)$	$\alpha \geq 0$	$L^*=n/d$, $U^*=1$ $(d \geq n>0)$ [1]	No patients will be treated since $V_P<0$ for π, $0 \leq \pi \leq 1$	
$n<0$ $(p+c_V<\alpha p-c_I)$	$0<\alpha \leq 1$	Not feasible since no p to satisfy $p<0$		
	$1<\alpha<\alpha_T$	Not Possible [2]	$L^*=0$, $U^*=n/d$ $(d<n<0)$	Not Possible [2]
	$\alpha>\alpha_T$	$L^*=0$, $U^*=1$	$L^*=0$, $U^*=n/d$ for $d<n<0$, $U^*=1$ for $n \leq d<0$ [3]	$L^*=0$, $U^*=1$
$n=0$ $(p+c_V=\alpha p-c_I)$	$0<\alpha \leq 1$	Not feasible since no p to satisfy $p<0$		
	$\alpha>1$	$L^*=0$, $U^*=1$; $\alpha>\alpha_T$	No patients will be treated since $V_P<0$ for π, $0 \leq \pi \leq 1$	$L^*=0$, $U^*=1$; [4] $p=b-c_V$, $\alpha=\alpha_T$, $V_P=0$

[1] If $p \leq b-c_V$, then $d \geq n>0$. If $p>b-c_V$ (i.e., $n>d>0$), then $V_P<0$ for π, $0 \leq \pi \leq 1$, i.e., no patients will be treated for $p>b-c_V$.

[2] Not possible since $\frac{c_V+c_I}{\alpha-1}<p<\frac{b+c_I}{\alpha}$ or $p=\frac{b+c_I}{\alpha}>\frac{c_V+c_I}{\alpha-1}$ results in $\alpha>\alpha_T$.

[3] If $p \leq b-c_V$ (i.e., $n \leq d<0$), then $n/d \geq 1$ and consequently $U^*=1$, i.e. all patients will be treated. It is to be noted that $n \leq d<0$ only if $\alpha>\alpha_T$.

[4] If $p=b-c_V$ when $\alpha=\alpha_T$, then $n=d=0$. It follows from $n=d=0$ that $V_p=0$ for L^*, $0 \leq L^* \leq 1$, and U^*, $0 \leq U^* \leq 1$. Presumably the payer chooses to treat all patients, i.e., $L^*=0$ and $U^*=1$.

We begin with two general observations. First, for $n < 0$, the optimal choice of the payer depends on whether $\alpha < \alpha_T$ or $\alpha > \alpha_T$. Second, regardless of the (probability) density of the probability of response, the marginal payoff to the payer from a patient depends solely on the administrative costs, price, and benefit of the drug, and the given probability of response. This implies that the payer's payoff will be maximized when any patient (with a given probability of response) who generates a negative marginal payoff is excluded from being treated by the drug.

Depending on the values of α, p, c_V, and c_I, d and n can take any real values in equation (1). In the following section I review the cases shown in Table 3-2 with regard to the values taken by d and n and the subsequent optimal decisions by the payer.

3.2.1 Payer's Optimal Decisions

First we consider the case in which $\alpha \geq 0$ and p has been chosen such that $d > 0$ and $n > 0$ (i.e., $p < (b + c_I)/\alpha$ for $\alpha \leq 1$, or $p < \min\{(b + c_I)/\alpha, (c_V + c_I)/(\alpha - 1)\}$ for $\alpha > 1$). This is similar to the case presented by Barros (2011) for which $\alpha = 1$. The condition $d > 0$ and $n > 0$ implies that the net benefit of a non-responding patient to the payer is smaller than the benefit and also the cost of a responding patient (i.e., $\alpha p - c_I < \min\{b, p + c_V\}$). If the price chosen by the manufacturer also satisfies $p \leq b - c_V$, which implies that the benefit of a responding patient to the payer is at least equal to the cost of the respective patient, then $d \geq n > 0$. It follows from $d \geq n > 0$ that $d \times \pi - n \geq 0$ for π, $n/d \leq \pi \leq 1$, which implies that the optimal decision for the payer is to choose $L^* = n/d$

and $U^* = 1$ (the formal proof is presented in the Appendix). Note that if $p > b - c_V$, then $n > d > 0$, therefore $V_P < 0$ for π, $0 \le \pi \le 1$. This would violate the manufacturer's constraint, meaning that the manufacturer would not choose any price in this range.

The next case is when $\alpha > 1$ and the manufacturer chooses *p* such that $d < 0$ and $n < 0$ (i.e., $p > \max\{(b + c_I)/\alpha,\ (c_V + c_I)/(\alpha - 1)\}$). As will be described in the next paragraph, the optimal solution for the payer under this case is to treat patients with lower probability of response (i.e., $\pi \le n/d$). This is an unusual case. However, I have included it in this analysis to highlight the policy implications of setting a too-large rebate rate.

The condition $d < 0$ and $n < 0$ would imply that the net benefit of a non-responding patient to the payer is greater than the benefit and also the cost of a responding patient (i.e., $\alpha p - c_I > \max\{b,\ p + c_V\}$). It follows from $d < 0$ and $n < 0$ that $d \times \pi - n \ge 0$ for π, $0 \le \pi \le n/d$. This conclusion implies that the optimal decision for the payer is to choose $L^* = 0$ and $U^* = n/d$ for $d < n < 0$, or $L^* = 0$ and $U^* = 1$ for $n \le d < 0$. Note that $d < n < 0$ if $p > b - c_V$, which in turn implies that the payer will choose the "perverse incentive" policy of treating patients whose $\pi < n/d$ if the benefit of a responding patient to the payer is smaller than the respective cost $(b < p + c_V)$. Under certain conditions for this case, the payer can extend the coverage of the drug to all patients while still achieving a positive payoff (see Proposition 1).

We continue with the following cases: $d \ge 0$ and $n < 0$ (i.e., $p \le (b + c_I)/\alpha$ while $p > (c_V + c_I)/(\alpha - 1)$), and $d > 0$ and $n = 0$ (i.e., $p = (c_V + c_I)/(\alpha - 1) < (b + c_I)/\alpha$). The

condition $d \geq 0$ and $n < 0$ implies that the benefit of a responding patient is at least equal to the net benefit of a non-responding patient, which is greater than the cost of the respective responding patient (i.e., $b \geq \alpha p - c_I > p + c_V$). The condition $d > 0$ and $n = 0$ implies that the benefit of a responding patient to the payer is greater than the cost of the respective patient, which is equal to the net benefit of a non-responding patient (i.e., $b > p + c_V = \alpha p - c_I$). It follows from $d \geq 0$ and $n < 0$, or $d > 0$ and $n = 0$, that $d \times \pi - n \geq 0$ for $\pi \geq 0$, implying that all patients will be treated, i.e., $L^* = 0$ and $U^* = 1$.

We continue further with the following cases: $d \leq 0$ and $n > 0$ (i.e., $p \geq (b + c_I)/\alpha$ for $\alpha \leq 1$, or $p \geq (b + c_I)/\alpha$ and $p > (c_V + c_I)/(\alpha - 1)$ for $\alpha > 1$), and $d < 0$ and $n = 0$ (i.e., $p = (c_V + c_I)/(\alpha - 1) > (b + c_I)/\alpha$). The condition $d \leq 0$ and $n > 0$ implies that the benefit of a responding patient is at most equal to the net benefit of a non-responding patient, which itself is smaller than the cost of the respective responding patient (i.e., $b \leq \alpha p - c_I < p + c_V$). The condition $d < 0$ and $n = 0$ implies that the benefit of a responding patient to the payer is smaller than the cost of the respective patient, which itself is equal to the net benefit of a non-responding patient (i.e., $b < \alpha p - c_I = p + c_V$). For these cases $V_P < 0$ for π, $0 \leq \pi \leq 1$ (since $d \times \pi - n < 0$). This would violate the manufacturer's constraint, meaning that the manufacturer would not choose any price leading to these cases.

Finally, we consider the case when the manufacturer chooses *p* such that $n = d = 0$, implying that the net benefit of a non-responding patient to the payer is equal to the

benefit and also to the cost of a responding patient, i.e., $\alpha p - c_I = b = p + c_V$. It is straightforward to show that $n = d = 0$ could only happen when the manufacturer chooses the price $p = b - c_V$ and $\alpha = \alpha_T$. Therefore, if the manufacturer chooses $p = b - c_V$ when $\alpha = \alpha_T$, then $n = d = 0$. It follows from $n = d = 0$ that $V_P = 0$, i.e., the payer would become indifferent to any combinations of L^*, $0 \le L^* \le 1$, and U^*, $0 \le U^* \le 1$, subject to $U^* \ge L^*$. From the health policy perspective, $V_P = 0$ implies that the payer pays exactly for the benefits obtained at its WTP. In this chapter I assume that for $n = d = 0$, the payer chooses $L^* = 0$ and $U^* = 1$. As noted, there is no closed-form solution for the optimal price p^*. However, in all examples presented later, $p^* = b - c_V$ for $\alpha = \alpha_T$.

3.2.2 Payer's Alternative Decision when $U^*<1$

The solutions found with $U^* < 1$ (i.e., the optimal decision for the payer would be to treat patients with lower probability of response) might be unacceptable from a policy perspective. Thus the payer may decide to relax U^*, such that all patients are treated (i.e., $L = 0$ and $U = 1$). Proposition 1 describes the condition for $V_P \ge 0$ (i.e., when the payer still derives some benefit).

Proposition 1:

Let $\alpha > 1$, $\mu_\pi = E[\pi]$, *and p such that* $d < n < 0$. *If* $n/d \ge \mu_\pi$, $L = 0$, *and* $U = 1$, *then* $V_p \ge 0$.

Thus according to Proposition 1, if $d < n < 0$ and $n/d \geq \mu_\pi$ then the payer may decide not to follow the optimal strategy and treat all patients (i.e., $L = 0$ and $U = 1$) while still achieving a non-negative expected payoff ($V_p \geq 0$).

3.2.3 Impacts of Changes in *p* on L^* or U^*=*n/d*

In this section I investigate how an increase in *p* would affect the payer's decisions for the cases when $L^* = n/d$ and $U^* = 1$ for $\alpha < \alpha_T$, and when $L^* = 0$ and $U^* = n/d$ for $\alpha > \alpha_T$ (see Table 3-2 for the corresponding conditions on the price *p*). In these cases, if the manufacturer increases the price *p* while the conditions on *p* remain unchanged, then the payer will choose to treat fewer patients (by adjusting the respective cut-off probability).

Furthermore, I consider the cases when $L^* = n/d$ and $U^* = 1$ for $\alpha > \alpha_T$, and when $L^* = 0$ and $U^* = n/d$ for α, $1 < \alpha < \alpha_T$ (see Table 3-2 for the corresponding conditions on the price *p*). For these cases, if the manufacturer increases the price *p* while the conditions on *p* remain unchanged, then the payer will conversely choose to treat more patients (Lemma 1; proof in Appendix).

Lemma 1:

If $\alpha < \alpha_T$, then $L^* = n/d$ is increasing in p. If $1 < \alpha < \alpha_T$, then $U^* = n/d$ is increasing in p. If $\alpha > \alpha_T$, then L^* or $U^* = n/d$ is decreasing in p.

3.2.4 Social Welfare

I define the social welfare function to be equivalent to the sum of the expected payer's payoff and the expected manufacturer's profit, i.e., $S = V_P + V_M$. Incorporating equations (1) and (2) in *S* for V_P and V_M, respectively, yields the following welfare equation:

$$S = \int_L^U \left((b + c_I)\pi - (w + c_V + c_I)\right) f(\pi) d\pi. \quad (3)$$

The following proposition shows the conditions under which the social welfare is always positive or negative.

Proposition 2:

(a) In the normal case where $L \geq 0$ *and* $U = 1$, *if* $\frac{n}{d} = \frac{p + c_V - (\alpha p - c_I)}{b - (\alpha p - c_I)} \geq \frac{w + c_V + c_I}{b + c_I}$,

then $S \geq 0$.

(b) In the high rebate case (associated with the perverse incentive policy) where $L = 0$

and $U < 1$, *if* $\frac{n}{d} = \frac{p + c_V - (\alpha p - c_I)}{b - (\alpha p - c_I)} < \frac{w + c_V + c_I}{b + c_I}$, *then* $S < 0$.

Note that (a) and (b) in Proposition 2 are not necessary conditions, i.e., it is still possible to obtain $S \geq 0$ or $S < 0$ without the corresponding condition being met.

3.3 Examples

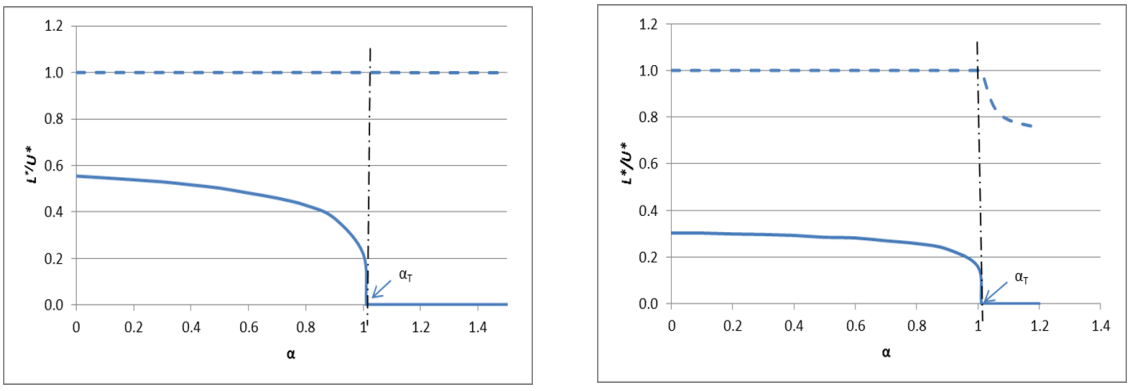
In this section I examine a number of examples to evaluate the performance of *p**, V_P^*, and V_M^* as functions of the rebate rate α. I use a beta distribution for π since this distribution is defined on the interval $[0,1]$ and it is very flexible and can be used to

model both symmetric and skewed distributions. I normalize the benefit of the drug $b=1$ and assume that all other costs are relative to this value and can be scaled up or down.

In Figure 3-2, $c_V = 0.01$, $c_I = 0.001$, and *w*=0.1. Panels (a) and (b) of this figure show L^* and U^* for π~β(1,1) (which is equivalent to a uniform distribution with $\mu_\pi = 0.5$) and π~β(2,5) (which is a right-skewed distribution with $\mu_\pi = 0.286$), respectively. Both panels illustrates that $L^* \le 1$ and $U^* = 1$ for $\alpha < \alpha_T$, $L^* = 0$ and $U^* = 1$ for $\alpha = \alpha_T$, and $L^* = 0$ and $U^* \le 1$ for $\alpha > \alpha_T$. Also, it can be seen from both panels that $U^* > \mu_\pi$ for $\alpha > \alpha_T$. Thus, by the implication of Proposition 1, the payer can choose not to follow the optimal decision (i.e., treating patients with lower probability of response) and instead choose to treat all patients and still obtain a positive payoff.

Figure 3-2: L^* (solid line) and U^* (dashed line) as functions of α for $c_V = 0.01$, $c_I = 0.001$, and *w*=0.1 ($\alpha_T = 1.011$)

(a) π~β(1,1), $\mu_\pi = 0.5$ **(b) π~β(2,5), $\mu_\pi = 0.286$**

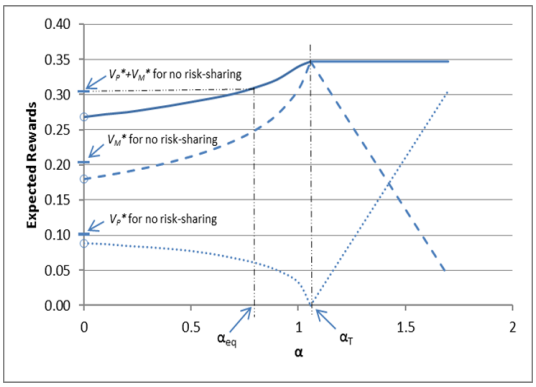


The results from Figure 3-2 also show that in these examples the following cases from Table 3-2 are not feasible after obtaining the optimal *p*: $L^* = 0$ and $U^* = n/d$ for α, $1 < \alpha < \alpha_T$, and $L^* = n/d$ and $U^* = 1$ for $\alpha > \alpha_T$. These results remain valid for the rest of examples used in this section.

In Figure 3-3 and Figure 3-4 $\pi \sim \beta(1,1)$ and w=0.1. Also, $c_V = 0.05$ and $c_I = 0.005$ in Figure 3-3 and $c_V = 0.01$ and $c_I = 0.001$ in Figure 3-4. Panel (a) of both figures shows V_P^* (dotted line), V_M^* (dashed line), and total social welfare $V_P^* + V_M^*$ (solid line) as functions of α. Panel (a) also shows α_{eq}, a threshold at which risk-sharing becomes welfare-improving when compared with no risk-sharing. Panel (b) of both figures shows p^* as a function of α. The respective values under no risk-sharing (i.e., when $\alpha = 0$, $c_V = 0$, and $c_I = 0$) are shown with solid dashes. The hollow circle in each panel shows the case where α=0, but $c_V \neq 0$ and/or $c_I \neq 0$ (representing a hypothetical situation where administrative costs are incurred but the rebate is zero).

Figure 3-3: *p, V_P^*, V_M^*, and $V_P^* + V_M^*$ as functions of α for π~β(1,1), $c_V = 0.05$, $c_I = 0.005$, and *w*=0.1**

(a) V_P^* (dotted line), V_M^* (dashed line), and $V_P^* + V_M^*$ (solid line) as functions of rebate rate α



(b) p^* as a function of rebate rate α

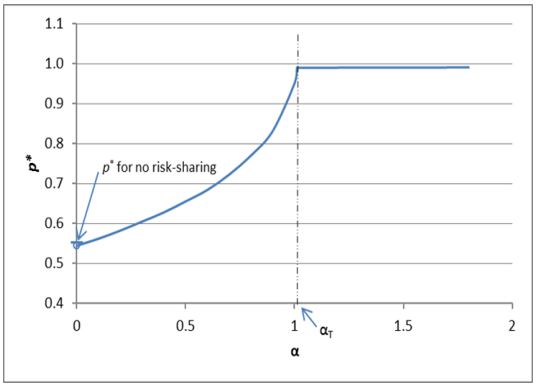
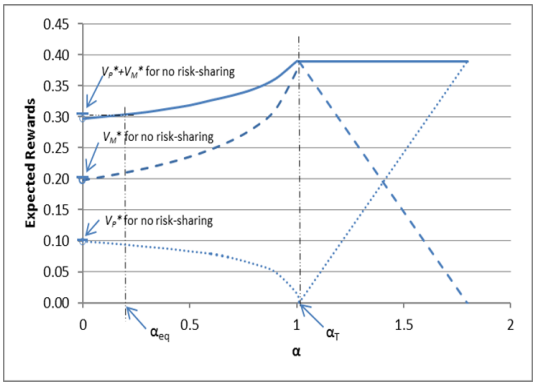
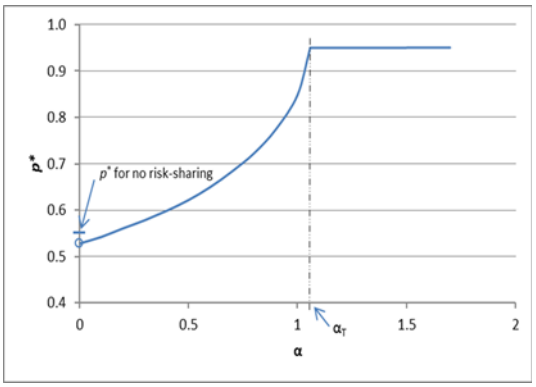


Figure 3-4: *p, V_P^*, V_M^*, and $V_P^* + V_M^*$ as functions of α for π~β(1,1), $c_V = 0.01$, $c_I = 0.001$, and *w*=0.1**

(a) V_P^* (dotted line), V_M^* (dashed line), and $V_P^* + V_M^*$ (solid line) as functions of rebate rate α



(b) p^* as a function of rebate rate α



Panel (a) in Figure 3-3 and Figure 3-4 shows that V_P^* is decreasing in $\alpha < \alpha_T$. This is because L^* is decreasing in $\alpha < \alpha_T$, i.e., the proportion of patients who are less likely to respond will become higher among those to be treated while the benefit of each marginal

non-responding patient is negative to the payer. On the other hand, V_P^* is increasing in $\alpha > \alpha_T$. This is due to the fact that U^* is decreasing in $\alpha > \alpha_T$, which also implies a higher proportion of patients who are less likely to respond among those to be treated. However, conversely in this case the benefit of each marginal non-responding patient is positive to the payer because of high rebate.

Similarly, panel (a) in Figure 3-3 and Figure 3-4 shows that V_M^* is increasing in $\alpha < \alpha_T$. This is also because L^* is decreasing in $\alpha < \alpha_T$, which results in more patients being treated while each marginal responding patient is profitable to the drug manufacturer. Additionally, each marginal non-responding patient is profitable to the drug manufacturer when $\alpha \le (p - w)/p$. On the other hand, V_M^* is decreasing in $\alpha > \alpha_T$. This is also owing to the fact that U^* is decreasing in $\alpha > \alpha_T$. As a result, the proportion of patients who are less likely to respond will become higher among those to be treated while each marginal non-responding patient is non-profitable to the drug manufacturer.

The plots for V_M^* also suggest that if in addition to the price, the rebate rate were also a decision variable for the drug manufacturer, then the manufacturer would choose $\alpha^* = \alpha_T$ (where α^* denotes the optimal rebate rate) and $p^* = b - c_V$. However, this decision is subject to the condition that the payer chooses to treat all patients when it becomes indifferent to any combinations of $0 \le L^* \le U^* \le 1$.

Panel (a) of Figure 3-3 shows that $\alpha_{eq} = 0.8$, whereas the same panel in Figure 3-4 shows that $\alpha_{eq} = 0.2$. On the other hand, the administrative costs in Figure 3-4 are lower than

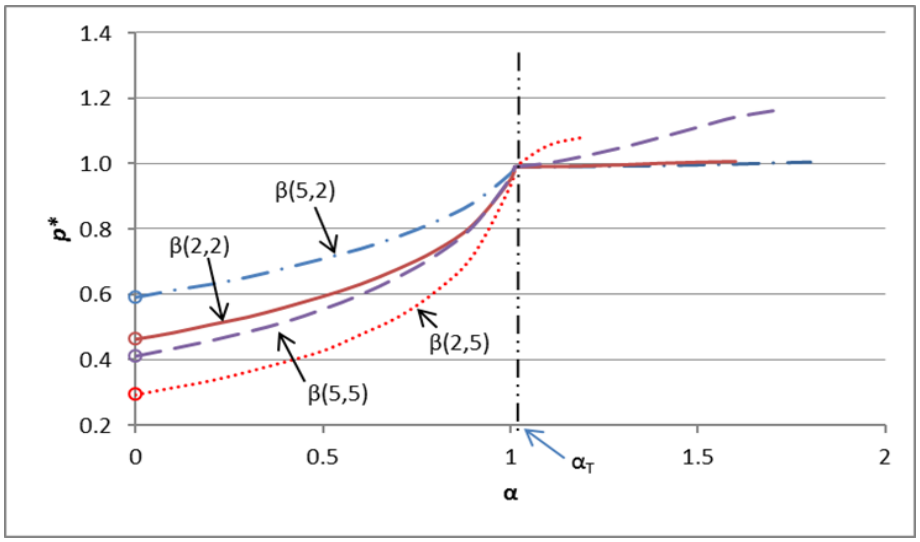
those costs in Figure 3-3. All other parameters are identical in these two figures. This implies that the risk-sharing agreement becomes welfare-improving at a lower rebate rate as the administrative costs are reduced.

Panel (b) in Figure 3-3 and Figure 3-4 shows that p^* under no risk-sharing (shown with solid dash) is larger than p^* when α=0 but c_V or c_I are non-zero (shown with hollow circle). This difference becomes larger as c_V or c_I increases (i.e., Figure 3-3 compared with Figure 3-3). This may occur because the optimal cut-off $L^* = n/d$ is increasing in both c_V and c_I (i.e., as c_V or c_I increases, fewer patients will be treated). If the marginal patient is profitable to the drug manufacturer, then the optimal decision by the manufacturer would be to decrease the price to offset the increase in L^* that was induced by an increase in c_V or c_I.

For the next examples we assume that $c_V = 0.01, c_I = 0.001,$ and w=0.1. Figure 3-5 shows p^* as a function of the rebate rate α for the following distributions for π: β(2,2) (solid line), β(5,5) (dashed line), right-skewed β(2,5) (dotted line), and left-skewed β(5,2) (dashed-dotted line). As depicted in Figure 3-5, p^* is increasing in $\alpha < \alpha_T$ since the optimal decision by the manufacturer is to increase the price to offset the loss induced by the increased rebate rate. This figure also shows that for a given $\alpha < \alpha_T$, the price for a right-skewed distribution is the smallest. This is due to the fact that for a high price, few patients will be treated under a right-skewed distribution (since L^* is large). By reducing the price, the manufacturer allows more patients to be treated while each marginal

responding patient as well as each marginal non-responding patient when $\alpha \le (p-w)/p$ is profitable to the drug manufacturer.

Figure 3-5: p^* as a function of rebate rate α for $c_V = 0.01$, $c_I = 0.001$, w=0.1, symmetric π~β(2,2) (solid line), symmetric π~β(5,5) (dashed line), right-skewed π~β(2,5) (dotted line), and left-skewed π~β(5,2) (dashed-dotted line)



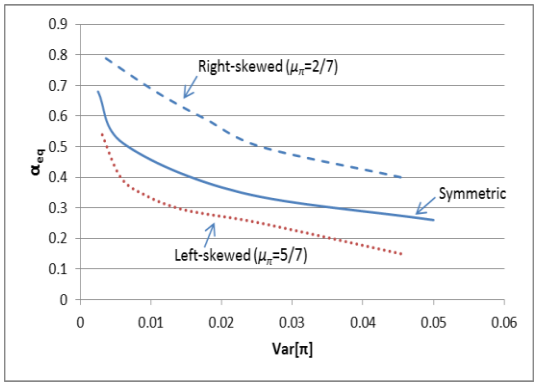
As also shown in Figure 3-5, p^* is increasing much faster in $\alpha > \alpha_T$ for symmetric distributions with smaller variances (e.g., β(5,5)) and asymmetric right-skewed distributions (e.g., β(2,5)) than p^* for symmetric distributions with larger variances (e.g., β(1,1) and β(2,2)) and asymmetric left-skewed distributions (e.g., β(5,2)). This pattern may occur because the proportion of patients who are less likely to respond will become higher among those to be treated when the distribution of π is right-skewed or has a smaller variance (i.e., U^* is smaller). Since each marginal non-responding patient is non-profitable to the manufacturer, the optimal decision by the manufacturer under these types of distributions would be to increase the price. This in turn results in fewer patients

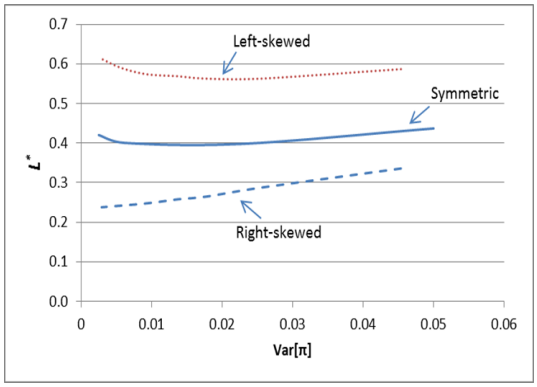
including fewer non-responding patients being treated (since U^* decreases) and as a result less loss will be induced.

We define α_{eq} as a threshold for α, above which risk-sharing is welfare-improving. Panel (a) of Figure 3-6 shows the variations of α_{eq} with respect to the variance of the probability of response. Three distributions are shown: the symmetric (solid line), right-skewed (dashed line), and left-skewed (dotted line) beta distributions. In this figure I have used $\pi \sim \beta(2k,5k)$ and $\pi \sim \beta(5k,2k)$ for the creation of the right-skewed distributions with μ_π=2/7 and the left-skewed distributions with μ_π=5/7, respectively, where k=1, 2, 3, 5, and 10. For a given variance of π, α_{eq} is greater for a right-skewed distribution because a right-skewed distribution has a higher density of patients with lower probability of response. This in turn induces a higher number of non-responding patients to be treated, which in turn could result in the risk-sharing agreement to become welfare-improving at larger rebate rates.

Figure 3-6: α_{eq} and L^* versus the variance of π for $c_V = 0.01$, $c_I = 0.001$, *w*=0.1, symmetrical π~β(*k*,*k*) where *k*=1, 2, 5, 20, and 50 (solid line); right-skewed π~β(2*k*,5*k*) where *k*=1, 2, 3, 5, and 10 (dashed line); and left-skewed π~β(5*k*,2*k*) where *k*=1, 2, 3, 5, and 10 (dotted line)

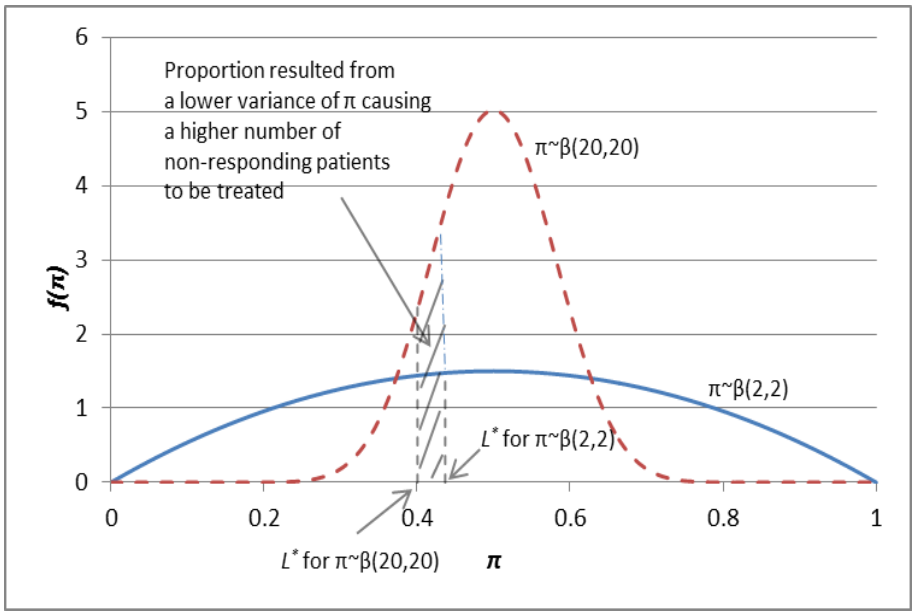
(a) α_{eq} versus variance of π **(b) L^* versus variance of π for α=0.5**





Also for all three types of beta distribution presented in panel (a) of Figure 3-6, α_{eq} is decreasing (i.e., the risk-sharing starts to be welfare-improving at a smaller rebate rate) in the variance of π. This pattern can be explained by panel (b) in Figure 3-6, in which L^* is depicted versus variance of π for $\alpha = 0.5$. All other parameters are the same in both panels. As shown in panel (b), for a given α, L^* is increasing in larger variances of π for all three types of distribution. This implies that a smaller number of non-responding patients will be treated in larger variances of π, which in turn induces the risk-sharing to become welfare-improving at a smaller rebate rate. This result is consistent with the results shown for α_{eq} in panel (a) for all three types of distribution. The effect of changing the variance of π in the number of patients treated is illustrated in Figure 3-7.

Figure 3-7: Effect of changing variance of π on the number of patients treated resulting from L^* for π~β(2,2) (solid line; Var[π]=0.05) and π~β(20,20) (dashed line; Var[π]=0.006) when $\alpha = 0.5,\ c_V = 0.01, c_I = 0.001,$ and *w*=0.1



3.4 Risk-Sharing Policy Not Known in Advance

I now consider the case in which the manufacturer sets the price of the drug before the payer announces α. There are two possibilities: either the manufacturer anticipates a risk-sharing scenario and thus sets a price higher than the optimal price of the drug under no risk-sharing; or the manufacture does not anticipate any risk-sharing. The former case is similar to the case presented in section 2, which leads to the optimization problems (OP1) and (OP2). I analyse the latter case in more detail in the following section.

3.4.1 Manufacturer Anticipates No Risk-sharing

In this case the manufacturer determines *p* as if there were no risk-sharing (i.e., $\alpha = 0,$ $c_V = 0,$ and $c_I = 0$). Let $V_P(0)$ and $V_M(0)$ denote the payoff of the payer and the profit of the manufacturer in this scenario, respectively. It follows from (1) and (2) that

$$V_P(0) = \int_L^U \left(d_0 \times \pi - n_0\right) f(\pi) d\pi,$$
$$V_M(0) = \int_L^U \left(p - w\right) f(\pi) d\pi,$$

where $d_0 = b$ and $n_0 = p$.

The setup of the problem is such that the manufacturer acts as the leader and determines the optimal price and then the payer chooses the optimal cut-off probabilities. Using backwards induction we find the optimal decisions for the payer under the no risk-sharing scenario for a given *p*, i.e., L_0^* and U_0^*, by solving the following optimization problem:

(OP3) $\max_{L,U} V_P(0)$
s.t. $0 \le L \le 1,$
$0 \le U \le 1.$

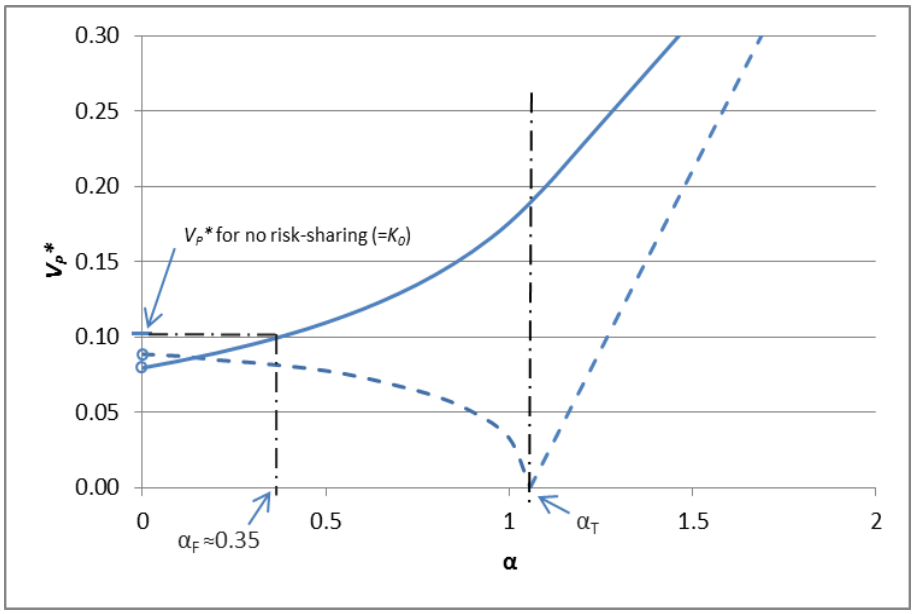
Then we find p_0^*, the drug manufacturer's optimal price under the no risk-sharing scenario for given L_0^* and U_0^*, by solving the following optimization problem:

(OP4) $\max_{p} V_M(0)$
s.t. $p \ge 0,$
$V_P(0)\big|_{L_0^*, U_0^*} \ge 0.$

To find the payer's optimal cut-off probabilities when α is introduced, the payer needs to solve the optimization problem of (OP1) by replacing *p* with p_0^*. As shown in Figure 3-8, it is possible for the payer to benefit from this special case since the manufacturer determines *p* as if there were no risk-sharing (i.e., $p = p_0^*$). The solid line in Figure 3-8 shows $V_P^*(\alpha, p_0^*)$, i.e., the optimal payoff for the payer when the price *p* is fixed at $p_0^* = 0.55$ (i.e., the optimal price under no risk-sharing). In this figure π~β(1,1),

$c_V = 0.05$, $c_I = 0.005$, and *w*=0.1. The solid dash shows that the payoff of the payer under no risk-sharing (denoted as K_0 on the graph) is equal to 0.101. As depicted in this figure, $V_P^*(\alpha, p_0^*)$ is increasing in α for the given $p_0^* = 0.55$. Proposition 3 outlines the condition for α in which the payer's payoff with the fixed price $p = p_0^*$ becomes larger than the payer's payoff under no risk-sharing (i.e., $V_P^*(\alpha, p_0^*) > K_0$).

Figure 3-8: V_P^* (solid line) as a function of α with π~β(1,1), $c_V = 0.05$, $c_I = 0.005$, *w*=0.1, and price fixed at *p*=0.55 (dashed line shows V_P^* when $p = p^*$ for each α)



Proposition 3:

Let p_0^* and K_0 denote the optimal price of the drug and the optimal payoff of the payer under the no risk-sharing scenario, i.e., when $\alpha = 0$, $c_V = 0$, and $c_I = 0$, respectively.

For a given $p = p_0^*$, *there is a threshold* $\alpha_F > 0$, *such that* $V_P^*(\alpha, p_0^*) < K_0$ *if* $\alpha < \alpha_F$, *and* $V_P^*(\alpha, p_0^*) > K_0$ *if* $\alpha > \alpha_F$.

Proposition 3 implies that the payer may still be worse off with risk-sharing in spite of the manufacturer choosing a price as if there were no risk-sharing. For example Figure 3-8 shows that the expected payoff of the payer under risk-sharing with $\alpha < \alpha_F \approx 0.35$ and $p = 0.55$ is always less than $K_0 = 0.101$.

It is easy to show that $L^* = n/d$ is decreasing and $U^* = n/d$ is increasing in α under a fixed price scheme (Lemma 2, Appendix). Thus if α increases when $L^* = n/d$ and $U^* = 1$ or $L^* = 0$ and $U^* = n/d$ (while *p* is fixed), then the payer will choose to treat more patients by adjusting the respective cut-off probability.

3.5 Social Welfare Maximization

Let S^C denote the welfare function when the social planner chooses the "coordinated" cut-off probabilities L^C and U^C resulting in the following:

$$\begin{aligned} S^C &= V_P^C + V_M^C \\ &= \int_{L^C}^{U^C} \left((b + c_I)\pi - (w + c_V + c_I) \right) f(\pi) d\pi. \end{aligned} \tag{4}$$

It follows from (4) that when $b \geq w + c_V$, then $U^C = 1$ is always the optimal upper cut-off probability. For $b < w + c_V$, $L^C = U^C = 0$, meaning that no patients will be treated. For the rest of this analysis I assume that $b \geq w + c_V$ and obtain the optimal $L^C = (w + c_V + c_I)/(b + c_I)$ by using the first-order condition $\partial S^C / \partial L^C = 0$. Since S^C is

the optimal value for *S*, $S^C - S \geq 0$. For $S^C - S > 0$, there is a welfare loss owing to the deviation from the social planner's optimal cut-off probability as both parties optimize separately. In the next sections I investigate two methods for reducing or eliminating this welfare loss. The first method is based on adjusting some of the existing cost parameters through taxes or subsidies and the second method is based on assigning a transfer payment function between the payer and the drug manufacturer through a properly designed contract.

3.5.1 Payment Schemes Based on Adjusted Cost Parameters

Barros (2011) examined the scenario in which the social planner imposes a verification cost in order to achieve the first-case allocation. In the context of this chapter we assume that the social planner imposes a verification cost τ_V or an administrative cost for invoicing the rebate τ_I to achieve the first-best allocation. Similar to Barros (2011), if these costs are less or more than the true costs (c_V and c_I), then we allow the social planner to subsidize or to tax them, respectively.

First we assume that the social planner imposes a verification cost τ_V and then the drug manufacture chooses the price $p(\tau_V)$. Let $\hat{L}^*(p(\tau_V)) = \hat{n} / \hat{d}$ (or alternatively $\hat{U}^*(p(\tau_V)) = \hat{n}/\hat{d}$ for the case where $\hat{n} < 0$ and $\hat{d} < 0$) be the optimal cut-off probability chosen by the payer, where $\hat{n} = p(\tau_V) + \tau_V - (\alpha p(\tau_V) - c_I)$ and $\hat{d} = b - (\alpha p(\tau_V) - c_I)$. The first-order condition of the coordinated social welfare function with regard to τ_V (i.e.,

$\partial S^C / \partial \tau_V = 0)$ results in the following relation for eliminating the welfare loss: $\hat{L}^* = L^C$ (see Appendix for details).

Similarly, we could assume that the social planner chooses the administrative cost for invoicing τ_I. Let $p(\tau_I)$ be the price and let $\tilde{L}^*\left(p(\tau_I)\right) = \tilde{n} / \tilde{d}$ be the optimal cut-off probability, where $\tilde{n} = p(\tau_I) + c_V - \left(\alpha p(\tau_I) - \tau_I\right)$ and $\tilde{d} = b - \left(\alpha p(\tau_I) - \tau_I\right)$. In this case $\partial S^C / \partial \tau_I = 0$ results in $\tilde{L}^* = L^C$ for eliminating the welfare loss (see Appendix for details).

Proposition 4 outlines the conditions for τ_V and τ_I such that the welfare loss can be eliminated (i.e., the first-best allocation can be achieved).

Proposition 4:

If $\tau_V = \tau_V^* = \dfrac{\alpha p}{b + c_I}(b - w - c_V) - (p - w - c_V)$ *or if*

$\tau_I = \tau_I^* = \alpha p - \dfrac{b(p - w - c_I) + c_I(p + c_V)}{(b - w - c_V)}$, *then the first-best allocation can be achieved.*

If $\tau_V^* > c_V$ or $\tau_I^* > c_I$, then the social planner will tax the administrative cost for verification or collecting the rebate and alternatively if $\tau_V^* < c_V$ or $\tau_I^* < c_I$, then the social planner will subsidize the respective cost.

3.5.2 Payment Schemes Based on Transfer Payment Functions

In this section we assume that the payment scheme for eliminating the welfare loss is based on assigning a transfer function between the two parties. Let *R* be a transfer

payment function from the manufacturer to the payer for every patient with a given π resulting in $\hat{V}_p$ for the payer's payoff and $\hat{V}_M$ for the manufacturer's profit.

Proposition 5 states the conditions for the existence of a transfer payment function *R* that will result in $\hat{V}_P + \hat{V}_M = S^C$ (and hence eliminate the welfare loss), where S^C is given by equation (4).

Proposition 5:

Let $R = Q_1 \times \pi - Q_2$ *be the transfer payment function from the manufacturer to the payer for every patient with a given π, and* Q_1 *and* Q_2 *are functions of α and* p. *If* $Q_1 = \alpha p$ *and* $Q_2 = w - p + \alpha p$, *then* $\hat{V}_P + \hat{V}_M = S^C$.

After making the transfer payment of R, we obtain the following profit function for the manufacturer:

$$\hat{V}_M = \int_L^U \left((\alpha p - Q_1) \times \pi + (p(1-\alpha) - w + Q_2) \right) f(\pi) d\pi. \qquad (5)$$

Incorporating $Q_1 = \alpha p$ and $Q_2 = w - p + \alpha p$ in (5) results in $\hat{V}_M = 0$. To guarantee that the manufacturer receives some arbitrary profit of $V_M^{\sim}$, the total transfer payment function from the manufacturer to the payer needs to be defined as in the following:

$$T_R = \int_{L^C}^1 R \times f(\pi) d\pi - V_M^{\sim}.$$

The total transfer function T_R is non-increasing in α, i.e.,

$\partial T_R / \partial \alpha = \int_{L^C}^{1} \left(p \times \pi - p \right) f(\pi) d\pi \leq 0.$ This implies that for lower rebate rates, T_R is positive and thus the transfer payment is from the manufacture to the payer. T_R may become negative for higher α, in which case the transfer payment is reversed from the payer to the manufacturer.

Proposition 5 also implies that by introducing *R* (and subsequently T_R) it is possible to reverse the perverse incentive policy of treating patients with lower probabilities of response to the normal policy of treating patients with higher probability of response (i.e., from $L^* = 0$ and $U^* = n/d$ to $\hat{L}^* = L^C$ and $\hat{U}^* = 1$).

3.6 Conclusions and Future Research

In this chapter I examined the performance of a pharmaceutical risk-sharing agreement between a payer and a drug manufacturer. My model generalizes on Barros (2011) by allowing the rebate to be different from 100% as well as by including two separate administrative costs. Allowing the rebate to be different from the price of the drug enabled me to explore the policy implications associated with different ranges of the rebate rate. Specifically, I showed that setting a large rebate rate generates a perverse incentive in which the optimal policy is to treat patients with lower probabilities of response.

I included administrative costs associated with invoicing the rebate for the following reasons. First, the task of invoicing the rebate is time-consuming and labour intensive. Second, failure to do so could incur a considerable loss to the payer as outlined in a report

on the implementation of a number of risk-sharing agreements in the UK (Williamson, 2009).

I sought to answer two important policy questions. The first is whether the payer benefits from the risk-sharing agreement. My results show that the optimal expected payoff of the payer is decreasing in the rebate rate when the rebate rate is less than a certain threshold. Under this condition the payer does not benefit from an increase in the rebate rate. This is because as the rebate rate increases, the drug manufacturer also increases the price in order to offset the associated loss. On the other hand, when the rebate rate is greater than the respective threshold, the payer's payoff is increasing in the rebate rate. This is owing to the fact that for large rebate rates, the optimal decision for the payer would be to treat patients who are less likely to respond.

The second policy question is whether the risk-sharing agreement is welfare-improving. We find that, depending on the administrative costs as well as the shape of the distribution for the probability of response, there is a range of rebate rates where the risk-sharing agreement is welfare-improving. Specifically, I showed that as administrative costs are reduced and/or the variability in the probability of response increases (regardless of the shape of the distribution), the risk-sharing agreement becomes welfare-improving for a wider range of rebate rates in comparison with no risk-sharing. Also for a given variability in the probability of response, the risk-sharing agreement becomes welfare-improving at a smaller rebate rate when the density of the probability of response is left-skewed because a left-skewed distribution induces a higher number of responding patients to be treated.

I investigated how to eliminate the welfare loss by imposing taxes, by paying subsidies, or through an appropriately designed contract. The latter establishes a new transfer payment function between the payer and the manufacturer (in addition to the rebate), which maximizes the social welfare while the payer obtains the optimal value for the payoff and the manufacturer maintains a reservation profit. A positive transfer payment from the manufacturer to the payer implies that the existing rebate scheme is too small to coordinate the supply chain, whereas a negative transfer payment implies that the rebate is too large to coordinate the chain.

There are many directions for future research. The model used in this chapter can be extended in a number of ways. I assumed that the rebate rate is fixed and exogenously given to the payer. One extension to the analysis is to assume that the rebate rate is a decision variable for the payer along with the cut-off probabilities, or that the rebate rate is a negotiated quantity. I assumed that the costs c_V and c_I are both incurred by the payer. A second extension would be to consider that proportions of these costs are incurred by the drug manufacture.

In this chapter I modeled uncertainty in the probability of the response of each patient to the drug. Parameter uncertainty could also be introduced to the model by assuming that the parameters of the probability distribution of the probability of response are uncertain (i.e., hyper-parameters) (Gelman et al., 2004). Furthermore, the monetary benefit of the drug, *b*, and the administrative costs, c_V and c_I, could also be other sources of uncertainty to be incorporated in the model. Finally, I assumed that the verification

process is perfect. In reality, verification is likely to be done by an imperfect test. Thus, another extension would be to consider error in the verification process.

Appendix to Chapter 3

Derivation of L^* and U^* for $d \geq n > 0$

The payoff of the payer for an uncertain π is given by:

$$V_P = \int_L^U \left(d \times \pi - n\right) f(\pi) d\pi.$$

To find the optimal L^*, we establish the first order condition:

$$\left.\frac{\partial V_P}{\partial L}\right|_{L=L^*} = 0 \Rightarrow \; -\left(d \times L^* - n\right) f(L^*) = 0 \; \Rightarrow \; d \times L^* - n = 0 \Rightarrow L^* = \frac{n}{d} \; \leq 1 \text{ for } d \geq n > 0.$$

In the following, we check whether $L^* = \frac{n}{d}$ is a maximizer:

$$\frac{\partial^2 V_P}{\partial L^2} = -d \times f(L) - \left(d \times L - n\right) f'(L);$$

$$\text{At } L^* = \frac{n}{d} \; \Rightarrow \left(d \times L^* - n\right) = 0 \Rightarrow \left.\frac{\partial^2 V_P}{\partial L^2}\right|_{L=L^*} = -d \times f(L^*) < 0 \text{ for } d > 0.$$

Thus $L^* = \frac{n}{d}$ is the maximizer for V_P.

To find the optimal U^*, we check the first derivative of V_P:

$$\frac{\partial V_P}{\partial U} = \left(d \times U - n\right) f(U) \geq 0 \text{ for } U \geq \frac{n}{d} \text{ (since } d \geq n > 0) \Rightarrow$$

V_P is non-decreasing in $U \geq \frac{n}{d}$. Since $U \leq 1 \Rightarrow \; U^* = 1.$

Derivation of L^* and U^* for $d<0$ and $n<0$

The payoff of the payer for an uncertain π is given by:

$$V_P = \int_L^U \left(d \times \pi - n\right) f(\pi) d\pi.$$

To find the optimal U^*, we establish the first order condition:

$$\left.\frac{\partial V_P}{\partial U}\right|_{U=U^*} = 0 \Rightarrow \left(d \times U^* - n\right) f(U^*) = 0 \Rightarrow d \times U^* - n = 0;$$

for $d < 0$ and $n < 0$, if $p > b - c_V$, i.e., $d < n < 0$, then $\frac{n}{d} < 1$.

Thus, $d \times U^* - n = 0$ results in $U^* = \frac{n}{d}$ for $d < n < 0$.

To check whether $U^* = \frac{n}{d}$ is the maximizer:

$$\frac{\partial^2 V_P}{\partial U^2} = d \times f(U) - \left(d \times U - n\right) f'(U);$$

at $U^* = \frac{n}{d} \Rightarrow \left(d \times U^* - n\right) = 0 \Rightarrow \left.\frac{\partial^2 V_P}{\partial U^2}\right|_{U=U^*} = d \times f(U^*) < 0$ for $d < 0$.

Thus, $U^* = \frac{n}{d}$ is the maximizer for $d < n < 0$.

For $d < 0$ and $n < 0$, if $p \le b - c_V$, i.e., $n \le d < 0$, then $\frac{n}{d} \ge 1$.

$\frac{n}{d}$ is the maximizer for V_P as shown above and $\frac{n}{d} \ge 1$ for $n \le d < 0$.

Thus, V_P is increasing in $U, 0 \le U \le 1$ for $n \le d < 0 \Rightarrow U^* = 1$ for $n \le d < 0$.

This concludes my proof for U^*, i.e., the optimal decision for the payer is to choose

$U^* = n/d$ for $d < n < 0$, or $U^* = 1$ for $n \le d < 0$.

To find the optimal L^*, we check the first derivative of V_P:

$\frac{\partial V_P}{\partial L} = -\left(d \times L - n\right) f(L) < 0$ for $L < \frac{n}{d}$ (since $d < 0$ and $n < 0$) $\Rightarrow$

V_P is decreasing in $L < \frac{n}{d}$. Since $L \geq 0 \Rightarrow \ L^* = 0.$

Proof of Proposition 1

For $n < 0$ and $d < 0,$ we need to show that if $n/d \geq \mu_\pi,$ then

$V_P = \int_0^1 \left(d \times \pi - n\right) f(\pi) d\pi \geq 0$:

Since $d < 0,$ it follows from $V_P \geq 0$ that $\int_0^1 \left(\pi - \frac{n}{d}\right) f(\pi) d\pi \leq 0 \ \Rightarrow$

$\int_0^1 \left(\pi - \frac{n}{d}\right) f(\pi) d\pi = \mu_\pi - \frac{n}{d} \leq 0 \quad \Rightarrow \frac{n}{d} \geq \mu_\pi.$

Q.E.D.

Proof of Lemma 1

For $L^* = \frac{n}{d}$ and U^*=1 when $\alpha<\alpha_T$ (i.e., $p < b - c_V$ when $\alpha \leq 1$ or

$p < \frac{b + c_I}{\alpha} < \frac{c_V + c_I}{\alpha - 1}$ and $p < b - c_V$ when $1<\alpha < \alpha_T$) or for $L^* = 0$ and $U^* = \frac{n}{d}$ when

$1<\alpha < \alpha_T$ (i.e., $p > \frac{c_V + c_I}{\alpha - 1} > \frac{b + c_I}{\alpha}$ and $p > b - c_V$):

$\frac{\partial\left(\frac{n}{d}\right)}{\partial p} = \frac{\partial\left(\frac{p - \alpha p + c_V + c_I}{b - \alpha p + c_I}\right)}{\partial p} = \frac{b - \alpha(b - c_V) + c_I}{(b - \alpha p + c_I)^2}; \quad \frac{\partial(n/d)}{\partial p} > 0$ if $b - \alpha(b - c_V) + c_I > 0$

or alternatively if $\alpha < \frac{b + c_I}{b - c_V} = \alpha_T$. Thus, $\frac{\partial(n/d)}{\partial p} > 0 \quad \forall \alpha < \alpha_T,$ that is

$L^* = \frac{n}{d}$ is increasing in p for $\alpha<\alpha_T$ and $U^* = \frac{n}{d}$ is increasing in p for $\alpha,\ 1<\alpha < \alpha_T.$

For $L^* = \frac{n}{d}$ and U^*=1 when $\alpha > \alpha_T$ (i.e., $p < \frac{c_V + c_I}{\alpha - 1} < \frac{b + c_I}{\alpha}$ and $p < b - c_V$) or

for $L^* = 0$ and $U^* = \frac{n}{d}$ when $\alpha > \alpha_T$ (i.e., $p > \frac{b + c_I}{\alpha} > \frac{c_V + c_I}{\alpha - 1}$ and $p > b - c_V$):

$\frac{\partial (n/d)}{\partial p} < 0$ if $b - \alpha(b - c_V) + c_I < 0$ or alternatively if $\alpha > \frac{b + c_I}{b - c_V} = \alpha_T \Rightarrow$

$\frac{\partial (n/d)}{\partial p} < 0 \quad \forall \alpha > \alpha_T$, that is $L^* = \frac{n}{d}^*$ or $U^* = \frac{n}{d}$ is decreasing in p for $\alpha > \alpha_T$.

Q.E.D.

Proof of Proposition 2

For $L = n/d$ and $U = 1$, if $\pi \geq (w + c_V + c_I)/(b + c_I)$, then $(b + c_I)\pi - (w + c_V + c_I) \geq 0$.

Thus, $S \geq 0$ for $L \geq (w + c_V + c_I)/(b + c_I)$. On the other hand for $L = 0$ and $U = n/d$, if

$\pi \leq (w + c_V + c_I)/(b + c_I)$, then $(b + c_I)\pi - (w + c_V + c_I) \leq 0$. Thus, $S \leq 0$ for

$U \leq (w + c_V + c_I)/(b + c_I)$.

Q.E.D.

Proof of Proposition 3

Let $V_P^*(\alpha, p_0^*)$ denote the optimal payoff of the payer when the price is fixed at p_0^*, i.e.,

$V_P^*(\alpha, p_0^*) = \int_{L^*}^{U^*} \left(b - (p_0^* + c_V)\pi + \left((\alpha p_0^* - c_I) - (p_0^* + c_V) \right)(1 - \pi) \right) f(\pi) d\pi$, where L^* and

U^* are as shown in Table 3-2 for the given price p_0^*. Let K_0 denote the fixed value for

$V_P^*(\alpha, p_0^*)$ when $\alpha = 0$, $c_V = 0$, and $c_I = 0$, i.e., $K_0 = \int_{L_0^*}^{1} \left((b - p_0^*)\pi - p_0^*(1 - \pi) \right) f(\pi) d\pi$,

where $L_0^* = \frac{p_0^*}{b}$. Let K_1 denote the fixed value for $V_P^*(\alpha, p_0^*)$ when $\alpha = 0$, i.e.,

$K_1 = \int_{L_1^*}^{1} \left(b - (p_0^* + c_V)\pi - \left(p_0^* + c_I + c_V \right)(1-\pi) \right) f(\pi) d\pi,$ where $L_1^* = \frac{p_0^* + c_V + c_I}{b + c_I}$.

First we show that $K_0 > K_1$: Since $b(c_V + c_I) > p_0^* c_I$, adding bp_0^* to the both sides of this inequality yields $b(p_0^* + c_V + c_I) > p_0^*(b + c_I)$. By rearranging the latter inequality we obtain $L_1^* > L_0^*$. Therefore K_0 can be rewritten as in the following:

$K_0 = \int_{L_0^*}^{L_1^*} \left((b - p_0^*)\pi - p_0^*(1-\pi) \right) f(\pi) d\pi + \int_{L_1^*}^{1} \left((b - p_0^*)\pi - p_0^*(1-\pi) \right) f(\pi) d\pi,$ or

alternatively, $K_0 = \int_{L_0^*}^{L_1^*} \left(b\pi - p_0^* \right) f(\pi) d\pi + \int_{L_1^*}^{1} \left((b - p_0^*)\pi - p_0^*(1-\pi) \right) f(\pi) d\pi.$ Since the first component in K_0 is always positive and c_V and c_I both appear with negative signs in the integrand for K_1, thus $K_0 > K_1$.

Now we show that $V_P^*(\alpha, p_0^*)$ is increasing in α by taking its derivative using Leibniz integral rule: When $L^* = \frac{p_0^* - \alpha p_0^* + c_V + c_I}{b - \alpha p_0^* + c_I}$ and $U^* = 1$,

$$\frac{\partial V_P^*(\alpha, p_0^*)}{\partial \alpha} = \int_{L^*}^{1} p_0^*(1-\pi) f(\pi) d\pi > 0.$$

(Note that for $V_P^*(\alpha, p_0^*) = \int_{L^*}^{1} \left(d_0 \times \pi - n_0 \right) f(\pi) d\pi,$ where $n_0 = p_0^* - \alpha p_0^* + c_V + c_I$ and $d_0 = b - \alpha p_0^* + c_I$, the term $\left(d_0 \times n_0 / d_0 - n_0 \right) f\left(n_0 / d_0 \right) = 0$ in the respective Leibniz formula).

On the other hand when $L^* = 0$ and $U^* = \frac{p_0^* - \alpha p_0^* + c_V + c_I}{b - \alpha p_0^* + c_I}$, due to the similar reason given above, $\frac{\partial V_P^*(\alpha, p_0^*)}{\partial \alpha} = \int_0^{U^*} p_0^*(1-\pi) f(\pi) d\pi > 0.$ Thus, $V_P^*(\alpha, p_0^*)$ is increasing in α for the fixed price p_0^*. This in turn implies that $V_P(\alpha_1, p_0^*) > V_P(\alpha_2, p_0^*) \ \ \forall \alpha_1 > \alpha_2$.

Next we show that $\lim_{\alpha \to \infty} V_P^*(\alpha, p_0^*) \to \infty$: For large α, both components $p_0^* - \alpha p_0^* + c_V + c_I$ and $b - \alpha p_0^* + c_I$ become negative. Thus from Table 3-2, as $\alpha \to \infty$, $L^* = 0$ and $U^* = \frac{p_0^* - \alpha p_0^* + c_V + c_I}{b - \alpha p_0^* + c_I}$. On the other hand, $\lim_{\alpha \to \infty} U^* = \lim_{\alpha \to \infty} \frac{p_0^* - \alpha p_0^* + c_V + c_I}{b - \alpha p_0^* + c_I} = 1.$ Thus,

$$\lim_{\alpha \to \infty} V_P^*(\alpha, p_0^*) = \lim_{\alpha \to \infty} \int_0^1 \Big(b - (p_0^* + c_V)\pi + \big((\alpha p_0^* - c_I) - (p_0^* + c_V)\big)(1-\pi) \Big) f(\pi) d\pi \to \infty.$$

Since $K_0 > K_1$ and $V_P^*(\alpha, p_0^*) > K_1 \ \forall \alpha > 0,$ for some arbitrary $\alpha_1 > 0$ one of the following cases can happen: i) $V_P^*(\alpha_1, p_0^*) = K_0,$ ii) $V_P^*(\alpha_1, p_0^*) > K_0,$ or iii) $V_P^*(\alpha_1, p_0^*) < K_0$.

i) If $V_P^*(\alpha_1, p_0^*) = K_0,$ then $\alpha_F = \alpha_1$ such that $V_P^*(\alpha, p_0^*) < K_0 \ \forall \alpha < \alpha_F$ and $V_P(\alpha, p_0^*) > K_0 \ \forall \alpha > \alpha_F$.

ii) If $V_P^*(\alpha_1, p_0^*) > K_0,$ then there is a threshold $\alpha_F < \alpha_1$ such that $V_P^*(\alpha_F, p_0^*) = K_0$ and $V_P^*(\alpha, p_0^*) < K_0 \ \ \forall \alpha < \alpha_F$.

iii) If $V_P^*(\alpha_1, p_0^*) < K_0,$ then since $\lim_{\alpha \to \infty} V_P^*(\alpha, p_0^*) \to \infty,$ there is a threshold $\alpha_F > \alpha_1$ such that $V_P^*(\alpha_F, p_0^*) = K_0$ and $V_P^*(\alpha, p_0^*) > K_0 \ \ \forall \alpha > \alpha_F$.

Q.E.D.

Lemma 2

$L^* = n/d$ is decreasing in α and $U^* = n/d$ is increasing in α.

Proof of Lemma 2

For $L^* = \frac{n}{d}$ (i.e., $p < b - c_V$ for $\alpha \le 1$ or

$p < \min\{(b - c_V), (b + c_I)/\alpha, (c_V + c_I)/(\alpha - 1)\}$ for α>1):

$\frac{\partial(n/d)}{\partial\alpha} = \frac{p(p - b + c_V)}{(b - \alpha p + c_I)^2}$; if $p<b - c_V$, then $(p - b + c_V)<0$;

since $\frac{\partial(n/d)}{\partial\alpha} < 0 \quad \forall p<b - c_V$, and $p < b - c_V$ is the necessary condition on p

for the case of $L^* = \frac{n}{d}$, thus $L^* = \frac{n}{d}$ is decreasing in α.

For $U^* = \frac{n}{d}$ (i.e., $p > \max\{(b - c_V), (b + c_I)/\alpha$ and $(c_V + c_I)/(\alpha - 1)\}$

for $\alpha > 1$):

since $\frac{\partial(n/d)}{\partial\alpha} > 0 \quad \forall p>b - c_V$, and $p > b - c_V$ is the necessary condition on p

for the case of $U^* = \frac{n}{d}$, thus $U^* = \frac{n}{d}$ is increasing in α.

Q.E.D.

Derivation of Optimal τ_V

The social planner chooses τ_V by sloving the following optimization problem:

$$\max_{\tau_V} S^C = \int_{\hat{L}^*}^{1} \left((b+c_I)\pi - (w+\tau_V+c_I)\right) f(\pi)d\pi + \int_{\hat{L}^*}^{1} (\tau_V - c_V) f(\pi)d\pi,$$

$$= \int_{\hat{L}^*}^{1} \left((b+c_I)\pi - (w+c_V+c_I)\right) f(\pi)d\pi$$

where $\hat{L}^* = \frac{\hat{n}}{\hat{d}}$, $\hat{n} = p(\tau_V) + \tau_V - (\alpha p(\tau_V) - c_I)$, and $\hat{d} = b - (\alpha p(\tau_V) - c_I)$.

$$FOC: \frac{\partial S^C}{\partial \tau_V} = 0 \Rightarrow -\frac{\partial \hat{L}^*}{\partial \tau_V}\left((b+c_I)\hat{L}^* - (w+c_V+c_I)\right) f(\hat{L}^*) = 0 \Rightarrow$$

$$(b+c_I)\hat{L}^* - (w+c_V+c_I) = 0 \Rightarrow \hat{L}^* = L^C, \text{where } L^C = \frac{w+c_V+c_I}{b+c_I}.$$

Now we investigate if $\hat{L}^* = L^C$ satisfies the second order condition:

$$\left.\frac{\partial S^{C2}}{\partial^2 \tau_V}\right|_{\hat{L}^* = L^C} = -\left(\frac{\partial \hat{L}^*}{\partial \tau_V}\right)^2 (b+c_I) f(\hat{L}^*) < 0.$$

Thus, $\hat{L}^* = L^C$ is the condition for the imposed τ_V to be the maximizer.

Derivation of Optimal τ_I

The social planner chooses τ_I by sloving the following optimization problem:

$$\max_{\tau_I} S^C = \int_{\tilde{L}^*}^{1} \left((b+c_I)\pi - (w+\tau_V+c_I)\right) f(\pi)d\pi + \int_{\tilde{L}^*}^{1} (\tau_I - c_I) f(\pi)d\pi,$$

$$= \int_{\tilde{L}^*}^{1} \left((b+c_I)\pi - (w+c_V+c_I)\right) f(\pi)d\pi$$

where $\tilde{L}^* = \frac{\hat{n}}{\hat{d}}$, $\tilde{n} = p(\tau_I) + c_V - (\alpha p(\tau_I) - \tau_I)$, and $\tilde{d} = b - (\alpha p(\tau_I) - \tau_I)$.

$$FOC: \frac{\partial S^C}{\partial \tau_I} = 0 \Rightarrow -\frac{\partial \tilde{L}^*}{\partial \tau_I}\left((b+c_I)\tilde{L}^* - (w+c_V+c_I)\right) f(\tilde{L}^*) = 0 \Rightarrow$$

$$(b+c_I)\tilde{L}^* - (w+c_V+c_I) = 0, \Rightarrow \tilde{L}^* = L^C, \text{where } L^C = \frac{w+c_V+c_I}{b+c_I}.$$

Now we investigate if $\tilde{L}^* = L^C$ satisfies the second order condition:

$$\left.\frac{\partial S^{C2}}{\partial^2 \tau_I}\right|_{\tilde{L}^* = L^C} = -\left(\frac{\partial \tilde{L}^*}{\partial \tau_I}\right)^2 (b+c_I) f(\tilde{L}^*) < 0.$$

Thus, $\tilde{L}^* = L^C$ is the condition for the imposed τ_V to be the maximizer.

Proof of Proposition 4

The following equations can be derived from $\tau_V = \frac{\alpha p}{b+c_I}(b-w-c_V) - (p-w-c_V)$:

$$\tau_V(b+c_I) = \alpha p(b-w-c_V) - (b+c_I)(p-w-c_V) \Rightarrow$$

$$\tau_V(b+c_I) = \alpha p(b-w-c_V+c_I-c_I) - (b+c_I)(p-w-c_V+c_I-c_I) \Rightarrow$$

$$\tau_V(b+c_I) - \alpha p(b+c_I) + (p+c_I)(b+c_I) = -\alpha p(w+c_V+c_I) + (b+c_I)(w+c_V+c_I) \Rightarrow$$

$$(b+c_I)\left(p+\tau_V - (\alpha p - c_I)\right) = (w+c_V+c_I)\left(b-(\alpha p - c_I)\right) \Rightarrow$$

$$\frac{p+\tau_V-(\alpha p - c_I)}{b-(\alpha p - c_I)} = \frac{w+c_V+c_I}{b+c_I}, \text{ i.e., } \hat{L}^* = L^C.$$

On the other hand, we showed earlier in the Appendix under the "Derivation of Optimal τ_V" that when $\hat{L}^* = L^C$, then the social welfare is maximized. Thus, if

$$\tau_V = \tau_V^* = \frac{\alpha p}{b+c_I}(b-w-c_V) - (p-w-c_V), \text{ then } \hat{L}^* = L^C, \text{ and consequently the social}$$

welfare is maximized (i.e., the first-best allocation can be achieved).

Similarly, from $\tau_I = \alpha p - \frac{b(p-w-c_I)+c_I(p+c_V)}{(b-w-c_V)}$:

$$\tau_I(b-w-c_V) = \alpha p(b-w-c_V) - b(p-w-c_I) - c_I p - c_I c_V \Rightarrow$$

$$= \alpha p(b-w-c_V) + b(w+c_I) - pb - c_I p - c_I c_V \Rightarrow$$

$$= \alpha p(b-w-c_V) + b(w+c_I) - p(b+c_I) - c_I c_V \Rightarrow$$

$$= \alpha p(b-w-c_V+c_I-c_I) + b(w+c_I+c_V) - bc_V - p(b+c_I) - c_I c_V \Rightarrow$$

$$= -\alpha p(w+c_V+c_I) + \alpha p(b+c_I) + b(w+c_I+c_V) - (b+c_I)(p+c_V) \Rightarrow$$

$$\tau_I(b-w-c_V+c_I-c_I) = (w+c_V+c_I)(b-\alpha p) - (b+c_I)(p+c_V-\alpha p) \Rightarrow$$

$$\tau_I(b+c_I) - \tau_I(w+c_V+c_I) = (w+c_V+c_I)(b-\alpha p) - (b+c_I)(p+c_V-\alpha p) \Rightarrow$$

$$\big(p+c_V-(\alpha p-\tau_I)\big)\big(b+c_I\big) = \big(w+c_V+c_I\big)\big(b-(\alpha p-\tau_I)\big).$$

Thus, $\frac{p+c_V-(\alpha p-\tau_I)}{b-(\alpha p-\tau_I)} = \frac{w+c_V+c_I}{b+c_I}$, i.e., $\tilde{L}^* = L^C$.

We also showed earlier in the Appendix under the "Derivation of Optimal τ_I" that when $\tilde{L}^* = L^C$, then the social welfare is maximized. Thus, if $\tau_I = \tau_I^* = \alpha p - \frac{b(p-w-c_I)+c_I(p+c_V)}{(b-w-c_V)}$, then $\tilde{L}^* = L^C$, and consequently the social welfare is maximized (i.e., the first-best allocation can be achieved).

Q.E.D.

Proof of Proposition 5

From (1) and (2) we have:

$$V_P = \int_L^U \big(d \times \pi - n\big) f(\pi) d\pi,$$

$$V_M = \int_L^U \big(\alpha p \times \pi + p(1-\alpha) - w\big) f(\pi) d\pi.$$

After making the transfer payment of $R = Q_1 \times \pi - Q_2$ for every patient with a given π, we obtain the following equations for the payer's payoff and the manufacturer's profit:

$$\hat{V}_P = \int_L^U \left((d + Q_1) \times \pi - (n + Q_2)\right) f(\pi) d\pi,$$

$$\hat{V}_M = \int_L^U \left((\alpha p - Q_1) \times \pi + (p(1-\alpha) - w + Q_2)\right) f(\pi) d\pi.$$

Let $\hat{L}^*$ and $\hat{U}^*$ be the optimal cut-off probabilities for $\hat{V}_P$. To obtain $\hat{V}_P + \hat{V}_M = S^C$, the following conditions should be fulfilled: $\hat{L}^* = L^C$ and $\hat{U}^* = 1$, where

$$\hat{L}^* = \frac{n + Q_2}{d + Q_1} = \frac{p - \alpha p + c_V + c_I + Q_2}{b - \alpha p + c_I + Q_1}, \text{ and } \quad L^C = \frac{w + c_V + c_I}{b + c_I}.$$

We insert $Q_1 = \alpha p$ and $Q_2 = w - p + \alpha p$ in $\hat{L}^*$ and obtain the following result:

$$\frac{p - \alpha p + c_V + c_I + w - p + \alpha p}{b - \alpha p + c_I + \alpha p} = \frac{w + c_V + c_I}{b + c_I} = L^C.$$

Thus, if $Q_1 = \alpha p$ and $Q_2 = w - p + \alpha p$, then $\hat{L}^* = L^C$ and consequently $\hat{V}_P + \hat{V}_M = S^C$. This in turn implies that a social planner can eliminate the welfare loss by choosing the transfer payment of $Q_1 \times \pi - Q_2$, where $Q_1 = \alpha p$ and $Q_2 = w - p + \alpha p$.

Q.E.D.

Calculation of Optimal Price under Uniform Distribution

We assume that π is uniformly distributed such that $f(\pi)=1$, $0 \le \pi \le 1$. By incorporating this assumption in (1) and (2), the following equations are obtained for V_P and V_M :

$$V_P = (U-L)\left(\frac{d}{2}(U+L)-n\right), \quad \text{(A-1)}$$

$$V_M = (U-L)\left(p-w-\alpha p+\frac{\alpha p}{2}(U+L)\right), \quad \text{(A-2)}$$

where $d = b-(\alpha p - c_I)$, $n = p + c_V - (\alpha p - c_I)$. The optimal values for L and U, i.e., L^* and U^*, are given according to the respective scenarios shown in Table 3-2.

For $L^* = n/d$ and $U^* = 1$, the following equation is obtained for the profit of the manufacturer from (A-2): $V_M = (1-\frac{n}{d})\left(p-w-\alpha p+\frac{\alpha p}{2}(1+\frac{n}{d})\right)$. Then the first order condition for the manufacturer's profit, $\partial V_M/\partial p=0$, results in the following cubic function:

$$\frac{\partial V_M}{\partial p} = \frac{1}{2(b-\alpha p+c_I)^3}(k_{13}p^3+k_{12}p^2+k_{11}p+k_{10}) = 0, \text{ where}$$

$$k_{13} = -\alpha^2,$$
$$k_{12} = 3\alpha(b+c_I),$$
$$k_{11} = -\alpha^2(b-c_V)(b-c_V-2w) - 2\alpha(b+c_I)\left(w-(b-c_V)\right) + 4(b+c_I)^2,$$
$$k_{10} = +\alpha b\left((b+c_I)(b-2c_V+2w)+c_V(c_V-2w)\right)$$
$$\quad -2b^2(b-c_V+2c_I+w) - 2c_I\left((2b+c_I)(c_V-w)-bc_I\right) - \alpha c_I c_V(c_V-w).$$

Solving for the roots of the above cubic function will yield the optimal price when π is uniformly distributed.

Calculation of Optimal Price for a Known π

For a known π, we obtain the following equation for the payer's payoff: $V_P = d \times \pi - n$, where $n = p - \alpha p + c_V + c_I$ and $d = b - \alpha p + c_I$. The drug manufacture chooses the optimal price such that $V_P \geq 0$. Therefore:

$$V_P \geq 0 \Rightarrow d \times \pi \geq n \Rightarrow (b - \alpha p + c_I)\pi \geq p - \alpha p + c_V + c_I \Rightarrow$$

$$\pi(b + c_I) - (c_V + c_I) \geq p\left(1 - \alpha(1 - \pi)\right) \Rightarrow$$

$$V_P \geq 0 \text{ for } p \leq \frac{\pi(b + c_I) - (c_V + c_I)}{1 - \alpha(1 - \pi)} \text{ and } 1 - \alpha(1 - \pi) > 0.$$

On the other hand for a known π, we have the following equation for the profit of the manufacturer: $V_M = p - w - \alpha p(1 - \pi)$. V_M is increasing in p if $1 - \alpha(1 - \pi) > 0$. Thus for a known π: $p^* = \frac{\pi(b + c_I) - (c_V + c_I)}{1 - \alpha(1 - \pi)}$ for $1 - \alpha(1 - \pi) > 0$. For $1 - \alpha(1 - \pi) < 0$, $V_M > 0$ if $p<0$ which is not feasible. For $1 - \alpha(1 - \pi) = 0$, the optimal price will become infinite.

From the above equation for the optimal price for a known π, we obtain the following optimal price for $\alpha = \alpha_T = \frac{b + c_I}{b - c_V}$: $p^* = b - c_V$. This result, which is consistent with the results obtained from the numerical examples, implies that for $\alpha = \alpha_T$, p^* is independent of π.

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Conclusions

This thesis set out to examine the complex dynamics arising from health-based pharmaceutical pay-for-performance risk-sharing agreements by focusing on the performance of two distinct types of such agreements. In the first type, the response of patients to a new drug is evaluated at an evaluation time specified in the contract. In the second type, patients are prescribed the drug only if their probability of response to the drug lies within a range of probabilities of success. The payer determines this range such that the use of the drug becomes cost-effective. In both types of agreements, the pharmaceutical firm provides the payer with a rebate for patients who do not respond to the drug.

In the first type of agreement each patient takes the drug over a number of time periods and stops taking the drug as the disease progresses. Also, the proportion of non-responding patients who are subject to the rebate is a function of the evaluation time. Because of these time-dependent properties, I chose a Poisson process in the context of a continuous time Markov chain to model patients' response to the drug. On the contrary, in the second type of agreement each patient takes the drug from the beginning of a time period, and her or his response is also evaluated in the same time period. Thus, I chose a simple Bernoulli distribution to model the stochastic response of a patient to the drug. However, I enriched the model with heterogeneity of response within the patient population by assuming a probability distribution for the probability of response.

In Chapter 1 of this thesis I studied the performance of the first type of agreement from the perspective of the drug manufacturer. In Chapter 2, I extended the model developed

in the first chapter and examined the performance of the agreement from the payer's perspective. In Chapter 3, I studied the performance of the second type of agreement from the perspective of a social planner in addition to the perspectives of the payer and the drug manufacturer. In the first two chapters the rebate rate and the evaluation time are the decision variables, while the price of the drug is fixed (e.g., set by an external process or regulators). In the third chapter, I assumed that in addition to the rebate rate and cut-off probabilities, the price of the drug is also a decision variable.

Main Insights From the Thesis

In the following I describe a few important findings from this thesis that can be applicable across different types of performance-based risk-sharing agreements. The results from this study demonstrate that optimal or feasible solutions for the payer or the drug manufacturer are not obvious. These results also highlight the trade-offs in negotiating these agreements. The analytical results supported by numerical examples in all three chapters show that, in many instances, the manufacturer's profit and the payer's payoff are non-monotonic for these agreements.

There are also two important findings from the policy perspective. First, setting a high rebate rate (usually greater than 100%) could potentially lead to a perverse incentive policy, in which treating patients who are least likely to respond to the drug becomes the optimal solution. Second, generally it is not possible to achieve a socially optimal contract by establishing only a rebate transfer payment from the manufacturer to the payer based on a performance-based risk-sharing agreement. Achieving this goal may also require taxes to be imposed, subsidies to be paid, or appropriate transfer payment

functions other than the rebate to be designed between the payer and the drug manufacturer.

By showing some promising results in practice, the bortezomib agreement has paved the way for more risk-sharing agreements to be implemented for similar types of treatments (e.g., the agreement for lenalidomide for the treatment of multiple myeloma in the UK). The analytical and numerical results in the first and second chapters of this thesis also confirm the existence of feasible solutions for both the payer and the manufacturer under such an agreement. Theoretically, it is possible to achieve more robust results by adding more complexity to the structure of these agreements. However the trade-off is that it may also make their administration more difficult and more costly. (This phenomenon is demonstrated in Chapter 2 when comparing different rebate classifications for the same agreement.)

My research on pharmaceutical risk-sharing has the following limitations. First, throughout this study I have been looking only into two specific types of performance-based risk-sharing agreements. In reality, depending on the treatment type and the contract parameters, risk-sharing agreements could become very different from one another from a structural point of view. This in turn implies that there is no universal solution or gold standard for these types of agreements.

Second, the main objective sought from risk-sharing in this study is to prevent the risk of paying for an unsuccessful outcome (i.e., type I error). Therefore, examining any further objectives for risk-sharing, such as increasing patient access to new treatments under a limited budget or maintaining the incentive for drug manufacturers to introduce new

drugs, has been out of the scope of this thesis (Pugatch et al., 2010). However, I believe that the results from this study can also be used in any future research that examines such objectives.

Third, risk-sharing is in its early stages of existence. Therefore it is too early to make any judgement with regard to its future, i.e., whether it is going to be a staple feature of pharmaceutical pricing and reimbursement policies or whether it is a temporary solution for an imminent problem.

Future Research

As explained earlier in this chapter, I narrowed the objective sought by performance-based risk-sharing to preventing risk of type I error for the payer. A direction for broader future research would be to examine the performance of these or other types of risk-sharing agreements with regard to further objectives such as cost controlling, increasing patient access to new treatments under limited budgets, or improving the incentive for drug manufacturers to introduce new drugs.

A recent financial analysis indicates a lower average profit margin for the health insurance sector compared with that of major drug manufacturers in 2012, i.e., 4.5% versus 16.7% , respectively (Aetna, 2013). Investigating the correlation between low average profit margin for the payers and their reluctance to cover new expensive drugs is by itself the subject of a separate study. However, envisioning the existence of such a correlation inspires the following future research with regard to the pharmaceutical risk-sharing modeling. We can assume the likelihood of covering a drug without risk-sharing is a function of the payer's expected profit margin and can thus incorporate it in the risk-

sharing model. The impact of this likelihood can be further analyzed on the expected value of the payer's payoff or the manufacturer's profit.

Investigating the performance of other types of pharmaceutical risk-sharing agreements is another direction for future research. For example, since 2002 there has been an on-going risk-sharing agreement between the UK government and several drug manufacturers for beta interferon and glatiramer acetate for the treatment of multiple sclerosis (MS). This agreement allows the coverage of these drugs conditional on a 10-year monitoring study to collect data on the progression of disease in treated patients. According to this scheme, the collected data would be reviewed every two years and, based on the effectiveness results for each individual drug, the drug manufacturers agreed to adjust the drug price to the National Health Service (Boggild et al., 2009; HSC, 2002). When the results from the first two years came out in 2009, they created controversial views among experts on the performance of this specific scheme. Some called it a costly failure (Raftery, 2010) or argued that continuing the scheme was unjustified (McCabe et al., 2010), while some decided that it was too early to reach any conclusion about the cost-effectiveness of those treatments based on this first interim analysis (Boggild et al., 2009). These discussions justify the need for more thorough analyses of the performance of such agreements. The results from such studies can be used for designing optimal risk-sharing schemes for other new drugs for the treatment of MS or other diseases with a similar course of treatment.

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Curriculum Vitae

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Post-secondary Education and Degrees:

Western University
London, Ontario, Canada
2008-2014 Ph.D., Management Science

Sharif University of Technology
Tehran, Iran
1993-1996 M.Sc., Industrial Management

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1979-1986 B.Sc., Electrical & Electronics Engineering

Related Work Experience

Lecturer
Western University
2011

Teaching Assistant
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2009-2010

Publications:

Mahjoub R, Odegaard F, Zaric GS, Health-based pharmaceutical pay-for-performance risk-sharing agreements, In Press (Published Online, Sep. 11, 2013), *Journal of the Operational Research Society (JORS)*