Improving Access to Rare Disease Treatments: Optimal Subsidies, Pricing, and Payment

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There are more than 7,000 known rare diseases, but pharmaceutical manufacturers developed treatments for only 500 of them. What should the government do to improve the availability and accessibility of treatments for these rare diseases? To improve patient welfare, governments have introduced several programs including subsidies, innovative pricing schemes, and outcome-based payment scheme but there is no consensus as to whether these programs would improve patient access to these treatments. Inspired by several on-going pilot programs for rare diseases launched in the United States and Europe, we analyze the effectiveness of innovative pricing and outcome-based payment schemes, and characterize the government's optimal subsidies.

In this paper, we consider two pricing schemes and two payment schemes. Besides the tradition that the pricing decision is controlled by the manufacturer, we consider an "exogenous pricing" strategy under which the pricing decision of an orphan drug is delegated to an independent consortium. Also, besides the standard payment to the manufacturer that is based on sales, we consider an outcome-based payment scheme that is known as "No Cure No Pay" scheme under which the manufacturer will not receive any payment when the drug is not efficacious. To examine the effectiveness of the exogenous pricing and outcome-based payment schemes when the government can decide on whether to subsidize the pharmaceutical manufacturer, the patients, or both, we develop a 3-stage Stackelberg game theoretic model to capture the interactions among the government, the manufacturer, and the patients.

By comparing the equilibrium outcomes associated with different pricing and payment schemes, we obtain several results that could have the following implications. Specifically, by using a case study inspired by the drug Spinraza, we show that it is always optimal to offer subsidies to the manufacturer only, when the pricing decision is delegated to the manufacturer; however, when the pricing decision is delegated to an independent consortium, subsidizing both the manufacturer and the patients can be optimal. Also, we find that delegating the pricing decision to an independent consortium can result in lower prices, while providing an attractive business environment for pharmaceutical manufacturers. Finally, we show that outcome-based payment does not necessarily improve patient welfare, and it may result in higher prices (if the government does not provide sufficient amount of subsidies).

Key words: government subsidies, rare diseases, social welfare, innovative pricing schemes, and outcome-based payment schemes

1. Introduction

More than 350 million patients worldwide suffer from rare diseases (IFPMA 2017). Currently, there are more than 7,000 known rare diseases, but drug treatments are available only for 500 of them (IQVIA 2018). Even if a treatment exists, the average cost of these treatments for rare diseases (known as *orphan drugs*) is seven times higher than non-orphan drugs (EvaluatePharma 2019). The limited availability and accessibility have raised public concerns worldwide, with a strong emphasis for change (Luzzatto et al. 2018). As a corrective measure, several initiatives are being proposed for orphan drugs including: (a) subsidy programs, (b) innovative pricing schemes, and (c) outcome-based payment schemes. Although these initiatives are promising for patients, there is open public debate as to whether they would indeed be effective in improving patient access to rare disease treatments.

First, governments have developed different subsidy programs that often take the form of tax credits and grants to stimulate research and development (R&D) efforts. Examples of such subsidy programs include the Orphan Drug Act in the United States (FDA 2017) and the legislation for Orphan Medicinal Products in Europe (EMA 2017). Subsidy programs were successful in stimulating the industry with 575 new approvals through the Orphan Drug Act between 1983 and 2017 (Luzzatto et al. 2018). However, since the inception of these programs, most of the subsidies were offered to pharmaceutical manufacturers only (except a few programs that provide price subsidies to patients) (Cohen 2017). This imbalance has recently created social turmoils around the world in which several rare-disease patients and their caregivers began demanding patient subsidies. One recent example is with the drug Spinraza, a drug for patients with spinal muscular atrophy (SMA). Although subsidies were offered to the manufacturer Biogen through the Orphan Drug Act, no subsidies were provided to patients (Elvidge 2017, Ring 2019). In 2018, hundreds of SMA patients protested and demanded for patient subsidies without prevail (Luxner 2018, 2019, Ring 2019). Consequently, orphan-drug subsidy programs are controversial: although they stimulated the R&D of new treatments, they did not necessarily improve patient access to these drugs. Currently, there is an on-going public debate questioning whether the current practice (i.e., subsidizing pharmaceutical manufacturers only) is putting rare-disease patients at a disadvantage (The Lancet Neurology 2017, Luxner 2018). These observations motivate us to examine the first research question: (1) To maximize patient welfare (due to affordability), should the government subsidize the manufacturer, the patients, or both?

Second, innovative pricing schemes are also perceived as effective means of improving patient access to orphan drugs. In current practice, when marketing authorization is granted for an orphan drug, the price is set by the pharmaceutical manufacturer. Recently, a new initiative has been introduced as part of a managed entry program: instead of the manufacturer setting the price, an

independent consortium *exogenously* pre-specifies the price of an orphan drug. The first example of such exogenous pricing was implemented in Europe, called the BeNeLuxA initiative (Sutton 2019). In this initiative, five European countries (Belgium, the Netherlands, Luxembourg, Austria, and Ireland) built an independent consortium to jointly decide the price of orphan drugs (Henrard et al. 2016, Beneluxa 2018). The independent consortium consisted of stakeholders representing policy-makers, pharmaceutical companies, health researchers, patient advocates, and payers (KCE 2017). The first positive outcome of BeNeLuxA was achieved in 2018, when the consortium reached a consensus on the price of Spinraza with the pharmaceutical manufacturer Biogen (Rijksoverheid 2018). This also inspired several follow up initiatives, including FINOSE (Finland, Norway, and Sweden) and the Valletta Declaration (southern European Union member states) (Sutton 2019). Despite these successful examples, pharmaceutical manufacturers are reticent about exogenous pricing schemes (Grubert 2019).

It is clear that exogenous pricing can regulate prices, but it may discourage manufacturers to exert R&D efforts for developing new drugs (Rijksoverheid 2018, McConaghie 2018). This dilemma motivate us to formulate our second research question: (2) What is the impact of exogenous pricing (i.e., when the drug price is specified by an independent consortium) on patient's welfare and manufacturer's profitability? To strike a balance between patient welfare and manufacturer profit, should the pricing decision be delegated to the manufacturer or an independent consortium?

Third, *outcome-based payment* schemes have been considered as one of the most attractive options for orphan drugs and expensive cancer treatments (Faulkner 2016). In 2019, an outcome-based payment scheme for a rare disease was tested as a pilot program that is known as the "No Cure No Pay" scheme. Under this scheme, the drug is paid for only if it is effective for a specific patient within a specified time frame (Impe 2019). Otherwise, the pharmaceutical manufacturer does not receive any payments for that individual patient. For example, Bristol-Myers Squibb provides Nivolumab – a drug for rare MSI-H-tumor cancers – under the "No Cure No Pay" scheme (Medscape 2019). Three other pilot programs are currently in progress as a follow-up to this initiative (Impe 2019). Clearly, the outcome-based payment scheme provides an opportunity for a patient to try and she does not have to pay for an expensive drug if it is not effective. However, insurers and experts argue that outcome-based payments might stimulate further increases in orphan drug prices (Meyer 2019). These conflicting views motivate us to formulate our third research question: (3) What is the impact of outcome-based payment scheme on patient welfare and manufacturer profit? To strike a balance between patient welfare and manufacturer profit, should the government impose the outcome-based payment scheme?

The on-going debate about the impact of various programs (subsidies, innovative pricing schemes, and outcome-based payment schemes) on patient welfare (due to availability and affordability)

and manufacturer's profitability has motivated us to develop a 3-stage Stackelberg game theoretic model to capture the strategic interactions among the government, the manufacturer, and the patients. In our model, we consider the case when the government uses a limited budget to allocate subsidies between the pharmaceutical manufacturer and patients to maximize patient welfare (and manufacturer profit). We also consider two pricing schemes: (1) the endogenous pricing scheme under which the manufacturer sets the selling price, and (2) the exogenous pricing scheme under which an independent consortium pre-specifies the price. Finally, we consider two payment schemes: (A) a sales-based payment scheme under which the manufacturer receives payment for selling each unit of drug regardless of patient outcome, and (B) an outcome-based payment scheme under which the manufacture receives payment for selling each unit of drug to a patient only when it is effective for that patient.

By comparing the equilibrium outcomes associated with different subsidy programs, pricing schemes, and payment schemes, we obtain answers to those three aforementioned research questions. More importantly, our results have the following implications for policy-makers and pharmaceutical manufacturers.

1. Optimal subsidies are dependent on the selected pricing scheme. When the pricing decision is made by the pharmaceutical manufacturer under the endogenous pricing scheme, it is optimal to offer subsidies to the manufacturer only. This result is consistent with the current practice. However, when the pricing decision is delegated to an independent consortium under the exogenous pricing scheme, it can be optimal to subsidize both the manufacturer and patients (depending on the price and budget).

2. Having the consortium to set the drug price under the exogenous pricing scheme can be beneficial to the patients and the manufacturer. We show that letting the consortium set the drug price under the exogenous pricing scheme can improve patient welfare significantly, while continuing to provide an attractive environment for manufacturers. This has critical implications for policy-makers and the orphan drug industry, as committing to exogenous pricing requires a substantial change in mindset.

3. Outcome-based payment scheme can result in higher prices. We show that if the subsidy budget is low, the outcome-based payment scheme can result in higher drug prices compared to the sales-based payment scheme (under both endogenous and exogenous pricing schemes). This finding supports the current public belief that, under the outcome-based payment scheme, the manufacturer will inflate their drug prices to compensate for those non-payments from patients who find the drug to be ineffective.

In summary, we believe our model formalizes our understanding of the interactions among different parties, and our results inform policy makers when developing programs for improving patient access to rare disease treatments.

The remainder of this paper is organized as follows. We provide a literature review in Section 2. We present our modeling framework in Section 3, and analyze the model in Section 4. In Section 5, we extend the model to the case where drug efficacy is random. In Section 6, we analyze another extension where the government cares about patient welfare and manufacturer simultaneously. We present a case study motivated by the drug Spinraza in Section 7, and provide concluding remarks in Section 8. For ease of exposition, all proofs are provided in the Appendix.

2. Literature Review

Our paper builds on a growing body of work on (1) government subsidy programs, (2) outcome-based payment schemes, and (3) empirical research on orphan drugs. We concentrate on the papers most directly related to our research, and refer the reader to the review papers of Dai and Tayur (2019) and Betcheva et al. (2019) for a comprehensive overview of the healthcare operations management literature.

2.1. Government subsidy programs

An emerging stream of research in healthcare operations management focuses on government subsidies. In this context, several papers analyze subsidy programs intended to improve the availability of drugs. For example, Taylor and Xiao (2014) study subsidies to improve the availability and affordability of malaria drugs in Africa. They consider whether a donor should subsidize the purchases and/or sales, and find that it is always optimal to subsidize purchases only. Similarly, Levi et al. (2016) formulates a Stackelberg game to increase the consumption of malaria drugs. They find that uniform subsidies are optimal in the setting of malaria drugs. Besides, Mamani et al. (2012) consider the problem of determining a socially optimal level of coverage for vaccines to prevent infectious diseases. A newsvendor setting is formulated by Chick et al. (2008) to study the government's decision on purchase quantities and manufacturer's decision on production volumes of vaccines. However, we note that aforementioned studies focus on government subsidies offered to non-orphan drugs (e.g., vaccines for pandemics such as malaria and influenza). To the best of our knowledge, government subsidies offered to orphan drugs have not received much attention in the healthcare operations management literature.

There is also a large body of work on government subsidies in non-healthcare related contexts. In this stream, we focus on papers that are the most recent and directly relevant to our research. For example, several studies examine the impact of subsidies on manufacturer's profit and consumer

welfare: Yu et al. (2016) study subsidy programs for consumers in rural areas of developing countries. They find that the optimal subsidy program depends on whether there is a well-established market selling price as well as the relative emphasis that the government places on consumer welfare and manufacturer profit. Knuckles et al. (2017) study subsidies in development supply chains, such as solar lanterns in Haiti. They find that the donor can subsidize the manufacturer, the retailer or customers, as long as the total subsidy per unit is maintained at the optimal level. In addition, Cohen et al. (2015) study government subsidies for green technology adoption, and Alizamir et al. (2019) consider government subsidies in the agricultural industry.

Although subsidy programs have been largely studied, their applications in the context of orphan drugs have not been fully addressed. To the best of our knowledge, this study is one of the first attempts to model and analyze subsidy programs for rare diseases in combination with innovative pricing and payment schemes.

2.2. Outcome-based payment schemes

There is only a limited amount of work related to outcome-based payment schemes in the healthcare operations management literature. So and Tang (2000) were the first to analytically model an outcome-based reimbursement policy for drug usage, and analyzed its implications on hospitals, patients and pharmaceutical firms. They showed that factors, such as initial health conditions and profit margins, would affect target prescription policies set by clinics. Fuloria and Zenios (2001) captured an outcome-adjusted reimbursement system by using a dynamic principal-agent model. They found that significant gains in patients' life expectancy could be achieved with an outcome-adjusted payment scheme. Most of the follow-up research in this stream focus on examining the performance of outcome-based payment in the context of healthcare services, such as referrals, outpatient medical services, and re-admissions (Jiang et al. 2012, Adida and Bravo 2018, Andritsos and Tang 2018).

There are also several empirical studies on outcome-based payment for orphan drugs. Ollendorf et al. (2018) provide an overview of the societal, ethical, and coverage/reimbursement landscape for rare disease treatments. In addition, Carlson (2014) provides a review of performance-based risk-sharing arrangements. Most empirical studies and opinion articles on outcome-based payment focus on understanding the risks and its implications on prices. On the one hand, several papers support outcome-based payment initiatives. For example, Edlin et al. (2014) showed that a payment-by-result reimbursement scheme could reduce the total budgetary impact of an innovative drug. Seeley and Kesselheim (2017) assessed the expected benefits and limitations of outcomes-based pharmaceutical contracts in the U.S. In contrast, another stream of research suggests that outcome-based payment might not necessarily improve social welfare. For example, Carlson (2014) and Edlin et

al. (2014), Seeley and Kesselheim (2017) conclude that there is no evidence that outcome-based payment has lowered healthcare spending. They also indicate that outcome-based rebates can raise a drug's initial price. Meyer (2019) discuss similar results, in which several insurers and experts came to the conclusion that outcome-based contracting has made slow and uncertain progress since it was introduced.

To complement the aforementioned studies, we build analytical models to investigate the implications of outcome-based payment schemes on government subsidies, orphan drug prices, welfare of patients and profitability of manufacturers. Our managerial insights shed light on the open public debate regarding the implications of outcome-based payment schemes.

2.3. Empirical research on orphan drugs

There are several empirical studies and opinion articles on orphan drugs. We refer to Richter et al. (2015) for a comprehensive review on the terminology and definitions used globally. In the context of subsidies offered to orphan drugs, there is a growing body of work that examines the challenges faced by governments. For instance, Schulenburg and Frank (2015) study the challenges posed by health care systems. They conclude that incentives are needed to stimulate research for developing and maintaining appropriate treatments for rare disease patients. However, resources spent on rare diseases also increase health care costs. Similarly, Vogler et al. (2015) conclude that access to orphan drugs might be limited due to high costs that can neither be funded by individuals nor by the communities. In addition, Wellman et al. (2010) investigate the issues associated with subsidies of the Orphan Drug Act. They find that the Orphan Drug Act has created issues which have led to commercial and ethical abuses in some cases.

Another stream of work focuses on orphan drug pricing. For instance, Simoens (2011) conduct a literature review to provide insights into the drivers of orphan drug pricing. In addition, Hughes et al. (2012) discuss whether the Orphan Medicinal Products Regulation is worthy, as high prices of orphan drugs are restricting patient access to treatments. A few papers examine new initiatives for regulating the prices of orphan drugs. For example, Sutton (2019) and Grubert (2019) discuss the recent developments around joint pricing initiatives, such as BeNeLuxA.

To the best of our knowledge, our work is one of the firsts to model and analyze the subsidy programs, exogenous pricing, and outcome-based payment schemes for rare diseases. Our analysis formalizes our understanding of these initiatives, and provides broader insights in healthcare policy-making for orphan drugs.

3. The Model

In this section, we present a model of a system of three parties (the government, the drug manufacturer, and the patients). Also, we describe different programs (government subsidies, two pricing

schemes, and two payment schemes) that aim to improve patient welfare. The goal is to examine those three aforementioned research questions that are intended to examine the implications of these programs.

3.1. Model Preliminaries

Manufacturer subsidies and patient subsidies. In our model, the government can offer subsidies to pharmaceutical manufacturers to reduce costs and stimulate research & development (R&D) of treatments for rare diseases. We assume that the developed drug is efficacious with probability e and non-efficacious with probability $(1-e)$. The manufacturer subsidy takes the form of cost subsidy $\alpha k e^2$, where ke^2 is the cost of R&D and $\alpha \in [0,1)$ is the proportion of the cost to be shared by the government. Therefore, the manufacturer incurs an effective R&D cost $(1-\alpha)ke^2$ to develop a drug with target efficacy e. We scale the unit cost of production to zero, as R&D typically constitutes the bulk of the costs.

Besides manufacturer subsidies, the government can provide subsidies to patients, to reduce the unit selling price and increase the number of patients who can afford the drug. The patient subsidy takes the form of price subsidy βp per unit, where p is the unit selling price and $\beta \in [0,1)$ is the portion of the unit selling price to be shared by the government. Therefore, the government needs to select the subsidy policy (α, β) to maximize patient welfare subject to a budget constraint B. Figure 1 summarizes the interactions among the government, the manufacturer, and the patients for any given subsidy policy (α, β).

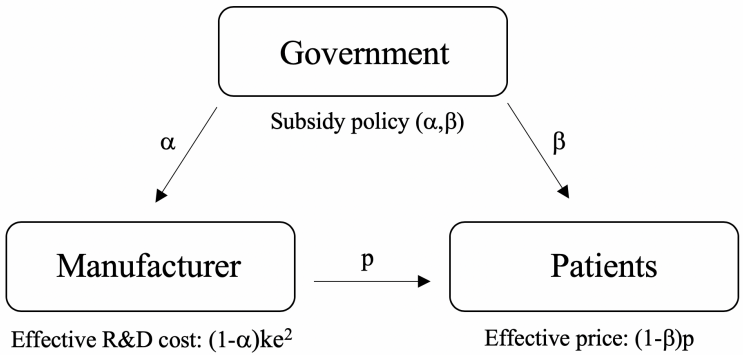

Figure 1 Interactions among government, manufacturer and patient

Endogenous and exogenous pricing schemes. In our model, we shall analyze two different pricing schemes as shown in Table 1: (1) the unit selling price is *endogenously* determined by the manufacturer; and (2) the unit selling price is *exogenously* specified by an independent consortium. In the endogenous pricing scheme (1), the manufacturer establishes the price by taking the subsidy policy and the target efficacy of the drug into account. In the exogenous pricing scheme (2), the unit selling price is pre-specified by the consortium (and the manufacturer cannot change it).

Table 1 **Four settings: two pricing schemes and two payment schemes**

	Payment scheme	
Pricing Scheme	(A) Sales-based	(B) Outcome-based
(1) Endogenous	Setting (1A)	Setting (1B)
(2) Exogenous	Setting (2A)	Setting (2B)

Sales-based and outcome-based payment schemes. In our model, we consider two payment schemes as shown in Table 1: (A) a sales-based payment scheme; and (B) an outcome-based payment scheme. In the sales-based payment scheme (A), the manufacturer receives payment from patients for each unit of drug that is sold to a patient. However, in the outcome-based payment scheme (B), the manufacturer receives payment from a patient only if the drug is efficacious for that individual patient. Note that this corresponds to the "No Pay No Cure" program as described earlier, which is used for orphan drugs and expensive cancer treatments (Impe 2019, Medscape 2019). Nevertheless, our model can be easily adjusted to other forms of outcome-based payments (e.g., rebate-based schemes for non-orphan drugs) and would result into similar insights.

Sequence of events. We model the interactions among the government, the manufacturer and the patients as a 3-stage Stackelberg game based on the following sequence of events:

0. A consortium determines the unit selling price *(for the exogenous pricing scheme only)*.

1. The government acts as the leader and has a budget B to allocate. The government selects the manufacturer subsidy α and the patient subsidy β to maximize patient welfare.

2. The manufacturer acts as a follower and sets its unit selling price p *(for the endogenous pricing scheme only)* and the target efficacy e to maximize its profit, given the subsidies (α, β) and the demand $d(\alpha, \beta)$.

3. The patients make the purchasing decision of the drug, given the subsidy β and the price p.

We assume that the size of the market N is known and scaled to one for exposition.

3.2. Demand, Patient Welfare, and Manufacturer Profit

To analyze our 3-stage Stackelberg game using backward induction based on the sequence of events as stated above, we now determine the demand $d(\alpha, \beta)$, the patient welfare $W(\alpha, \beta)$ and the manufacturer's profit $\pi_m(\alpha, \beta)$ for Settings (A) and (B). These quantities will be enable us to formulate the manufacturer's problem for specifying the efficacy level e (and the price p) that maximizes its own profit π_m, and the government's problem that specifies the subsidy program (α, β) that maximizes patient welfare W in the next section.

3.2.1. Model for Setting (A): Sales-based payment scheme We consider a utility function that is based on the Willingness-To-Pay model with uniform valuation. If the drug is successful, patients live and enjoy an "extra" utility V. Given price p and subsidy β, the effective price of

the drug for each patient is $(1-\beta)p$. For any effective price, each patient's base utility is either U (no purchase of the drug) or $U+eV-(1-\beta)p$ (purchase of the drug). We scale the patient's base utility U to zero. Hence, a patient will accept the drug if $eV-(1-\beta)p \geq 0$. This implies that the patient will purchase the drug if $V \geq \frac{(1-\beta)p}{e}$, and purchase nothing otherwise. Because $V \sim U[0,1]$, the demand of the drug under a subsidy policy (α,β) is given as

$$d(\alpha,\beta) = Prob\{V \geq \frac{(1-\beta)p}{e}\} = 1 - \frac{(1-\beta)p}{e}. \tag{1}$$

By considering the fact that a patient will purchase the drug if $V \geq \frac{(1-\beta)p}{e}$ and $V \sim U[0,1]$, we compute the patient welfare $W(\alpha,\beta)$ as

$$W(\alpha,\beta) = \int_{\frac{(1-\beta)p}{e}}^{1} [ev-(1-\beta)p]dv = \frac{(e-(1-\beta)p)^2}{2e}. \tag{2}$$

Next, we determine the manufacturer's objective in Settings (1A) and (2A). In Setting (1A), the manufacturer sets the target efficacy e and unit selling price p. The government shares the R&D cost ke^2, where α is the portion of the cost shared by the government. Anticipating the demand $d(\alpha,\beta)$ and subsidy policy (α,β), the manufacturer's optimal profit is

$$\pi_m(\alpha,\beta) = \max_{p,e} \{p\,[1-\frac{(1-\beta)p}{e}] - (1-\alpha)ke^2\}. \tag{3}$$

The first term $p\,[1-\frac{(1-\beta)p}{e}]$ corresponds to the revenue of the drug and the second term $(1-\alpha)ke^2$ to the effective cost of the drug. Note that we scale the unit production cost to zero.

In Setting (2A), the unit selling price p is exogenously specified by a consortium, and the manufacturer can only set the target efficacy e. Anticipating the demand $d(\alpha,\beta)$ and subsidy policy (α,β), the manufacturer's optimal profit (for any given p specified by a consortium) is

$$\pi_m(\alpha,\beta) = \max_{e} \{p\,[1-\frac{(1-\beta)p}{e}] - (1-\alpha)ke^2\}. \tag{4}$$

The government determines the optimal subsidy policy (α,β) that maximizes the patient welfare $W(\alpha,\beta)$ subject to a budget constraint B. The government pays the manufacturer αke^2 and pays βp for each patient. Hence, the government's problem is formulated as

$$\pi_g(\alpha,\beta) = \max_{\alpha,\beta} \Big\{\frac{(e-(1-\beta)p)^2}{2e}\Big\}, \tag{5}$$

$$s.t.\ \alpha ke^2 + \beta p\,[1-\tfrac{(1-\beta)p}{e}] \leq B.$$

3.2.2. Model for Setting (B): Outcome-based payment scheme In the outcome-based payment scheme, the manufacturer offers the drug for free if it is not efficacious for a patient (e.g., "No Cure No Pay" program of Bristol-Myers Squibb). Therefore, we reformulate the demand $d(\alpha,\beta)$ and patient welfare $W(\alpha,\beta)$ under the outcome-based payment scheme. With probability e, the patient pays the effective price $(1-\beta)p$ and the government pays βp. We scale the patient's base utility to zero. If the patient decides to purchase the drug with effective cost $(1-\beta)pe$, she will enjoy an extra utility eV, leading to patient welfare $e(V-(1-\beta)p)$. Hence, a patient will accept the drug if $e(V-(1-\beta)p)\geq 0$, and it is sufficient to have $V\geq(1-\beta)p$. As $V\sim U[0,1]$, we formulate the demand under the outcome-based payment scheme and subsidy policy (α,β) as

$$d(\alpha,\beta)=Prob\{V\geq(1-\beta)p\}=1-(1-\beta)p. \tag{6}$$

By considering the fact that a patient will purchase the drug if $V\geq(1-\beta)p$ and $V\sim U[0,1]$, we compute the patient welfare $W(\alpha,\beta)$ as

$$W(\alpha,\beta)=\int_{(1-\beta)p}^{1} e[v-(1-\beta)p]dv=\frac{1}{2}e(1-(1-\beta)p)^2. \tag{7}$$

Next, we determine the manufacturer's objective under the outcome-based payment scheme in Settings (1B) and (2B). In Setting (1B) the manufacturer sets the target efficacy e and unit selling price p for any given subsidy policy (α,β) and $d(\alpha,\beta)$. Hence, the manufacturer's optimal profit is

$$\pi_m(\alpha,\beta)=\max_{p,e}\{e\,p\,[1-(1-\beta)p]-(1-\alpha)ke^2\}. \tag{8}$$

In Setting (2B), the unit selling price is exogenously specified by a consortium, and the manufacturer sets the target efficacy e. Given subsidy policy (α,β) and anticipating the demand $d(\alpha,\beta)$, we formulate the manufacturer's optimal profit as

$$\pi_m(\alpha,\beta)=\max_{e}\{e\,p\,[1-(1-\beta)p]-(1-\alpha)ke^2\}. \tag{9}$$

The government determines the optimal subsidy policy (α,β) that maximizes the patient welfare $W(\alpha,\beta)$. By allocating the subsidy budget B, the government has to pay αke^2 to the manufacturer and only has to pay the price $e\beta p$ per patient when the drug is efficacious. Hence, the government's problem is formulated as

$$\begin{aligned}\pi_g(\alpha,\beta)=\max_{\alpha,\beta}\{&\frac{1}{2}e(1-(1-\beta)p)^2\},\\ s.t.\ &\alpha ke^2+e\beta p[1-(1-\beta)p]\leq B.\end{aligned} \tag{10}$$

In Appendix A, we shall examine the robustness of our results. Instead of maximizing the patient welfare, we consider an alternative objective function that focuses on maximizing the demand $d(\alpha,\beta)$. By considering this alternative objective function that focuses on drug adoption, we find that our results are robust and continue to hold.

4. Optimal price, efficacy, and subsidies under different pricing and payment schemes

We now analyze the 3-stage Stackelberg game for each of the four settings shown in Table 1. For each setting, we derive the optimal subsidy policy by using backward induction. All proofs are provided in the Appendix.

4.1. Setting (1A): Endogenous pricing scheme and sales-based payment scheme

First, we consider Setting (1A) where the manufacturer determines the unit selling price and a sales-based payment scheme is used. Using Equation (3), the optimal price p^* satisfies

$$p^* = \frac{1}{16(1-\alpha)k(1-\beta)^2}, \tag{11}$$

and the optimal target efficacy e^* satisfies

$$e^* = \frac{1}{8(1-\alpha)k(1-\beta)}. \tag{12}$$

We observe in Equation (11) that the manufacturer will charge a higher price p, if the government offers a higher patient subsidy β or a manufacturer subsidy α, as a portion of the price is shared by the government. Moreover, we observe that the effect of patient subsidy β is stronger than the effect of manufacturer subsidy α on the unit selling price p. We observe in Equation (12) that the manufacturer subsidy α and the patient subsidy β have an identical beneficial effect on the target efficacy e. By considering Equations (11) and (12), we obtain the corresponding patient welfare $W(\alpha,\beta) = \frac{1}{64(1-\alpha)k(1-\beta)}$. Hence, we reformulate the government's problem as

$$\pi_g(\alpha,\beta) = \max_{\alpha,\beta} \left\{ \frac{1}{64(1-\alpha)k(1-\beta)} \right\}, \tag{13}$$
$$s.t.\ \tfrac{\alpha}{64(1-\alpha)^2k(1-\beta)^2} + \tfrac{\beta}{32(1-\alpha)k(1-\beta)^2} \le B.$$

We observe in Equation (13) that the manufacturer subsidy α and the patient subsidy β have an identical beneficial effect on the patient welfare $W(\alpha,\beta)$. We establish the optimal subsidy policy (α,β) in Proposition 1.

Proposition 1. *When the unit selling price is endogenously determined by the manufacturer and a sales-based payment scheme is used, the budget constraint is binding and the optimal subsidy policy satisfies* $(\alpha,\beta) = (\frac{1+128Bk-\sqrt{256Bk+1}}{128Bk}, 0)$. *The corresponding patient welfare* $W^*(\alpha,\beta) = \frac{2B}{\sqrt{256Bk+1}-1}$ *and the manufacturer's profit* $\pi_m^*(\alpha,\beta) = \frac{2B}{\sqrt{256Bk+1}-1}$.

Proposition 1 suggests that it is optimal for the government to offer subsidies to manufacturers only (i.e., $\beta = 0$) under an endogenously determined price and sales-based payment scheme. In this setting, providing subsidies to manufacturers would also benefit the patients, as higher manufacturer subsidy would entice the manufacturer to increase the efficacy e^* in Equation (12), which will improve patient welfare. Moreover, we observe that the patient welfare is equal to the manufacturer's profit (i.e., $\pi_m^*(\alpha,\beta) = W^*(\alpha,\beta)$) under the optimal subsidy policy.

4.2. Setting (1B): Endogenous pricing scheme and outcome-based payment scheme

In Setting (1B), the price is endogenously determined and the manufacturer uses an outcome-based payment scheme. Recall from Section 3.2 that the manufacturer decides the target efficacy e and price p. However, the manufacturer only receives revenue with probability e. Using Equation (9), the optimal price p^* satisfies

$$p^* = \frac{1}{2(1-\beta)}, \tag{14}$$

and the target efficacy e^* satisfies

$$e^* = \frac{1}{8(1-\alpha)k(1-\beta)}. \tag{15}$$

We observe in Equation (14) that the manufacturer's optimal price p^* in the outcome-based payment scheme is equal to the price of the sales-based payment scheme, presented in Equation (11), divided by the optimal target efficacy e^*. Also, in the outcome-based payment scheme, the manufacturer's price only depends on the patient subsidy β. If the government offers a higher patient subsidy β, the manufacturer will charge a higher price p. Moreover, we observe in Equation (15) that the optimal target efficacy e^* is identical to that of Setting (1A). By considering Equations (14) and (15), we obtain the corresponding patient welfare $W(\alpha,\beta) = \frac{1}{64(1-\alpha)k(1-\beta)}$. Hence, we reformulate the government's problem as

$$\pi_g(\alpha,\beta) = \max_{\alpha,\beta} \Big\{ \frac{1}{64(1-\alpha)k(1-\beta)} \Big\}, \tag{16}$$

$$s.t.\ \tfrac{\alpha}{64(1-\alpha)^2k(1-\beta)^2} + \tfrac{\beta}{32(1-\alpha)k(1-\beta)^2} \le B.$$

We observe in Equation (16) that the government's objective $\pi_g(\alpha,\beta)$ of Setting (1B) is identical to that of Setting (1A). Hence, for Setting (1), with an endogenously determined price, the optimal subsidy policy is the same for the sales- or outcome-based payment schemes. In both settings, it is optimal for the government to offer subsidies to manufacturers only (i.e., $\beta = 0$) and Proposition 1 continues to hold. Subsequently, we observe that the optimal patient welfare $W^*(\alpha,\beta)$ is the same under the sales- and outcome-based payment schemes. However, Corollary 1 shows that the optimal price p^* does not necessarily need to be the same under these two payment schemes.

Corollary 1. *When the unit selling price is endogenously determined by the manufacturer, the optimal price p^* depends on the budget B and cost k, and has the following characteristics:*

1. *When $B < k - \frac{1}{8}$, the sales-based payment scheme results in a lower price compared to the outcome-based payment scheme.*

2. *When $B \ge k - \frac{1}{8}$, the sales-based payment scheme results in a higher price compared to the outcome-based payment scheme.*

To generate Corollary 1, we substituted the optimal subsidy policy $(\alpha,\beta)=(\frac{1+128Bk-\sqrt{256Bk+1}}{128Bk},0)$ into the price of Setting 1A (as given in Equation (11)) and that of Setting 1B (as given in Equation (14)), and then obtained the optimal price p^* as a function of the budget B. Corollary 1 provides important managerial insights: when the subsidy budget is low (e.g., $B<k-\frac{1}{8}$), the outcome-based payment scheme results in a higher price compared to the sales-based payment scheme. This insight supports the current public concern that outcome-based payment might stimulate further increases in orphan drug prices. However, Corollary 1 also indicates that if the government provides a sufficient amount of subsidy budget (e.g., $B\geq k-\frac{1}{8}$), the outcome-based payment can lead to a lower price compared to the sales-based payment scheme.

4.3. Setting (2A): Exogenous pricing scheme and sales-based payment scheme

In Setting (2A), the price is exogenously specified by an independent consortium and the manufacturer uses a sales-based payment scheme. Using the objective function of the manufacturer in Equation (4), we derive the optimal target efficacy e^* as

$$e^*=\sqrt[3]{p\frac{(1-\beta)p}{2(1-\alpha)k}}. \tag{17}$$

We observe in Equation (17) that the target efficacy e^* is increasing in α and decreasing in β. The manufacturer is willing to invest more in the efficacy when the government offers subsidies to the manufacturer. By considering the optimal target efficacy in (17), we reformulate the government's problem as

$$\pi_g(\alpha,\beta)=\max_{\alpha,\beta}\{\frac{\left(\sqrt[3]{p\frac{(1-\beta)p}{2(1-\alpha)k}}-(1-\beta)p\right)^2}{2\sqrt[3]{p\frac{(1-\beta)p}{2(1-\alpha)k}}}\}, \tag{18}$$

$$s.t.\ \alpha k\left(\sqrt[3]{p\frac{(1-\beta)p}{2(1-\alpha)k}}\right)^2+\beta p\left(1-\frac{(1-\beta)p}{\sqrt[3]{p\frac{(1-\beta)p}{2(1-\alpha)k}}}\right)\leq B.$$

Because the government's expenditure is increasing in α and β, the budget constraint is binding at the optimal solution. We establish the optimal subsidy policy (α,β) in Proposition 2.

Proposition 2. *When the price is exogenously specified and a sales-based payment scheme is used, the optimal subsidy policy (α,β) is increasing in budget B and the budget constraint is binding. Moreover, the manufacturer subsidy α is decreasing in the unit selling price p, and the patient subsidy β is increasing in the unit selling price p.*

Proposition 2 suggests that when the price is exogenously specified by an independent consortium and a sales-based payment scheme is used, the optimal subsidy policy depends on the unit selling price p. When the price set by the consortium is relatively high, the government can afford to offer

a lower manufacturer subsidy α (because the manufacturer will still develop a high efficacy e^*, see Equation 17). However, the government needs to offer a higher subsidy β for the patients. When the consortium sets a relatively low unit selling price p, the opposite holds.

4.4. Setting (2B): Exogenous pricing scheme and outcome-based payment scheme

We analyze the exogenous pricing scheme with an outcome-based payment. Using the objective function of the manufacturer in Equation (10), we derive the optimal target efficacy e^* as

$$e^* = \frac{p\,(1-(1-\beta)p)}{2(1-\alpha)k}. \tag{19}$$

We observe in Equation (19) that the manufacturer's target efficacy is increasing in α and β. This is different than Setting (2A), where the efficacy is only increasing in β. Given the optimal e^*, the government's problem is written as

$$\pi_g(\alpha,\beta) = \max_{\alpha,\beta}\Big\{\frac{p\,(1-(1-\beta)p)^3}{4(1-\alpha)k}\Big\}, \tag{20}$$
$$s.t.\ \tfrac{\alpha p^2(1-(1-\beta)p)^2}{4(1-\alpha)^2k} + \tfrac{\beta p^2(1-(1-\beta)p)^2}{2(1-\alpha)k}) \le B.$$

It is easy to check in Equation (20) that the patient welfare and government's expenditure (i.e., the left hand side of the budget constraint) are increasing in α and β. We denote α_{max} as the maximum manufacturer subsidy that satisfies the binding budget constraint when $\beta = 0$, and establish the optimal subsidy policy (α,β) in Proposition 3.

Proposition 3. *When the price is exogenously specified and an outcome-based payment scheme is used, the budget constraint is binding and the optimal subsidy policy can be characterized as follows:*

1. *When* $p \ge \frac{2}{(5-\alpha_{max})}$, *it is optimal to subsidize patients only (i.e.,* $\alpha = 0$*). The optimal patient subsidy satisfies* $(\alpha,\beta) = (0, \frac{c}{3p^4} + \frac{p^8+p^6-2p^7}{c} - \frac{2(p^3-p^4)}{3p^4})$ *where* $c = \sqrt[3]{3\sqrt{3}\sqrt{Bkp^{16}(27Bk-2p^4+6p^3-6p^2+2p)}+p^8(27Bk-p^4+3p^3-3p^3+p)}$.
2. *When* $\frac{2}{(5-\alpha_{max})} > p > \frac{2(1-\alpha_{max})}{5}$, *it is optimal to subsidize both patients and manufacturers.*
3. *When* $p \le \frac{2(1-\alpha_{max})}{5}$, *it is optimal to subsidize manufacturers only (i.e.,* $\beta = 0$*). The optimal manufacturer subsidy satisfies* $(\alpha,\beta) = (\frac{8Bk+p^4-2p^3+p^2-(p-p^2)\sqrt{16Bk+p^4-2p^3+p^2}}{8Bk}, 0)$.

Proposition 3 suggests that when the price is exogenously specified and an outcome-based payment scheme is used, the optimal subsidy policy depends on the unit selling price p set by the consortium in a similar way as stated in Proposition 2. Specifically, when the price is relatively high, there is no need to subsidize manufacturer, and the government should only subsidize patients. When the price is medium, the government should subsidize both patients and manufacturers. When the price p is relatively low, the government needs to subsidize the manufacturer to provide incentive to increase the efficacy of the drug e. For ease of exposition, we summarize the optimal subsidy policy that corresponds to each of the four settings in Table 2.

Table 2 Summary of optimal subsidy policies for all four settings

	Payment scheme	
Pricing Scheme	(A) Sales-based	(B) Outcome-based
(1) Endogenous	Subsidize manufacturer	Subsidize manufacturer
(2) Exogenous	When p is high, subsidize patients	When p is high, subsidize patients
	When p is medium, subsidize both	When p is medium, subsidize both
	When p is low, subsidize manufacturer	When p is low, subsidize manufacturer

5. Extension: Uncertain Efficacy

We extend the base model presented in Section 3 to capture randomness in drug efficacy. More specifically, we let $e+x$ be the realized efficacy of the drug after clinical trials, where e is the target efficacy and x is the realization of random error X that is uniformly distributed in the range $[-\varepsilon,\varepsilon]$ (i.e., $X \sim U[-\varepsilon,\varepsilon]$). To ensure that the realized efficacy $e+x \in [0,1]$, we shall focus on the case when ε satisfies $e+\varepsilon \leq 1$ and $e-\varepsilon \geq 0$. This implies that, although the manufacturer invests in achieving a target efficacy e, it is uncertain whether the developed drug would eventually result in a higher or lower efficacy in real life. We model the interactions among the government, the manufacturer and the patients as a five-stage Stackelberg game:

0. A consortium determines the unit selling price *(for the exogenous pricing scheme only)*.

1. The government acts as the leader and has a budget B to allocate. The government selects the manufacturer subsidy α and the patient subsidy β to maximize patient welfare.

2. The manufacturer acts as a follower and sets the target efficacy e to maximize its profit, given the subsidies (α,β) and the demand $d(\alpha,\beta,X)$.

3. The manufacturer observes the realized efficacy $e+x$.

4. The manufacturer decides the unit selling price p by taking the demand $d(\alpha,\beta,x)$ and realized efficacy $e+x$ into consideration *(for the endogenous pricing scheme only)*.

5. The patients make the purchasing decision of the drug, given the subsidy β, the price p and the realized efficacy $e+x$. We assume that the market size is known and scaled to one for exposition.

By using backward induction, we solve this game for each of the four settings considered in Table 1. We show that when the efficacy is uncertain, the structural results obtained in Section 4 continue to hold. The details are provided in Appendix B.

6. Extension: Patient Welfare and Manufacturer's Profit

We consider the case in which the government cares about the manufacturer's profit $\pi_m(\alpha,\beta)$ and the patient welfare $W(\alpha,\beta)$ simultaneously. Instead of assuming a manufacturer's profit of $\pi_m(\alpha,\beta) > 0$, we define a new social welfare function $S(\lambda) = \lambda \cdot W(\alpha,\beta) + (1-\lambda)\cdot \pi_m(\alpha,\beta)$, where

$\lambda \in [0,1]$ is the relative emphasis on patient welfare. When $\lambda = 1$, the objective function corresponds to the base model presented in Section 4.

6.1. Setting (1A): Endogenous pricing scheme and sales-based payment scheme

Recall from Equation (13) that the patient welfare is $W(\alpha,\beta) = \frac{1}{64(1-\alpha)k(1-\beta)}$ and the manufacturer's profit is $\pi_m(\alpha,\beta) = \frac{1}{64(1-\alpha)k(1-\beta)}$. By considering these expressions along with the budget constraint $\frac{\alpha}{64(1-\alpha)^2k(1-\beta)^2} + \frac{\beta}{32(1-\alpha)k(1-\beta)^2} \leq B$, the government's problem for any given λ is

$$\pi_g(\alpha,\beta) = \max_{\alpha,\beta} \Big\{\lambda \cdot \Big(\frac{1}{64(1-\alpha)k(1-\beta)}\Big) + (1-\lambda)\cdot \Big(\frac{1}{64(1-\alpha)k(1-\beta)}\Big)\Big\}, \tag{21}$$

$$s.t.\ \tfrac{\alpha}{64(1-\alpha)^2k(1-\beta)^2} + \tfrac{\beta}{32(1-\alpha)k(1-\beta)^2} \leq B.$$

Note that in Setting (1A), the patient welfare $W(\alpha,\beta)$ is equal to the manufacturer's profit $\pi_m(\alpha,\beta)$. Therefore, although the objective function is different due to the concern about manufacturer profit, it results into the same government's problem as presented in Section 4.1. This means that when the government also cares about the manufacturer's profit $\pi_m(\alpha,\beta)$, the optimal subsidy policy (α,β) is equal to Proposition 1. Hence, for Setting (1A) it is optimal for the government to offer subsidies to manufacturers only (i.e., $\beta = 0$).

6.2. Setting (1B): Endogenous pricing scheme and outcome-based payment scheme

Recall from Equation (16) that in Setting (1B), the patient welfare is $W(\alpha,\beta) = \frac{1}{64(1-\alpha)k(1-\beta)}$ and the manufacturer's profit is $\pi_m(\alpha,\beta) = \frac{1}{64(1-\alpha)k(1-\beta)}$. By considering these expressions along with the budget constraint $\frac{\alpha}{64(1-\alpha)^2k(1-\beta)^2} + \frac{\beta}{32(1-\alpha)k(1-\beta)^2} \leq B$, the government's problem for any given λ is

$$\pi_g(\alpha,\beta) = \max_{\alpha,\beta} \Big\{\lambda \cdot \Big(\frac{1}{64(1-\alpha)k(1-\beta)}\Big) + (1-\lambda)\cdot \Big(\frac{1}{64(1-\alpha)k(1-\beta)}\Big)\Big\}, \tag{22}$$

$$s.t.\ \tfrac{\alpha}{64(1-\alpha)^2k(1-\beta)^2} + \tfrac{\beta}{32(1-\alpha)k(1-\beta)^2} \leq B.$$

Note that in Setting (1B), the patient welfare $W(\alpha,\beta)$ is also equal to the manufacturer's profit $\pi_m(\alpha,\beta)$. Therefore, although the objective function is different due to the concern about manufacturer profit, it results into the same government's problem as presented in Section 4.2. This means that the optimal subsidy (α,β) in Setting (1A) is equal to that obtained in Setting (1B), and the results of Section 4.2 continue to hold in Section 6.2.

Next, we compare the optimal price p^* of the sales- and outcome-base payment schemes, when the government cares about the manufacturer's profit and the patient welfare (with a relative emphasis λ on patient welfare). By substituting the optimal subsidy policy $(\alpha,\beta) = (\frac{1+128Bk-\sqrt{256Bk+1}}{128Bk}, 0)$ into the optimal price of Setting (1A) (as given in Equation (11)) and that of Setting (1B) (as given in Equation (14)), we obtain Corollary 2.

COROLLARY 2. *When the price is endogenously determined by the manufacturer and the government cares about the manufacturer's profit $\pi_m(\alpha,\beta)$ and the patient welfare $W(\alpha,\beta)$ simultaneously, the characteristics of the optimal price as established in Corollary 1 continue to hold.*

Corollary 2 indicates that the managerial insights obtained from Corollary 1 continue to hold when the government cares about the social welfare (with a relative emphasis λ on patient welfare). This means that the sales-based payment scheme results in a lower price compared to the outcome-based payment scheme when the subsidy budget is low (e.g., $B < k - \frac{1}{8}$). On the other hand, when the budget is high (e.g., $B \geq k - \frac{1}{8}$), the sales-based payment scheme results in higher prices compared to the outcome-based payment scheme. In addition, we note that the optimal social welfare $S^*(\alpha,\beta)$ is the same under the sales- and outcome-based payment schemes, and does not dependent on the relative emphasis λ (as the corresponding values of the optimal manufacturer's profit and patient welfare are the same in Equation (22)).

6.3. Setting (2A): Exogenous pricing scheme and sales-based payment scheme

Recall from Equation (18) that the patient welfare $W(\alpha,\beta) = \frac{\left(\sqrt[3]{p\frac{(1-\beta)p}{2(1-\alpha)k}} - (1-\beta)p\right)^2}{2\sqrt[3]{p\frac{(1-\beta)p}{2(1-\alpha)k}}}$ and the manufacturer's profit $\pi_m(\alpha,\beta) = p[1 - \frac{(1-\beta)p}{\sqrt[3]{p\frac{(1-\beta)p}{2(1-\alpha)k}}}] - (1-\alpha)k(\sqrt[3]{p\frac{(1-\beta)p}{2(1-\alpha)k}})^2$. By considering these expressions along with the budget constraint $\alpha k \sqrt[3]{p\frac{(1-\beta)p}{2(1-\alpha)k}}^2 + \beta p\,(1 - \frac{(1-\beta)p}{\sqrt[3]{p\frac{(1-\beta)p}{2(1-\alpha)k}}}) \leq B$, the government's problem for any given λ is

$$\pi_g(\alpha,\beta) =$$

$$\max_{\alpha,\beta}\Big\{\lambda\cdot\Big(\frac{\left(\sqrt[3]{p\frac{(1-\beta)p}{2(1-\alpha)k}} - (1-\beta)p\right)^2}{2\sqrt[3]{p\frac{(1-\beta)p}{2(1-\alpha)k}}}\Big) + (1-\lambda)\cdot\Big(p[1 - \frac{(1-\beta)p}{\sqrt[3]{p\frac{(1-\beta)p}{2(1-\alpha)k}}}] - (1-\alpha)k(\sqrt[3]{p\frac{(1-\beta)p}{2(1-\alpha)k}})^2\Big)\Big\}, \tag{23}$$

$$s.t.\ \alpha k \sqrt[3]{p\frac{(1-\beta)p}{2(1-\alpha)k}}^2 + \beta p\,(1 - \frac{(1-\beta)p}{\sqrt[3]{p\frac{(1-\beta)p}{2(1-\alpha)k}}}) \leq B.$$

Although the government's problem includes the manufacturer's profit, the budget constraint in Equation (23) is the same as in Section 4.3. Moreover, it is easy to check that the objective function is increasing in α and β, and the budget constraint is binding at the optimal solution. We establish the optimal subsidy policy (α,β) in Proposition (4).

PROPOSITION 4. *When the price is exogenously specified and a sales-based payment scheme is used, the optimal subsidy policy (α,β) is increasing in budget B and the budget constraint is binding. Moreover, the optimal subsidy policy (α,β) is uniquely determined.*

Hence, the structural results obtained in Proposition 2 continue to hold when the government cares about the manufacturer's profit $\pi_m(\alpha,\beta)$ and the patient welfare $W(\alpha,\beta)$ simultaneously.

6.4. Setting (2B): Exogenous pricing scheme and outcome-based payment scheme

Recall from Equation (20) that the patient welfare $W(\alpha,\beta) = \frac{p\,(1-(1-\beta)p)^3}{4(1-\alpha)k}$ and $\pi_m(\alpha,\beta) = \frac{p^2\,(1-(1-\beta)p)^2}{4(1-\alpha)k}$. By considering these expressions along with the budget constraint $\frac{\alpha p^2(1-(1-\beta)p)^2}{4(1-\alpha)^2k} + \frac{\beta p^2(1-(1-\beta)p)^2}{2(1-\alpha)k}) \leq B$, the government's problem for any given λ is

$$\pi_g(\alpha,\beta) = \max_{\alpha,\beta} \Big\{\lambda \cdot \big(\frac{p\,(1-(1-\beta)p)^3}{4(1-\alpha)k}\big) + (1-\lambda)\cdot\big(\frac{p^2\,(1-(1-\beta)p)^2}{4(1-\alpha)k}\big)\Big\}, \tag{24}$$

$$s.t.\ \tfrac{\alpha p^2(1-(1-\beta)p)^2}{4(1-\alpha)^2k} + \tfrac{\beta p^2(1-(1-\beta)p)^2}{2(1-\alpha)k} \leq B.$$

Note that the budget constraint in Equation (24) is the same as in Section 4.4. Moreover, it is easy to check that the objective function is increasing in α and β, and the budget constraint is binding at the optimal solution. We establish the optimal subsidy policy (α,β) in Proposition (5).

Proposition 5. *When the price is exogenously specified and an outcome-based payment scheme is used, the optimal subsidy policy (α,β) is increasing in budget B and the budget constraint is binding.*

There exists two thresholds θ_1 and θ_2 with $0<\theta_1<\theta_2<1$ so that it is optimal to subsidize patients only (i.e. $\alpha=0$) when $\lambda<\theta_1$, it is optimal to subsidize the manufacturer only (i.e. $\beta=0$) when $\lambda>\theta_2$, and else it is optimal to subsidize both manufacturer and patients (i.e. $\alpha>0$ and $\beta>0$).

Hence, the structural results obtained in Proposition 3 continue to hold when the government cares about the manufacturer's profit $\pi_m(\alpha,\beta)$ and the patient welfare $W(\alpha,\beta)$ simultaneously.

7. A Numerical Study Motivated by the Development of Spinraza

Let us consider a case study based on the drug Spinraza. In 2016, Spinraza was approved by the Food and Drug Administration (FDA) for patients with spinal muscular atrophy (SMA), a rare and often fatal genetic disease. The efficacy of Spinraza is $e=0.57$ (EMA 2017). In addition, the U.S. government delegated the pricing decision to the manufacturer Biogen (FDA 2017). The R&D cost of Spinraza is confidential but we shall assume that the average development cost of orphan drugs, ke^2, is $\$291,300,000$ (Jayasundara et al. 2019). To stimulate the R&D of Spinraza, the U.S. government provided a subsidy to the manufacturer Biogen through the Orphan Drug Act, including a 50% Tax Credit on R&D cost and a 30 million R&D grant (EvaluatePharma 2013). No subsidies were provided to the patients (FDA 2016). Using the average development cost of orphan drugs, this leads to a cost subsidy of $\alpha = 0.5 + \frac{30,000,000}{291,300,000} = 0.6$ and $\beta=0$. Moreover, we assume that Spinraza is developed to treat $2,900$ patients with SMA (Cure SMA 2019), so that the R&D cost per patient is $\frac{\$291,300,000}{2,900} = \$100,448$. We set the R&D cost per patient as $s\cdot ke^2 = \$100,448$, where s is a scaling factor to ensure $k\in(0,1)$. By setting $s=1/10^6$ and using the fact that $e=0.57$, we get $k=0.31$. Next, we estimate that $B=0.2$ (i.e., obtained through the budget constraint of

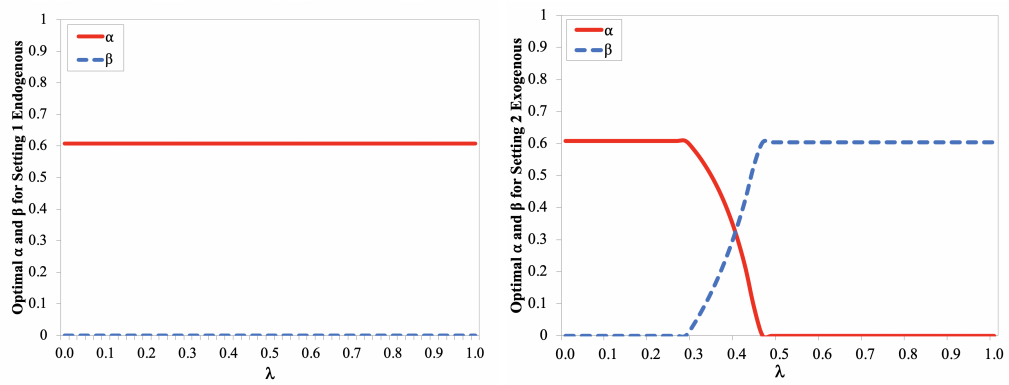

Figure 2 **Optimal subsidy policy** (α, β)

Equation (21) and by using the estimated value of $k = 0.31$) so that the optimal subsidy program is equal to (α, β)=$(0.6, 0)$, which mimics the actual subsidy provided by the government for the drug Spinraza. Our numerical analysis is based on the model presented in Section 6, where the government cares about the patient welfare and manufacturer's profit simultaneously.

7.1. Impact of relative emphasis λ

We examine the impact of the relative emphasis λ on the optimal subsidy policy, patient welfare, and manufacturer's profit. Figure 2 presents the numerical results on the optimal subsidy policy (α, β), as analyzed in Section 6. In alignment with the analytical results as stated in Section 6.1 and Proposition 1, Figure 2 shows that it is optimal to subsidize the manufacturer in the endogenous pricing setting (for any value of the relative emphasis λ); whereas, subsidies can be provided to both manufacturer and patients in the exogenous setting (depending on the relative emphasis λ), as discussed in Section 6.2 and Proposition 2.

Next, we examine the impact of λ on the patient welfare W, manufacturer's profit π_m and social welfare S. We observe from Figure 3 that the government can always improve the patient welfare, manufacturer's profit and social welfare in the exogenous pricing setting (Setting 2) by selecting an appropriate relative emphasis λ and the corresponding optimal subsidy policy (α, β). Clearly, the government needs to compromise on the manufacturer's profit to improve the patient welfare, however, the magnitude of this trade-off can be controlled through the parameter λ. For example, Figure 3 shows that the parameter value $\lambda = 0.3$ provides a good balance in this specific case study, such that, the exogenous pricing setting can achieve a higher welfare compared to the endogenous pricing setting, and still enable similar levels of profit for the manufacturer. The consortium cares about patient welfare and manufacturer profit, because the consortium consists of all stakeholders including the manufacturer. Therefore, we assume $\lambda = 0.3$ in the remainder of our analysis in this section. In other words, we assume that the consortium cares more about patient welfare W with weight of 0.7, than the manufacturer profit π_m with weight 0.3. In doing so, it will allow us to determine the exogenous price p^* specified by the consortium that is based on $\lambda = 0.3$.

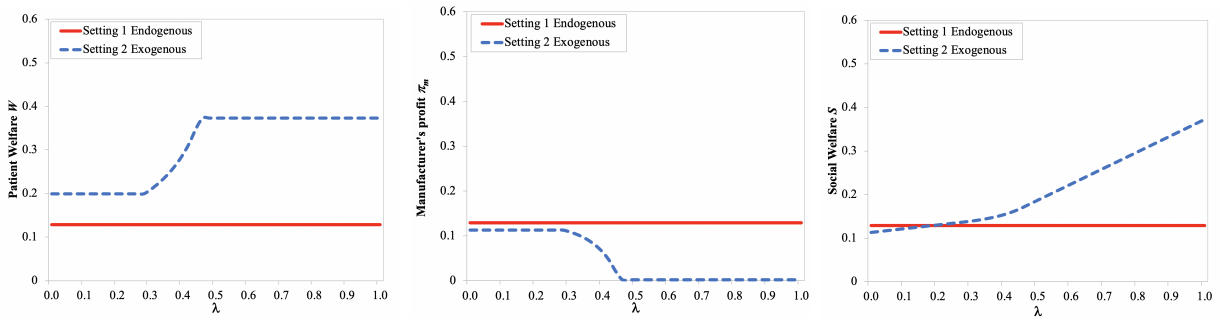

Figure 3 **Optimal patient welfare W, manufacturer's profit π_m and social welfare S**

7.2. Impact of budget B

Our main objective in this section is to evaluate the potential room for improvement in current practice, based on the Spinraza case study. For this purpose, we examine the patient welfare, manufacturer's profit and social welfare under the endogenous (Setting 1) and exogenous (Setting 2) pricing schemes, and evaluate their sensitivity to the subsidy budget B. Based on the insights obtained from Section 7.1, we focus on the case where the relative emphasis on patient welfare is $\lambda = 0.3$, and vary the budget in the range $B \in [0, 0.5]$. We assume that the endogenously-determined price is $p = 0.52$ (i.e., obtained through Equation (11), and closely aligns with the market price of Sprinraza) and the exogenous price determined by the consortium is $p = 0.38$ (i.e., generated through numerical optimization with the objective of maximizing social welfare at $\lambda = 0.3$).

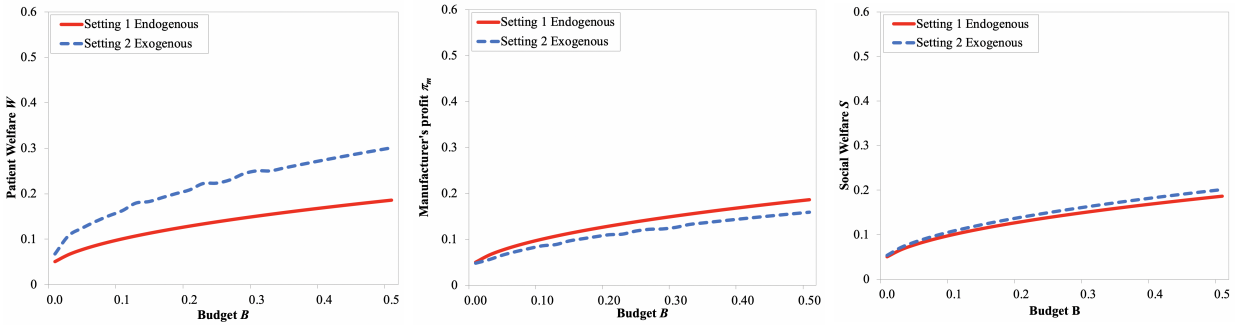

Figure 4 **Optimal patient welfare W, manufacturer's profit π_m and social welfare S**

Figure 4 presents the numerical results under the endogenous (Setting 1) and exogenous (Setting 2) pricing settings. Note that Sprinraza received a subsidy budget of $B = 0.2$. Therefore, at $B = 0.2$, Figure 4 shows that 62% improvement in patient welfare and 8% improvement in social welfare could have been achieved in practice, if the price was set by an independent consortium instead of the manufacturer. On the other hand, Figure 4 indicates that the manufacturer's profit would have decreased by 15%, as a direct consequence of the lower price suggested by the consortium. Nevertheless, Figure 4 shows that the exogenous pricing scheme continues to be an attractive

environment for manufacturers. Figure 4 indicates that, by delegating the pricing decision to an independent consortium, the government can achieve a higher social welfare with a lower price, and continue to provide an attractive environment for the manufacturer.

In addition, we analyze the impact of subsidy budget on patient welfare and manufacturer's profit. For example, if the government could have increased the budget from $B = 0.2$ to $B = 0.3$, then Figure 4 shows that the patient welfare, the manufacturer's profit and the social welfare would have increased by 17% (in the endogenous setting). However, as a consequence of higher subsidies, the unit selling price of Sprinraza would also have increased from $p = 0.52$ to $p = 0.60$. There is a complex inter-dependency between the subsidy budget, price and the resulting welfare. However, we observe that the relative impact of an additional subsidy is higher at low budgets (e.g., $B \leq 0.2$).

7.3. Analysis of the outcome-based payment scheme

We analyze the impact of adopting an outcome-based payment scheme on optimal prices. Note that the patient welfare, manufacturer's profit and social welfare obtained under the outcome-based payment scheme are the same as those reported in Figure 4. This aligns with our analytical results, as we showed that optimal prices in the outcome-based payment scheme are adjusted in such a way that the patient welfare and manufacturer profit remain the same as the sales-based payment scheme. Therefore, it is critical to understand the magnitude of the difference between the prices of the outcome-based and sales-based payment schemes. Figure 5 presents the optimal price of Spinraza under all four settings (i.e., the endogenous price is generated based on analytical results, whereas the exogenous price is obtained through numerical optimization with the objective of maximizing the social welfare at $\lambda = 0.3$). Figure 5 provides critical managerial insights: if the subsidy budget is low (e.g., $B \leq 0.2$), then the outcome-based payment scheme may result in higher prices compared to the sales-based scheme (in both endogenous and exogenous settings). This implies that patients for whom the drug is effective may have to pay a higher price. This observation validates the current public concern on the outcome-based payment scheme. On the other hand, we observe that the outcome-based payment may be effective in reducing prices at higher levels of subsidy budget (in both endogenous and exogenous settings). The underlying intuition is that subsidies start absorbing the system's risks (instead of the patients for whom the drug is effective) as the budget increases. These managerial insights shed light on the open debate on the social implications of the outcome-based payment scheme.

To summarize, our analysis provides the following insights for policy-makers and pharmaceutical manufacturers:

1. If the price is endogenously determined by the pharmaceutical manufacturer, it is optimal for the government to offer subsidies to the manufacturer only. This result complies with the current

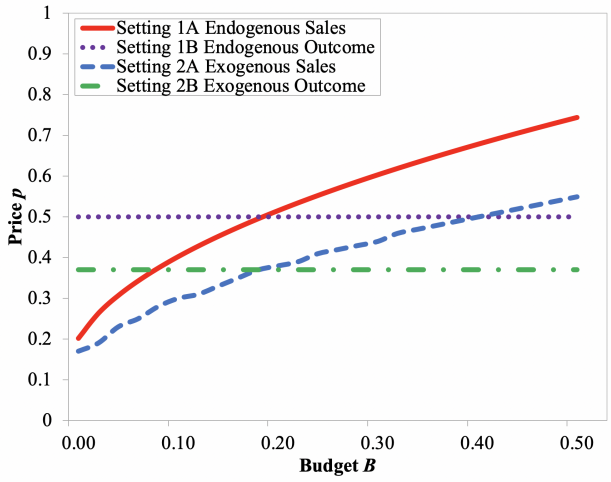

Figure 5 **Optimal price p for all four settings**

practice, despite growing reactions against it. However, if the pricing decision is delegated to an independent consortium, we show that it can be optimal to subsidize both the manufacturer and patients (depending on the price and budget) .

2. The Spinraza case study showed that the manufacturer's profit and social welfare achieved with exogenous pricing were similar to those of endogenous pricing (see Figure 4). However, exogenous pricing was capable of leveraging the patient welfare significantly (i.e., 62% improvement compared to endogenous pricing).

3. Our results complement the open public debate on outcome-based payment: adopting outcome-based payment schemes might trigger higher prices (see Figure 5) if the government budget for subsidies is low.

8. Conclusions

The R&D costs and timelines for developing an orphan drug could be as intensive as its non-orphan counterparts. However, the market for an orphan drug is restricted to only a few hundreds of thousands of patients. Several pharmaceutical companies have therefore been reluctant about investing in rare disease research, and this has led to an important problem: only 500 out of 7,000 known rare diseases have some form of medical treatments. To address this problem, several new initiatives are being proposed or tested in pilot programs. Among these, we focus on subsidy programs, innovative pricing and outcome-based payment schemes. In particular, we consider an exogenous pricing strategy, where an independent consortium is delegated to set the price of orphan drugs. This is a new initiative with a first successful example in BeNeLuxA. In addition, we consider an outcome-based payment scheme, "No Cure No Pay," which was proposed for orphan drugs.

Inspired by these initiatives, we build analytical models to understand their implications on drug prices, R&D efforts as well as patient welfare and manufacturer's profit. Although these initiatives

are widely discussed as part of open public debate, their implications on patients and manufacturers are not clearly understood. To the best of our knowledge, this study is one of the first attempts to analytically formalize and analyze them in the context of rare diseases. For this purpose, we build a Stackelberg game that captures the strategic interactions among the government, the pharmaceutical manufacturer and patients. For each different pricing and payment scheme, we characterize an optimal allocation of a limited subsidy budget.

Our analysis provides several insights for policy-makers and pharmaceutical companies: (1) we show that it is optimal to offer subsidies to the pharmaceutical manufacturer only, if the pricing decision is delegated to the manufacturer. This finding supports the current practice, although there is an intense public reaction against it. The underlying intuition of the optimal policy is to encourage R&D efforts and improve the amount of available treatments with higher efficacy. (2) If the price is delegated to an independent consortium, it can be optimal to subsidize both manufacturers and patients, depending on the price and budget. In addition, our numerical analysis shows that exogenous pricing can be effective in improving patient welfare by reducing prices. In practice, exogenous pricing is mostly criticised because of its potential for restricting the profitability of pharmaceutical manufacturers. However, our analysis shows that exogenous pricing would indeed continue to provide an attractive business environment for the industry. As a direct implication, we believe that this would encourage further communication between healthcare policy-makers and pharmaceutical companies, and stimulate managed entry programs. (3) Our findings support the public concern on outcome-based payments. We show that patients for whom the drug is effective might have to pay higher prices, if the government budget for subsidies is low.

Future research could investigate other managed-entry programs, such as conditional reimbursement. As more pilot programs continue to run in practice, empirical studies could be conducted based on real-world data. Another stream of research could extend our models and insights in the context of personalized medicine.

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Appendix A: Alternative Government's Objective

To examine the robustness of our results, we consider an alternative government's objective that maximizes the demand, instead of the patient welfare. We reformulate the government's problem for each of the four settings shown in Table 1.

Setting (1A): Endogenous pricing scheme and sales-based payment scheme

In Setting (1A), the demand of the drug is given by $d(\alpha,\beta) = (1 - \frac{(1-\beta)p}{e})$. We reformulate the government's problem as

$$\pi_g(\alpha,\beta) = \max_{\alpha,\beta}\{1 - \frac{(1-\beta)p}{e}\},$$
$$s.t.\ \alpha k e^2 + \beta p[1 - \tfrac{(1-\beta)p}{e}] \le B.$$

By using the optimal price $p^* = \frac{1}{16(1-\alpha)k(1-\beta)^2}$ and the optimal target efficacy $e^* = \frac{1}{8(1-\alpha)k(1-\beta)}$, we find that the demand is $d^*(\alpha,\beta) = \frac{1}{2}$.

Remark 1. By using an alternative objective function for the government that maximizes the demand, we obtain that the optimal demand is $d^*(\alpha,\beta) = \frac{1}{2}$ for Setting (1A). In this case, the optimal demand $d^*(\alpha,\beta)$ is independent of the subsidy policy (α,β).

Setting (1B): Endogenous pricing scheme and outcome-based payment scheme

In Setting (1B), the demand of the drug is given by $d(\alpha,\beta) = (1 - (1-\beta)p)$. We reformulate the government's problem as

$$\pi_g(\alpha,\beta) = \max_{\alpha,\beta}\{1 - (1-\beta)p\},$$
$$s.t.\ \alpha k e^2 + e\beta p[1 - \tfrac{(1-\beta)p}{e}] \le B.$$

By using the optimal price $p^* = \frac{1}{2(1-\beta)}$ and the optimal target efficacy $e^* = \frac{1}{8(1-\alpha)k(1-\beta)}$, we find that the demand is $d^*(\alpha,\beta) = \frac{1}{2}$.

Remark 2. By using an alternative objective function for the government that maximizes the demand, we obtain that the optimal demand is $d^*(\alpha,\beta) = \frac{1}{2}$ for Setting (1B). In this case, the optimal demand $d^*(\alpha,\beta)$ is independent of the subsidy policy (α,β).

Setting (2A): Exogenous pricing scheme and sales-based payment scheme

In Setting (2A), the demand of the drug is given by $d(\alpha,\beta) = (1 - \frac{(1-\beta)p}{e})$. We reformulate the government's problem as

$$\pi_g(\alpha,\beta) = \max_{\alpha,\beta}\{1 - \frac{(1-\beta)p}{e}\},$$
$$s.t.\ \alpha k e^2 + \beta p[1 - \tfrac{(1-\beta)p}{e}] \le B.$$

By using the optimal target efficacy $e^* = \sqrt[3]{p\frac{(1-\beta)p}{2(1-\alpha)k}}$, we reformulate the government's problem as

$$\pi_g(\alpha,\beta) = \max_{\alpha,\beta}\{1 - \frac{(1-\beta)p}{\sqrt[3]{p\,\frac{(1-\beta)p}{2(1-\alpha)k}}}\},$$

$$s.t.\ \alpha k \sqrt[3]{p\,\frac{(1-\beta)p}{2(1-\alpha)k}}^2 + \beta p\,[1 - \frac{(1-\beta)p}{\sqrt[3]{p\,\frac{(1-\beta)p}{2(1-\alpha)k}}}] \le B.$$

Because the government's expenditure is increasing in α and β, the budget constraint is binding at the optimal solution. Although the objective function is different (due to maximizing the demand), the budget constraint is exactly the same as presented in Equation (18). Therefore, the structural results proposed in Proposition 3 continue to hold when the government's objective is to maximize demand.

REMARK 3. By using an alternative objective function for the government that maximizes the demand, we obtain the same optimal subsidy policy for Setting (2A).

Setting (2B): Exogenous pricing scheme and outcome-based payment scheme

In Setting (2B) the demand of the drug is given by $d(\alpha,\beta) = (1-(1-\beta)p)$. We reformulate the government's problem as

$$\pi_g = \max_{\alpha,\beta}\{1-(1-\beta)p\},$$

$$s.t.\ \alpha k e^2 + e\beta p[1 - \tfrac{(1-\beta)p}{e}] \le B.$$

By using the optimal target efficacy $e^* = \frac{p(1-(1-\beta)p)}{2(1-\alpha)k}$, we reformulate the government's problem as

$$\pi_g = \max_{\alpha,\beta}\{1-(1-\beta)p\},$$

$$s.t.\ \tfrac{\alpha p^2(1-(1-\beta)p)^2}{4(1-\alpha)^2 k} + \tfrac{\beta p^2(1-(1-\beta)p)^2}{2(1-\alpha)k} \le B.$$

We observe that the government's objective is only increasing in β and the budget constraint is binding at the optimal solution.

REMARK 4. By using an alternative objective function for the government that maximizes the demand, we obtain that it is optimal to subsidize patients only (i.e. $\alpha = 0$) for Setting (2B). The optimal patient subsidy satisfies $\beta^* = \frac{c}{3p^4} + \frac{p^8+p^6-2p^7}{c} - \frac{2(p^3-p^4)}{3p^4}$ where $c = \sqrt[3]{3\sqrt{3}\sqrt{Bkp^{16}(27Bk-2p^4+6p^3-6p^2+2p)}+p^8(27Bk-p^4+3p^3-3p^3+p)}$.

Appendix B: Uncertain Efficacy

We consider an extension to the base model presented in Section 3 that captures randomness in drug efficacy. By using backward induction, we derive optimal subsidy policies for each of the four settings shown in Table 1.

Setting (1A): Endogenous pricing scheme and sales-based payment scheme

After the efficacy $e+x$ is realized, a patient will purchase the drug if $V \geq \frac{(1-\beta)p}{e+x}$, and purchase nothing, otherwise. As $V \sim U[0,1]$, the demand under the subsidy policy (α,β) and the realized efficacy $e+x$ is given as

$$d(\alpha,\beta,x) = Prob\{V \geq \frac{(1-\beta)\,p}{e+x}\} = 1 - \frac{(1-\beta)p}{e+x}. \tag{25}$$

Hence, the demand $d(\alpha,\beta,x)$ is increasing in the realized efficacy $e+x$. Subsequently, we compute the patient welfare $W(\alpha,\beta,x)$ under the realized efficacy $e+x$ as

$$W(\alpha,\beta,x) = \int_{\frac{(1-\beta)p}{e+x}}^{1} [(e+x)v - (1-\beta)p]dv = \frac{((e+x)-(1-\beta)\,p)^2}{2(e+x)}. \tag{26}$$

Next, we determine the manufacturer's optimal price. Note that the manufacturer decides on the unit selling price p after the efficacy $e+x$ is realized. Therefore, the manufacturer's pricing problem given the subsidy policy (α,β) can be reformulated as

$$\max_{p} \{p\,[1 - \frac{(1-\beta)\,p}{e+x}]\}. \tag{27}$$

By solving the manufacturer's pricing problem, the optimal unit selling price $p^*(x)$ given the realization x is

$$p^*(x) = \frac{e+x}{2(1-\beta)}. \tag{28}$$

We observe in Equation (28) that the manufacturer will charge a higher price p, if the government offers a higher patient subsidy β, as a portion of the price is shared by the government. By using Equation (28), we determine the manufacturer's profit. For any given subsidy policy (α,β), the manufacturer's objective function is formulated as

$$\pi_m(\alpha,\beta) = \max_{e} \Big\{ \int_{-\varepsilon}^{\varepsilon} [\frac{e+x}{4(1-\beta)} - (1-\alpha)ke^2] \frac{1}{2\varepsilon} dx \Big\} = \max_{e} \Big\{ \frac{e}{4(1-\beta)} - (1-\alpha)ke^2 \Big\}. \tag{29}$$

Using Equation (29), the optimal target efficacy e^* satisfies

$$e^* = \frac{1}{8(1-\alpha)k(1-\beta)}. \tag{30}$$

We observe in Equation (30) that the optimal target efficacy e^* is the same as the one of the base model (i.e., see Equation (12)). Moreover, we observe that the manufacturer subsidy α and the patient subsidy β have an identical beneficial effect on the optimal target efficacy e^*. By considering Equations (28) and (30), we obtain the corresponding patient welfare under the realization $e+x$ as $W(\alpha,\beta,x) = \frac{1+8(1-\alpha)(1-\beta)kx}{64(1-\alpha)k(1-\beta)}$. Hence, the government's objective is represented as follows

$$\pi_g(\alpha,\beta) = \max_{\alpha,\beta} \Big\{ \int_{-\varepsilon}^{\varepsilon} [\frac{1+8(1-\alpha)(1-\beta)kx}{64(1-\alpha)k(1-\beta)}] \frac{1}{2\varepsilon} dx \Big\} = \max_{\alpha,\beta} \Big\{ \frac{1}{64(1-\alpha)k(1-\beta)} \Big\}. \tag{31}$$

We denote $E[M(\alpha,\beta,x)]$ as the expected government's expenditure, which is given by

$$\begin{aligned} E[M(\alpha,\beta,x)] &= \int_{-\varepsilon}^{\varepsilon} \Big[\frac{\alpha}{64(1-\alpha)^2k(1-\beta)^2} + \frac{\beta(1+8(1-\alpha)(1-\beta)kx)}{32(1-\alpha)k(1-\beta)^2}\Big]\frac{1}{2\varepsilon}dx \\ &= \frac{\alpha}{64(1-\alpha)^2k(1-\beta)^2} + \frac{\beta}{32(1-\alpha)k(1-\beta)^2}. \end{aligned} \tag{32}$$

Given Equations (31)-(32), the government's problem is written as

$$\pi_g(\alpha,\beta) = \max_{\alpha,\beta}\Big\{\frac{1}{64(1-\alpha)k(1-\beta)}\Big\} \tag{33}$$

$$s.t.\ \tfrac{\alpha}{64(1-\alpha)^2k(1-\beta)^2} + \tfrac{\beta}{32(1-\alpha)k(1-\beta)^2} \le B.$$

We observe in Equation (33) that the government's objective in this extension is the same as the government's objective in Equation (13). This means that when the efficacy is uncertain, it is optimal for the government to offer subsidies to manufacturers only (i.e., $\beta = 0$) and the structural results obtained in Section 4.1 are robust and continue to hold.

Remark 5. By considering an extension with uncertain efficacy, we obtain the same government's objective $\pi_g(\alpha,\beta)$ and manufacturer's profit $\pi_m(\alpha,\beta)$, and can also obtain the same structural results regarding the optimal subsidy policy (α,β) for Setting (1A).

Setting (1B): Endogenous pricing scheme and outcome-based payment scheme

We consider Setting (1B) where the price is endogenously determined and the manufacturer uses outcome-based payment. Once the drug efficacy $e+x$ is realized, the manufacturer will receive payment from each patient only when the drug is efficacious (i.e., with probability $e+x$). We reformulate the demand $d(\alpha,\beta,x)$ and patient welfare $W(\alpha,\beta,x)$ under the outcome-based payment scheme. The patient pays the effective price $(1-\beta)p$ and the government pays βp with probability $e+x$. Hence, a patient will accept the drug if $(e+x)(V-(1-\beta)p) \ge 0$, and it is sufficient to have $V \ge (1-\beta)p$. Because $V \sim U[0,1]$, we formulate the demand under the realized efficacy $e+x$ as

$$d(\alpha,\beta,x) = Prob\{V \ge (1-\beta)\,p\} = 1-(1-\beta)\,p. \tag{34}$$

We observe in Equation (34) that the demand $d(\alpha,\beta,x)$ for the outcome-based payment scheme is not a function of the realized efficacy $e+x$. By considering the fact that a patient will purchase the drug if $V \ge (1-\beta)p$ and $V \sim U[0,1]$, we compute the patient welfare $W(\alpha,\beta,x)$ under the realized efficacy $e+x$ as

$$W(\alpha,\beta,x) = \int_{(1-\beta)\,p}^{1} [(e+x)(v-(1-\beta)\,p]dv = \frac{1}{2}(e+x)(1-(1-\beta)\,p)^2. \tag{35}$$

Next, we determine the manufacturer's optimal price. Note that the manufacturer decides on the unit selling price p after the efficacy $e+x$ is realized. Therefore, the manufacturer's pricing problem for subsidy policy (α,β) is reformulated as

$$\max_{p}\{p\,[1-(1-\beta)\,p]\}. \tag{36}$$

By solving the manufacturer's pricing problem, the optimal unit selling price $p^*(x)$ under the realization x satisfies

$$p^*(x)=\frac{1}{2(1-\beta)}. \tag{37}$$

We observe in Equation (37) that the optimal unit selling price $p^*(x)$ only depends on the patient subsidy β. If the government offers a higher patient subsidy β, the manufacturer will charge a higher price p. The manufacturer sets the target efficacy e before the efficacy $e+x$ is realized. Hence, for any given subsidy policy (α,β), the manufacturer's objective function is reformulated as

$$\pi_m(\alpha,\beta)=\max_{e}\{\int_{-\varepsilon}^{\varepsilon}[\frac{1}{4(1-\beta)}-(1-\alpha)ke^2]\frac{1}{2\varepsilon}dx\}=\max_{e}\{\frac{1}{4(1-\beta)}-(1-\alpha)ke^2\}. \tag{38}$$

Using Equation (34), the optimal target efficacy e^* satisfies

$$e^*=\frac{1}{8(1-\alpha)k(1-\beta)}. \tag{39}$$

We observe in Equation (39) that the optimal target efficacy e^* is the same as the one obtained in the base (i.e., see Equation (15)). By considering Equations (37) and (39), we obtain the corresponding patient welfare under the realization $e+x$ as $W(\alpha,\beta,x)=\frac{1+8(1-\alpha)(1-\beta)kx}{64(1-\alpha)k(1-\beta)}$. By using Equation (37)-(39), the government's problem is written as

$$\pi_g(\alpha,\beta)=\max_{\alpha,\beta}\Big\{\frac{1}{64(1-\alpha)k(1-\beta)}\Big\} \tag{40}$$

$$s.t.\ \tfrac{\alpha}{64(1-\alpha)^2k(1-\beta)^2}+\tfrac{\beta}{32(1-\alpha)k(1-\beta)^2}\le B.$$

We observe in Equation (40) that the government's objective based on the outcome-based payment scheme is equal to the government's objective based on the sales-based payment scheme presented in Equation (33). This means that it is optimal for the government to offer subsidies to manufacturers only (i.e., $\beta=0$) while using the outcome-based payment scheme. Hence, the structural results obtained in Section 4.2 are robust and continue to hold under random efficacy.

Remark 6. By considering an extension with uncertain efficacy, we obtain the same government's objective $\pi_g(\alpha,\beta)$ and manufacturer's profit $\pi_m(\alpha,\beta)$, and can also obtain the same structural results regarding the optimal subsidy policy (α,β) for Setting (1B).

Setting (2A): Exogenous pricing scheme and sales-based payment scheme

In Setting (2A), the demand $d(\alpha,\beta,x)$ and the patient welfare $W(\alpha,\beta,x)$ are equal to those in Setting 2A. Recall from Equations (25) and (26) that $d(\alpha,\beta,x)=(1-\frac{(1-\beta)p}{e+x})$ and $W(\alpha,\beta,x)=\frac{((e+x)-(1-\beta)p)^2}{2(e+x)}$ under the realization $e+x$. In Setting (2A), the manufacturer can only set the target efficacy e before the actual efficacy $e+x$ is realized. To maximize the profit, the manufacturer's problem is given by

$$\begin{aligned}\pi_m(\alpha,\beta)&=\max_e\Big\{\int_{-\varepsilon}^{\varepsilon}p\,[1-\frac{(1-\beta)p}{e+x}]-(1-\alpha)ke^2]\frac{1}{2\varepsilon}dx\Big\}\\&=\max_e\Big\{\frac{((1-\beta)p^2)(ln(e-\varepsilon)-ln(e+\varepsilon))-2(1-\alpha)ke^2\varepsilon}{2\varepsilon}\Big\}\end{aligned}\tag{41}$$

Using Equation (41), we derive the optimal target efficacy e^* as

$$e^*=\frac{2\sqrt[3]{2}(1-\alpha)k\varepsilon^2}{\Delta}+\frac{\Delta}{6\sqrt[3]{2}(1-\alpha)k},\tag{42}$$

where,

$$\Delta=\sqrt[3]{\sqrt{((108(1-\alpha)^2k^2(1-\beta)p^2)^2-6912((1-\alpha)k)^3((1-\alpha)k\varepsilon^2)^3}-108(1-\alpha)^2k^2(1-\beta)p^2}.$$

By considering Equation (42), we obtain the corresponding patient welfare $W(\alpha,\beta,x)$. Note that the government determines the subsidy policy (α,β) before the efficacy $e+x$ is realized. Hence, the government's objective is represented as follows

$$\pi_g(\alpha,\beta)=\max_{\alpha,\beta}\Big\{\int_{-\varepsilon}^{\varepsilon}\frac{(\frac{2\sqrt[3]{2}(1-\alpha)k\varepsilon^2}{\Delta}+\frac{\Delta}{6\sqrt[3]{2}(1-\alpha)k}+x)-(1-\beta)p)^2}{2(\frac{2\sqrt[3]{2}((1-\alpha)k\varepsilon^2}{\Delta}+\frac{\Delta}{6\sqrt[3]{2}((1-\alpha)k)}+x)}\frac{1}{2\varepsilon}\Big\}.\tag{43}$$

The analysis of the government's problem in this extension for Setting (2A) is intractable and we shall defer such analysis as future research.

Setting (2B): Exogenous pricing scheme and outcome-based payment scheme

In Setting (2B), the demand $d(\alpha,\beta)$ and the patient welfare $W(\alpha,\beta,x)$ are equal to those in Setting 2B. Recall from Equations (34) and (35) that $d(\alpha,\beta,x)=(1-(1-\beta)p)$ and $W(\alpha,\beta,x)=\frac{1}{2}(e+x)(1-(1-\beta)p)^2$. To maximize the profit, the manufacturer's problem is given by

$$\pi_m(\alpha,\beta)=\max_e\Big\{\int_{-\varepsilon}^{\varepsilon}[(e+x)p\,[1-(1-\beta)p]-(1-\alpha)ke^2]\frac{1}{2\varepsilon}dx\Big\}=\max_e\Big\{e\,p[1-(1-\beta)p]-(1-\alpha)ke^2\Big\}.\tag{44}$$

Using Equation (44), the optimal target efficacy e^* satisfies

$$e^*=\frac{p(1-(1-\beta)p)}{2(1-\alpha)k}.\tag{45}$$

We observe in Equation (45) that the optimal target efficacy e^* is the same as the one in the base model presented in Equation (19). The government determines the subsidy policy (α, β) before the efficacy $e+x$ is realized. Hence, the government's objective is represented as follows:

$$\pi_g(\alpha,\beta) = \max_{\alpha,\beta}\Big\{\int_{-\varepsilon}^{\varepsilon}\big[\frac{p(1-(1-\beta)p)^3}{4(1-\alpha)k}+\frac{1}{2}x(1-(1-\beta)p)^2\big]\frac{1}{2\varepsilon}dx\Big\} = \max_{\alpha,\beta}\Big\{\frac{p(1-(1-\beta)p)^3}{4(1-\alpha)k}\Big\}. \quad (46)$$

We denote $E[M(\alpha,\beta,x)]$ as the expected government's expenditure, which is given by

$$\begin{aligned} E[M(\alpha,\beta,x)] &= \int_{-\varepsilon}^{\varepsilon}\big[\frac{\alpha p^2(1-(1-\beta)p)^2}{4(1-\alpha)^2k}+\frac{\beta p^2(1-(1-\beta)p)^2}{2(1-\alpha)k}+\beta px(1-(1-\beta)p)\big]\frac{1}{2\varepsilon} \\ &= \frac{\alpha p^2(1-(1-\beta)p)^2}{4(1-\alpha)^2k}+\frac{\beta p^2(1-(1-\beta)p)^2}{2(1-\alpha)k}. \end{aligned} \quad (47)$$

Given Equations (46)-(47), the government's problem is written as

$$\begin{aligned} &\pi_g(\alpha,\beta) = \max_{\alpha,\beta}\Big\{\frac{p(1-(1-\beta)p)^3}{4(1-\alpha)k}\Big\}, \quad (48)\\ &s.t.\ \tfrac{\alpha p^2(1-(1-\beta)p)^2}{4(1-\alpha)^2k}+\tfrac{\beta p^2(1-(1-\beta)p)^2}{2(1-\alpha)k}\le B. \end{aligned}$$

We observe in Equation (48) that the government's objective in this extension is equal to the government's objective in Equation (20). Hence, the structural results from Section 4.4 are robust and continue to hold when the efficacy is uncertain.

REMARK 7. By considering an extension with uncertain efficacy, we obtain the same government's objective $\pi_g(\alpha,\beta)$ and manufacturer's profit $\pi_m(\alpha,\beta)$, and can also obtain the same structural results regarding the optimal subsidy policy (α,β) for Setting (2B).

Appendix C: Proofs

Proof of Proposition 1 For any given α, we determine the optimal patient subsidy β as a function of α by using the fact that the budget constraint of Equation (13) is binding. We get

$$\beta(\alpha) = \frac{(1-\alpha)(64Bk+1-64\alpha Bk)-\sqrt{2c-\alpha c+(1-\alpha)^2}}{c}$$
$$c = 64(1-\alpha)^2Bk > 0.$$

Since the patient welfare is increasing in α and β at the same rate, the objective function is equivalent to minimizing $(1-\alpha)(1-\beta)$. Hence, for any given α, we use the optimal $\beta(\alpha)$ to simplify the objective function as $Z(\alpha) = (1-\alpha)(1-\beta(\alpha))$ with a single decision variable α. Then by taking the first-order derivative of $Z(\alpha)$, we obtain

$$\frac{\partial Z(\alpha)}{\partial\alpha} = -\frac{(1-\alpha)}{2\sqrt{(1-\alpha)^2(1+64(2-\alpha)Bk)}} < 0.$$

It is easy to check that $(1+64(2-\alpha)Bk > 0)$, such that the objective function $Z(\alpha)$ decreases in α. To minimize $Z(\alpha)$, α should be as high as possible. Hence the optimal solution is $\beta = 0$. By substituting $\beta = 0$, we obtain the optimal $\alpha = \frac{1+128Bk-\sqrt{256Bk+1}}{128Bk}$. We further compute the corresponding $W^*(\alpha,\beta)$ and $\pi_m^*(\alpha,\beta)$ via substitution.

Proof of Proposition 2 By taking the first order derivative of π_g with respect to α and β, we obtain

$$\frac{\partial \pi_g}{\partial \alpha} = \frac{\sqrt[3]{2}\, c^2 - 2(1-\beta)^2 p^2}{6(\sqrt[3]{2})^2(1-\alpha)c} > 0$$

$$\frac{\partial \pi_g}{\partial \beta} = p - \frac{10(1-\alpha)kc^2(1-\beta) + \sqrt[3]{2}c}{6(1-\beta)(\sqrt[3]{2})^2} > 0$$

where $c = \sqrt[3]{\frac{(1-\beta)p^2}{(1-\alpha)k}}$. It is easy to check that $[c^2\sqrt[3]{2} - 2(1-\beta)^2p^2] > 0$ and we find that $\frac{\partial \pi_g}{\partial \alpha} > 0$. Notice that $\alpha k + \beta p < 1$ always holds, because at maximum demand $d(\alpha, \beta)$ and maximum efficacy e, the budget $B < 1$. Hence, $\frac{\partial \pi_g}{\partial \beta} > 0$. To show that the budget constraint is binding in the optimal solution, we denote $M(\alpha, \beta)$ as the government's expenditure (i.e., the left hand side of (18)) and by taking the first order derivative of $M(\cdot)$ with respect to α, β, we obtain

$$\frac{\partial M}{\delta \alpha} = \frac{(3 - \alpha + 2\beta - 2\alpha\beta)kc^2}{3\sqrt[3]{2}^2(1-\alpha)} > 0$$

$$\frac{\partial M}{\partial \beta} = p - \frac{\sqrt[3]{2}(3 - 2\alpha - 5(1-\alpha))kc^2}{3(1-\beta)} > 0$$

where $c = \sqrt[3]{\frac{(1-\beta)p^2}{(1-\alpha)k}}$. It is easy to check that $[3 - \alpha + 2\beta - 2\alpha\beta] > 0$, so $\frac{\partial M}{\delta \alpha} > 0$. Moreover, $3(1-\beta)p > \sqrt[3]{2}(3 - 2\alpha - 5(1-\alpha))kc^2$, and $\frac{\partial M}{\delta \beta} > 0$. We conclude that $M(\alpha, \beta)$ is increasing in both α and β and the budget constraint is binding. Next, by considering the objective function given in Equation (18) and by setting $x = \sqrt[3]{p\frac{(1-\beta)p}{2(1-\alpha)k}}$, we obtain

$$\pi_g(\alpha, \beta) = \max_{\alpha, x, \beta} \{\frac{x}{2} - (1-\beta)p + \frac{(1-\beta)^2p^2}{2x}\}$$

$$s.t.\ \alpha k\, x^2 + \beta p\,(1 - \tfrac{(1-\beta)p}{x}) \leq B.$$

By taking the first derivative of $\pi_g(\alpha, \beta)$ with respect to x and β, and using the first order condition (ignoring the bounds), we get $x = (1-\beta)p$. By using the fact that the budget constraint is binding and by substituting $x = (1-\beta)p$, we obtain

$$\alpha k (1-\beta)^2 p^2 = B$$

By taking the first order derivative of α and β with respect to p, we get $\frac{\delta \alpha}{\delta p} < 0$, $\frac{\delta \beta}{\delta p} > 0$. Hence, we conclude that the manufacturer subsidy α is decreasing in the unit selling price p and the patient subsidy β is increasing in the unit selling price p.

Proof of Proposition 3 We know that the government's objective is increasing in α and β as

$$\frac{\partial \pi_g}{\partial \alpha} = \frac{p(1 - (1-\beta)p)^3}{4(1-\alpha)^2 k} > 0,$$

$$\frac{\partial \pi_g}{\partial \alpha} = \frac{3p^2(1-(1-\beta)p)^2}{4(1-\alpha)k} > 0.$$

Moreover, we know that α and β are also increasing in the government's expenditure as

$$\frac{\partial M}{\partial \alpha} = \frac{p^2(1-(1-\beta)p)^2}{4(1-\alpha)^2 k} + \frac{\alpha p^2(1-(1-\beta)p)^2}{2(1-\alpha)^3 k} + \frac{\beta p^2(1-(1-\beta)p)^2}{2(1-\alpha)^2 k} > 0,$$

$$\frac{\partial M}{\partial \beta} = \frac{\alpha p^3(1-(1-\beta)p)}{2(1-\alpha)^2 k} + \frac{\beta p^3(1-(1-\beta)p)}{(1-\alpha)k} + \frac{p^2(1-(1-\beta)p)^2}{2(1-\alpha)k} > 0.$$

We assume that the subsidy policy (α, β) satisfies the binding constraint. Because the expenditure M is increasing in α and β, a small increment of β (denoted as $\Delta\beta$) will result in a small decrement of α (denoted as $-\Delta\alpha$). That is, given $\Delta\beta \to 0$, we have $\frac{\partial M}{\partial \beta} \cdot \Delta\beta = \frac{\partial M}{\partial \alpha} \cdot \Delta\alpha > 0$ so that the binding budget constraint still holds with $\frac{\partial M}{\partial \beta}\Delta\beta - \frac{\partial M}{\partial \alpha} \cdot \Delta\alpha = 0$ and we use ΔM to represent the value of $\frac{\partial M}{\partial \beta} \cdot \Delta\beta$. We calculate the increment of the government's objective resulting from the small increment of α and β:

$$\begin{aligned}\Delta\pi_g(\alpha,\beta) &= \frac{\partial \pi_g}{\partial \beta} \cdot \Delta\beta - \frac{\partial \pi_g}{\partial \alpha} \cdot \Delta\alpha \\ &= \Delta M\,[\frac{\partial \pi_g/\partial\beta}{\partial M/\partial\beta} - \frac{\partial \pi_g/\partial\alpha}{\partial M/\partial\alpha}] \\ &= \Delta M \cdot \frac{f_1}{f_2}\end{aligned}$$

where

$$f_1 = (1-\alpha)((5-\alpha)p - 2(1-\alpha))(1-(1-\beta)p)$$

$$f_2 = 2p(1+2\beta+\alpha-2\alpha\beta)(1+2\alpha p+3\beta p-3\alpha\beta p-\alpha-p)$$

By simplification, we check that the sign of $\Delta\pi_g(\alpha,\beta)$ is equal to the sign of $[(5-\alpha)p-2(1-\alpha)]$.

1. If for any $\alpha, \beta \in [0,1), \Delta\pi_g(\alpha,\beta) \geq 0$ always holds, then the government can always improve the patient welfare by increasing β at the cost of α. Hence, the optimal solution is to subsidize patients only (i.e., $\alpha^* = 0$ and $\beta^* = \beta_{max}$ that satisfies the binding budget constraint). For any $\alpha, \beta \in [0,1), \Delta\pi_g(\alpha,\beta) \geq 0$ holds if and only if for any $\alpha, \beta \in [0,1)$ the term $[(5-\alpha)p-2(1-\alpha)] \geq 0$ always holds, which requires

$$p \geq \max\{\frac{2(1-\alpha)}{(5-\alpha)}\} = \frac{2}{(5-\alpha_{max})}$$

2. If for any $\alpha, \beta \in [0,1), \Delta\pi_g(\alpha,\beta) \leq 0$ always holds, then the government can always improve the patient welfare by increasing α at the cost of β. Hence, the optimal solution is to subsidize manufacturers only (i.e., $\beta^* = 0$ and $\alpha^* = \alpha_{max}$ that satisfies the binding budget constraint). For any $\alpha, \beta \in [0,1), \Delta\pi_g(\alpha,\beta) \leq 0$ holds if and only if for any $\alpha, \beta \in [0,1)$ the term $[(5-\alpha)p-2(1-\alpha)] \leq 0$ always holds, which requires

$$p \leq \min\{\frac{2(1-\alpha)}{(5-\alpha)}\} = \frac{2(1-\alpha_{max})}{5}$$

3. Else when $\frac{2(1-\alpha_{max})}{5} < p < \frac{2}{(5-\alpha_{max})}$, $\Delta\pi_g(\alpha,\beta)$ can be either larger or smaller than 0. Given the budget constraint, $\Delta\pi_g(\alpha,\beta)$ is first increasing in α and then decreasing in α. Therefore, it is optimal to subsidize both patients and the manufacturers in this case.

Proof of Proposition 4 By taking the first order derivative of π_g with respect to α and β, we obtain

$$\frac{\partial \pi_g}{\partial \alpha} = \lambda \cdot \frac{\sqrt[3]{2}\,\Delta^2 - 2(1-\beta)^2 p^2}{6(\sqrt[3]{2})^2(1-\alpha)\Delta} + (1-\lambda)\cdot \frac{k\Delta^2}{(\sqrt[3]{2})^2}$$

$$\frac{\partial \pi_g}{\partial \beta} = \lambda \cdot \frac{1}{12}(10\,\sqrt[3]{2}\,(1-\alpha)k\,\Delta^2 + \frac{(\sqrt[3]{2})^2\Delta}{(1-\beta)} - 12p) + (1-\lambda)\cdot \frac{\sqrt[3]{2}\,p^2}{\Delta}$$

where $\Delta = \sqrt[3]{\frac{(1-\beta)p^2}{(1-\alpha)k}}$. Similar to Proposition 2, we denote $M(\alpha,\beta)$ as the government's expenditure (i.e., the left hand side of (51)) and by taking the first order derivative of $M(\cdot)$ with respect to α,β, we obtain

$$\frac{\partial M}{\delta \alpha} = \frac{(3-\alpha+2\beta-2\alpha\beta)k\Delta^2}{3\sqrt[3]{2}^2(1-\alpha)} > 0$$

$$\frac{\partial M}{\partial \beta} = p - \frac{\sqrt[3]{2}(3-2\alpha-5(1-\alpha))k\Delta^2}{3(1-\beta)} > 0.$$

From Proposition 2, we conclude that $M(\alpha,\beta)$ is increasing in both α and β. As the objective function π_g is also increasing in α and β, we know that we can solve the unique α^* and β^* based on the binding budget constraint.

Proof of Proposition 5 We know that the government's objective is increasing in α and β as

$$\frac{\partial \pi_g}{\partial \alpha} = \frac{p(1-(1-\beta)p)(\beta p\lambda - p + \lambda)}{4(1-\alpha)^2 k} > 0,$$

$$\frac{\partial \pi_g}{\partial \alpha} = \frac{p^2(2\lambda - p(1+\lambda-2\beta\lambda)}{4(1-)k} > 0.$$

Moreover, we know that α and β are also increasing in the government's expenditure as

$$\frac{\partial M}{\partial \alpha} = \frac{p^2(1-(1-\beta)p)^2}{4(1-\alpha)^2 k} + \frac{\alpha p^2(1-(1-\beta)p)^2}{2(1-\alpha)^3 k} + \frac{\beta p^2(1-(1-\beta)p)^2}{2(1-\alpha)^2 k} > 0,$$

$$\frac{\partial M}{\partial \beta} = \frac{\alpha p^3(1-(1-\beta)p)}{2(1-\alpha)^2 k} + \frac{\beta p^3(1-(1-\beta)p)}{(1-\alpha)k} + \frac{p^2(1-(1-\beta)p)^2}{2(1-\alpha)k} > 0.$$

We assume that the subsidy policy (α,β) satisfies the binding constraint. Because the expenditure M is increasing in α and β, a small increment of β (denoted as $\Delta\beta$) will result in a small decrement of α (denoted as $-\Delta\alpha$). That is, given $\Delta\beta \to 0$, we have $\frac{\partial M}{\partial \beta}\cdot\Delta\beta = \frac{\partial M}{\partial \alpha}\cdot\Delta\alpha > 0$ so that the binding budget constraint still holds with $\frac{\partial M}{\partial \beta}\Delta\beta - \frac{\partial M}{\partial \alpha}\cdot\Delta\alpha = 0$ and we use ΔM to represent the value of $\frac{\partial M}{\partial \beta}\cdot\Delta\beta$. We calculate the increment of the government's objective resulting from the small increment of α and β:

$$\Delta\pi_g(\alpha,\beta) = \frac{\partial \pi_g}{\partial \beta}\cdot\Delta\beta - \frac{\partial \pi_g}{\partial \alpha}\cdot\Delta\alpha$$

$$= \Delta M [\frac{\partial \pi_g / \partial \beta}{\partial M / \partial \beta} - \frac{\partial \pi_g / \partial \alpha}{\partial M / \partial \alpha}]$$
$$= \Delta M \cdot \frac{f_1}{f_2}$$

where

$$f_1 = (1-\alpha)(2(1+2\alpha p+3\beta p-3\alpha\beta p-\alpha-p)(p+\lambda-(2-\beta)p\lambda)$$
$$+ (1+\alpha+2\beta-2\alpha\beta)p(((5-3\beta)\lambda-2)p)-3\lambda)$$

$$f_2 = 2p(1+2\beta+\alpha-2\alpha\beta)(1+2\alpha p+3\beta p-3\alpha\beta p-\alpha-p)$$

By simplification, we check that the sign of $\Delta\pi_g(\alpha,\beta)$ is equal to the sign of $[(1-\alpha)(2(1+2\alpha p+3\beta p-3\alpha\beta p-\alpha-p)(p+\lambda-(2-\beta)p\lambda)+(1+\alpha+2\beta-2\alpha\beta)p(((5-3\beta)\lambda-2)p)-3\lambda)]$.

1. If for any $\alpha,\beta\in[0,1), \Delta\pi_g(\alpha,\beta)\le 0$ always holds, then the government can always improve the patient welfare by increasing α at the cost of β. Hence, the optimal solution is to subsidize manufacturers only (i.e., $\beta^*=0$ and $\alpha^*=\alpha_{max}$ that satisfies the binding budget constraint). For any $\alpha,\beta\in[0,1), \Delta\pi_g(\alpha,\beta)\le 0$ holds if and only if for any $\alpha,\beta\in[0,1)$ the term $[(1-\alpha)(2(1+2\alpha p+3\beta p-3\alpha\beta p-\alpha-p)(p+\lambda-(2-\beta)p\lambda)+(1+\alpha+2\beta-2\alpha\beta)p(((5-3\beta)\lambda-2)p)-3\lambda)]\le 0$ always holds, which requires

$$\lambda \ge \max\{\ \frac{2(1-\alpha)p(1-\alpha-p+\alpha(2-3\beta)p+3\beta p)-2(1-\alpha)(1+\alpha(1-2\beta)+2\beta)p^2}{(1-\alpha)(1+\alpha(1-2\beta)+2\beta)p+(3-(5-3\beta)p)-2(1-\alpha)(1-\alpha-p+\alpha(2-3\beta)p+3\beta p)(1-(2-\beta)p)}\}$$
$$= \frac{2(1-\alpha_{max})p(1-\alpha_{max}-p+2\alpha_{max}p-2(1-\alpha_{max})(1+\alpha_{max})p^2}{(1-\alpha_{max})(1+\alpha_{max})p+(3-5p)-2(1-\alpha_{max})(1-\alpha_{max}-p+2\alpha_{max}p)(1-2p)}$$

Hence, we obtain threshold $\theta_1 = \frac{2(1-\alpha_{max})p(1-\alpha_{max}-p+2\alpha_{max}p-2(1-\alpha_{max})(1+\alpha_{max})p^2}{(1-\alpha_{max})(1+\alpha_{max})p+(3-5p)-2(1-\alpha_{max})(1-\alpha_{max}-p+2\alpha_{max}p)(1-2p)}$.

2. If for any $\alpha,\beta\in[0,1), \Delta\pi_g(\alpha,\beta)\ge 0$ always holds, then the government can always improve the patient welfare by increasing β at the cost of α. Hence, the optimal solution is to subsidize patients only (i.e., $\alpha^*=0$ and $\beta^*=\beta_{max}$ that satisfies the binding budget constraint). For any $\alpha,\beta\in[0,1), \Delta\pi_g(\alpha,\beta)\ge 0$ holds if and only if for any $\alpha,\beta\in[0,1)$ the term $[(1-\alpha)(2(1+2\alpha p+3\beta p-3\alpha\beta p-\alpha-p)(p+\lambda-(2-\beta)p\lambda)+(1+\alpha+2\beta-2\alpha\beta)p(((5-3\beta)\lambda-2)p)-3\lambda)]\ge 0$ always holds, which requires

$$\lambda \le \min\{\ \frac{2(1-\alpha)p(1-\alpha-p+\alpha(2-3\beta)p+3\beta p)-2(1-\alpha)(1+\alpha(1-2\beta)+2\beta)p^2}{(1-\alpha)(1+\alpha(1-2\beta)+2\beta)p+(3-(5-3\beta)p)-2(1-\alpha)(1-\alpha-p+\alpha(2-3\beta)p+3\beta p)(1-(2-\beta)p)}\}$$
$$= \frac{2p(1-p+3\beta_{max}p)-2(1+2\beta_{max})p^2}{(1+2\beta_{max})p+(3-(5-3\beta_{max})p)-2(1-p+3\beta_{max}p)(1-(2-\beta_{max})p)}$$

Hence, we obtain threshold $\theta_2 = \frac{2p(1-p+3\beta_{max}p)-2(1+2\beta_{max})p^2}{(1+2\beta_{max})p+(3-(5-3\beta_{max})p)-2(1-p+3\beta_{max}p)(1-(2-\beta_{max})p)}$.

3. Else when $\theta_1<\lambda<\theta_2$, $\Delta\pi_g(\alpha,\beta)$ can be either larger or smaller than 0. Given the budget constraint, $\Delta\pi_g(\alpha,\beta)$ is first increasing in α and then decreasing in α. Therefore, it is optimal to subsidize both patients and the manufacturers in this case.