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Conditional Approval and Value-Based Pricing for New Health Technologies

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Abstract. Health technology assessments often inform decisions made by public payers, such as the UK's National Health Service, as they negotiate the pricing of companies' new health technologies. A common assessment mechanism compares the incremental cost-effectiveness ratio (ICER) of the new health technology, relative to a standard of care, to a maximum threshold on the cost per quality-adjusted life year. In much research and practice, these assessments may not distinguish between cost-per-patient and negotiated price, effectively ignoring the value-based-pricing principle that better health outcomes merit higher prices. Other research makes this distinction, but it does not account for uncertainty in the ICER associated with clinical trial data that are limited in size and scope. This paper models the strategic behavior of a payer and a company as they price a new health technology, and it considers the use of conditional approval (CA) schemes whose post-marketing trials reduce ICER uncertainty before final pricing decisions are made. Analytical results suggest a very different view of the value-based pricing negotiations underlying these schemes: interim prices used during CA post-marketing trials should reflect cost-sharing for the CA scheme, not just cost-effectiveness goals for a treatment. Moreover, the types of caps on interim prices used by entities such as the UK Cancer Drugs Fund may hinder the development of new technologies and lead to suboptimal CA designs. We propose a new risk-sharing mechanism to remedy this. Numerical results, calibrated to approval data of an oncology drug, illustrate the issues in a practical setting.

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1. Introduction

Many jurisdictions use health technology assessments (HTAs) when making reimbursement approval and pricing decisions about new health technologies (Panteli et al. 2015). Typically, HTAs follow soon after clinical "marketing authorization" by regulatory bodies, such as the European Medicines Agency and the UK's Medicines & Healthcare products Regulatory Agency, whose decisions are based on evidence of treatment safety and efficacy from clinical trials (European Medicines Agency 2022, Medicines and Healthcare Products Regulatory Agency 2023). Emanuel et al. (2020) review the purchasing processes of six countries and find that all except the United States have centralized, state-level mechanisms designed to improve health value for money.

In making access and reimbursement decisions, many HTAs compare a new health technology's incremental cost-effectiveness ratio (ICER), a widely used measure of cost-effectiveness, to a threshold (Claxton et al. 2015). The ICER is a ratio whose numerator measures the difference between a new technology's overall cost and that of an existing standard and whose denominator measures an analogous increment in health benefits. Overall costs include the price of the new technology (e.g., drug, device, diagnostic) and the costs of the broader treatment process in which it is used. Benefits are often measured in quality-adjusted life years (QALYs; e.g., Organisation for Economic Co-operation and Development 2019). A new technology is more likely be approved for reimbursement if its ICER is below a cost-per-QALY (CPQ) threshold that reflects a maximum willingness to pay for health. In the United Kingdom, for example, the relevant CPQ threshold might be 30,000£/QALY (National Institute for Health and Care Excellence 2014).

But there exist several important issues regarding how to make such access and reimbursement decisions for new health technologies. We note two of them here.

One important issue arises because incremental cost depends on the price of the new health technology. HTAs often do not explicitly distinguish the reimbursement price from the marginal cost to the for-profit company that provides the technology (European Commission 2018), nor the potential for the price to be an endogenous function of health value. But health economic surplus is central to *value-based pricing* initiatives that reward better health outcomes with better prices (Claxton et al. 2008) and, hence, a firm's profit margin. Here, surplus is the per-patient improvement in health-economic value times number of patients treated.

On the one hand, if the reimbursement is set to the health technology provider's marginal cost, then the payer takes all of the surplus—a disincentive for the company to further invest in new technologies. On the other hand, if the reimbursement price is set so that the estimated ICER exactly matches the CPQ threshold, then the provider of the technology captures all health surplus (Claxton 2007, Brouwer et al. 2021), which may raise concerns about inflationary effects. The European Commission (2018, p. 44) explicitly notes the importance of breaking up the per-patient price into costs and a surplus as a crucial part of obtaining fair and sustainable prices and splits of surpluses. Although this point of view is consistent with others' observations (e.g., Claxton 2007, Brouwer et al. 2021, Wouterse et al. 2023), those works have not explicitly modeled strategic behavior in price negotiations.

A second significant issue concerns uncertainty regarding the ICER of the new health technology. HTAs, which are based on limited data collected from patients who satisfy clinical trial inclusion criteria under controlled treatment conditions, provide only imperfect estimates regarding effectiveness, safety, and costs (Walker et al. 2012, Bravo et al. 2021), and the importance of including in HTAs the probability that a given technology is cost-effective is well established (O'Hagan and Stevens 2002, Claxton et al. 2005). Thus, for example, after a Phase III trial and an initial health economic assessment for a new drug, there may be value to considering additional options, beyond rejecting the new drug for reimbursement approval or adopting it with a negotiated price, options that can help reduce the potential of poorly calibrated reimbursement and pricing decisions.

Conditional-approval (CA) schemes are increasingly important options for reducing uncertainty. They use *post-marketing trials* that collect additional data regarding cost-effectiveness to better calibrate reimbursement approval and pricing decisions. Examples include the UK's first CA scheme, which was designed to use post-marketing data to update prices for multiple sclerosis therapies to maintain an ICER that matched a 36,000£/QALY threshold (UK Department of Health 2002), Sweden's pricing decision for Duodopa (Willis et al. 2010), the UK's patient access scheme with GSK for Votrient (Griffiths et al. 2011), "coverage with evidence development" schemes of the U.S.'s Centers for Medicare and Medicaid Services (Centers for Medicare and Medicaid Services 2014), and the UK's Cancer Drugs Fund (CDF; NHS England 2016) and Innovative Medicines Fund (NHS England 2022). But CA schemes are designed on a case-by-case basis, and there remain questions regarding how much data to collect, how to structure reimbursement for a new health technology during a scheme, and, at the scheme's end, how to reappraise reimbursement approval and pricing decisions.

In comparing the use of a CA scheme to immediate approval, HTA agencies and producers of new health technologies must weigh the costs and benefits of the data-collection enterprise. On the cost side lies the expense of conducting the post-marketing trial, along with the lost health-economic value that might have accrued had the technology's approval for reimbursement not been delayed. On the benefit side is the value of the sample data to be collected, data that allow the HTA agency to reduce uncertainty regarding population-level cost-effectiveness and, in turn, the risk of poorly calibrated approval and pricing decisions (Gandjour 2009, Grimm et al. 2017).

In this paper, we develop a stylized model of reimbursement decisions and price negotiations that split the total health economic surplus (derived from costs and QALYs) between a single payer and a single for-profit company that brings a new health technology to market. Here, we seek to:

- Identify conditions under which a CA scheme is preferred to immediate approval or rejection;
- Assess trade-offs for the optimal design of a CA scheme;
- Inform reimbursement decisions for the so-called interim price for the new technology that's used during the CA's post-marketing trial, as well as for the price that's used if the technology is ultimately approved for reimbursement; and
- Assess whether introducing CA schemes increases or reduces the likelihood that: (a) a company submits a new technology for reimbursement approval and pricing decisions, (b) an adopted technology is cost-effective, and (c) the process of implementing a given CA scheme itself is cost-effective.

In Section 2, we further place our approach within the context of additional, related literature. The review differentiates our work from previous research, such as our novel modeling of interim prices and how they are set, and it motivates our modeling choices, such as the use of risk-neutral objectives and cooperative bargaining, which, in turn, define the scope of our work.

Our model, formalized in Section 3, has two players that strategically interact: one represents a public healthcare system (the payer), such as the UK's National Health Service (NHS), and the other the provider of a new health technology (the company). To simplify exposition and fix ideas, we focus on new health technologies that are drugs, may refer to them as *treatments*, and assume that a Phase III clinical trial and initial HTA are complete. The payer may then immediately approve the new treatment for reimbursement and negotiate a price, may immediately decline to reimburse the new treatment, or may run one of two types of CA scheme (Claxton et al. 2016).

One variety of CA scheme, the *only in research* (OIR) scheme analyzed in Section 4, allows only patients who participate in the post-marketing trial to obtain access to the new treatment during the trial. The other type, the *only with research* (OWR) scheme analyzed in Section 5, allows all patients, not just those in the post-marketing trial, to access the new treatment during the trial. Both types run two-arm trials that further compare the cost-effectiveness of the new treatment to that of the existing standard of care.

For both schemes, we identify how much data to collect by maximizing the expected value of information, less the cost of data collection, with respect to the sample size. Given that a CA scheme is to be pursued, we also show how the choice of whether to run an OIR or OWR scheme depends on the initial strength of evidence in favor of the new treatment, as well as any reversal costs (van de Wetering et al. 2017) that are associated with removing broad access to the new technology, should an OWR scheme be chosen and the treatment ultimately not be approved for reimbursement.

From a managerial or policy perspective, we provide new insights in Sections 4 and 5 regarding the interim prices that are used during the post-marketing trial. Although they have not been extensively studied in the literature, these interim prices turn out to be critical in determining whether immediate approval, immediate rejection, or an OIR or OWR scheme is optimal.

Moreover, we show in Section 6 that caps on the interim price, such as those recommended in current UK Cancer Drugs Fund guidance (NHS England 2016), have the potential to disrupt cooperative bargaining, lead to misalignment between the players' incentives, negatively influence the design of the post-marketing trial, and negatively affect a treatment's prospects for conditional approval. We propose a new risk-sharing mechanism to realign incentives that works in most cases, but find that, in some contexts, a price cap can nevertheless prevent an otherwise valuable treatment from reaching market and thereby reduce societal value. In Section 7, we quantify those model-based insights with a numerical example that is motivated by a CA scheme pursued by the NHS and GSK for the oncology drug Votrient. This case study quantifies and adds nuance to the discussion in Section 6.

In Section 8, we show how negotiating power links directly to pricing decisions that, in turn, affect the probability that a given health technology is cost-effective. Unless the technology developer has the power to extract all surplus, bargaining outcomes are likely to deviate from the 50% chance of cost-effectiveness, given residual uncertainty in health benefits and costs at the end of the post-marketing trial, that is implicit in some other analysis (e.g., Danzon et al. 2018).

We note that CA schemes themselves are expensive, and it is reasonable to ask whether the cost of a CA scheme is more than balanced by the expected gains in health economic value that follow from having more information before making reimbursement approval and pricing decisions. Section 7 shows that a CA scheme might not always have a high probability of being cost-effective. We also discuss in Section 8 how a provider of an existing technology might respond to a new treatment that could supplant its position as a supplier and the effect on the CA decision process.

Our analysis targets the United Kingdom and other socialized health systems, so we focus on the case of one company and one payer. It is less well suited for the United States, which has multiple payers, multiple copayment options, and more price-sensitive demand. We model a treatment that is assessed for potential approval for a single group of patients, but do not preclude the possibility that the accept/reject/CA decision pertains to a single subpopulation of interest that has been identified from an earlier Phase III trial. We assume that the company's cost of production can be adequately captured by variable costs per treatment, without significant fixed costs. Thus, our insights are more appropriate for small-molecule drugs, for example, where contract manufacturers may be available, rather than for a biological medicine that may require larger fixed capital investments, if it is approved. Our analysis also assumes there is a relatively constant incidence over time of patients with the medical condition in question, rather than a large backlog of chronic patients for whom the new treatment is a potential cure. These points delimit the scope of our work and identify areas of future work, as noted in Section 9.

An online appendix provides Nash bargaining results used for our model (Online Appendix A), proofs of mathematical claims (Online Appendix B), comparative statics (Online Appendix C), further case study analysis (Online Appendices D and E), and results that relax some assumptions of our model (Online Appendix F).

2. Literature Review

We discuss how our paper relates to other work on conditional approval schemes and the negotiation process

for the approval of new health technologies, as well as other work that links to or complements our model. The discussion also motivates some of our modeling assumptions.

2.1. Conditional Approval Schemes

There are many papers that develop schema that provide qualitative guidance regarding the choices to be made among CA schemes and multiple alternative risk-sharing agreements (RSAs). Among them, Walker et al. (2012), Garrison et al. (2013), and Claxton et al. (2016) provide comprehensive views of the trade-offs regarding OIR and OWR conditional-approval schemes, discounts, and other risk-sharing mechanisms. Piatkiewicz et al. (2018) and Zampirolli Dias et al. (2020) address risk sharing and market entry more broadly.

There is also work that quantifies those trade-offs. Claxton (2007) shows that a risk-neutral payer should be indifferent between the expected value of information (VoI) gained through conditional approval and an up-front price reduction that is equivalent to that gain. van de Wetering et al. (2017) provide details on reversal costs, which follow a payer's decision to stop reimbursement at the end of an OWR trial. Eckermann and Willan (2007) characterize the effect of reversal costs on the decision to employ an OIR or OWR conditional-approval scheme.

In addition, there exists work that mathematically analyzes discounting and CA schemes. Gandjour (2009) and Zaric (2021) characterize the nature and value of price discounting for risk-averse payers. We note, however, that much of the health-economic literature argues that payers should be risk-neutral with respect to uncertainty regarding a treatment's expected population-level effectiveness (e.g., Barnsley et al. 2016, Danzon et al. 2018). We also assume that the payer is risk neutral for most of the paper, and we discuss measures of the payer's risk in Section 8.

The above mathematical studies of CA schemes do not consider the company's strategic behavior—for example, its willingness to accept price discounts. Nor do they fully model the interim prices that are relevant to conditional approval schemes. But most CA schemes follow a similar timeline and involve an agreed-upon interim price per treatment, at which the payer reimburses the company while data regarding effectiveness are collected (Willis et al. 2010, Griffiths et al. 2011, NHS England 2016). We explicitly model the strategic negotiation of these interim pricing decisions.

Some analytical papers do consider the strategic incentives of both the payer and the company. Zaric and Xie (2009) compare alternative schemes for addressing a treatment that is found not to be cost-effective—the provision of a rebate from the company to the payer versus the delisting of the treatment from the payer's formulary. Levaggi (2014) compares two initial pricing schemes—value-based pricing (VBP) and a traditional "listing" model in which the company proposes a price and the payer accepts the offer with a probability which declines with the price. Levaggi (2014) emphasizes the ability of VBP to offer an efficient split of social welfare to company and payer, a feature of our Nash bargaining framework. These two papers do not address the VoI obtained from conditional approval schemes, though. We include VoI in the negotiated value, applying to post-marketing trials the approach of previous work that uses VoI (Barton et al. 2008) to design earlier-stage trials (Chick et al. 2022, Alban et al. 2023).

2.2. Negotiation

There is recent work on pricing and RSAs for new health technologies that explicitly considers the price negotiation process. Whittal et al. (2022) develop a qualitative "value-based negotiating framework" that is intended to guide the payer and company as they select the type of RSA, contract terms, and data that allow for a "fair split of key risks" encountered in the approval a new treatment. Gladwell et al. (2020) model the VoI of conditional approval schemes and note that much related work focuses on the payer's point of view, not that of the company. They model negotiation choices assuming a Stackelberg game in which the company moves first and the price reflects the payer's maximum willingness to pay. We use Nash bargaining to characterize both interim and final prices, and we demonstrate that a Stackelberg game can be viewed as special case of our Nash bargaining model and discuss the implications of the result.

Nash bargaining is a representation that fits our context well for two reasons. First, payers such as the NHS explicitly note a societal interest in maintaining a financially viable health-technology sector. The UK Department of Health and Social Care and the Association of the British Pharmaceutical Industry (2018) recognize, " … the importance of collaboration between the public and private sectors in delivering improved health gains from medicines … and in supporting the pharmaceutical industry in the United Kingdom so that it can continue to innovate now and in the future." Cooperative bargaining models naturally allow for the inclusion of fractional sharing of gains. Second, in using axiomatic, cooperative bargaining, we need not specify the details of the negotiation process. For instance, UK guidance (NHS England 2016, National Institute for Health and Care Excellence 2021) states that the approval process involves negotiations with the company, but the structure and timeline of these negotiations are fluid and can be adapted on a case-by-case basis.

Berdud et al. (2023) also use a stylized Nash bargaining model for a finite set of new treatments to study how to split surpluses between payer and drug producers,

but they assume that ICERs are known and do not model uncertainty about them. Other work also uses a Nash bargaining framework to characterize strategic outcomes for various forms of risk sharing (Antoñanzas et al. 2011, Critchley and Zaric 2019, Gamba et al. 2020, Hlávka et al. 2021, Zorc et al. 2024). But these works do not consider the conditional-approval schemes that are the focus of this paper.

2.3. Other Related Work

There has been work in the health economics and operations management literature that studies other types of uncertainty that create a risk for the payer, such as uncertainty about the size of the population that will use the treatment (Zhang et al. 2011, Gavious et al. 2014, Zhang and Zaric 2015, Levaggi and Pertile 2020) and about the safety profile of new treatments (Ahuja et al. 2021). Another RSA mechanism, implemented after approval, links reimbursement for a given patient to that patient's response to treatment (Mahjoub et al. 2017, Adida 2021, Olsder et al. 2022, Xu et al. 2022). Our paper and those papers are complements.

3. Two-Stage Bargaining Model

We present a sequential, game-theoretic model with two players. One is an organization that develops and produces health technologies, and the other is a decision maker in a publicly funded healthcare system that is responsible for health outcomes and expenditures in its jurisdiction (e.g., UK NHS). We refer to these players as *the company* and *the payer*, respectively. We use a stylized cooperative bargaining model to capture how the payer and company jointly reach pricing and data collection decisions. Our cooperative model uses two stages of Nash bargaining and explicitly represents uncertainty regarding health-economic benefits. Table EC.1 in the online appendix summarizes its notation.

3.1. Timeline of the Cooperative Bargaining Model

To fix ideas, we focus on new drug treatments. Figure 1 sketches the model's timeline, which follows NHS England (2016) and National Institute for Health and Care Excellence (2021). In a *presubmission stage*, the company completes Phase III clinical trials for a new treatment, obtains marketing authorization from a regulatory authority, and presents trial results to the payer. The payer uses those results to conduct an HTA. We focus on a single indication for a specific group of patients that may be identified in the Phase III trial and do not consider subgroup analysis within the CA scheme. We model the stages that follow.

There are three types of outcomes at the *initial submission stage*. First, the players have the option of immediately approving reimbursement of the new treatment at a per-patient price, p_0. That price effectively shares the expected gain between the company and the payer. Second, the new treatment may be rejected for reimbursement at the time of submission. In this case, the payer continues offering the current standard of care to patients, and the company cancels any plans for additional trials or for reimbursement by the payer. Third, the payer and company can agree to have the treatment conditionally approved and to collect additional data through a post-marketing trial. Here, the company conducts the trial and pays for its nominal cost, while the payer reimburses the company at an interim price, p_i, for each patient in the trial who receives the new treatment.

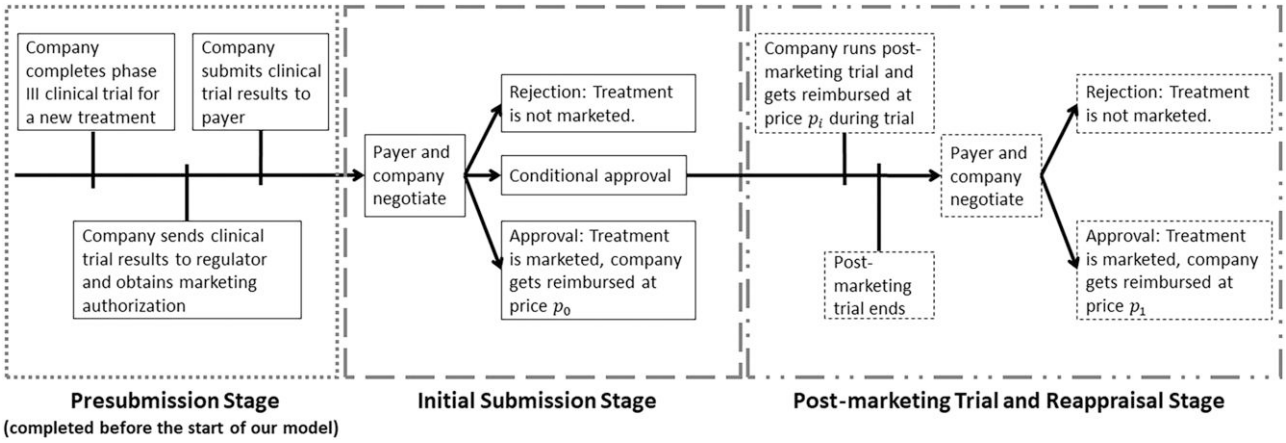
The negotiation for CA determines three quantities: the trial's sample size, n; duration, t; and interim price, p_i. The sample size is the number of pairwise observations in the post-marketing trial, a two-arm trial that compares the new treatment with an existing standard of care.

After the CA scheme's post-marketing trial concludes, another round of negotiation occurs in *the reappraisal stage*. If, given the new evidence from the post-marketing trial, the payer and company agree on reimbursement of the new treatment, then negotiation yields a reappraisal price, p_1, that allocates the expected health-economic gains between the company and the payer. If the payer and company cannot agree on reimbursement of new treatment at this time, then the payer offers the current standard of care to future patients, and the company abandons any plans for reimbursement by the payer. We do not consider the option of conducting a second post-marketing trial to collect even more data, which is consistent with our motivating example (NHS England 2016).

We model two variants of CA scheme (Walker et al. 2012, Claxton et al. 2016). The only-in-research scheme in Section 4 limits the use of the new treatment during the post-marketing trial to patients who are trial subjects. The only-with-research scheme (also called approval with research) in Section 5 allows all patients access to the new treatment during the post-marketing trial. For the OWR scheme, but not the OIR scheme, there is a reversal cost, f_r, if the new treatment is rejected for reimbursement at the time of reappraisal (Eckermann and Willan 2007). We assume the reversal cost is independent of the duration of the post-marketing trial.

In Sections 4 and 5, we will use a cooperative game theory model and Nash bargaining to determine the outcomes of negotiations, which we label as follows. Approval of the treatment at initial submission at price p_0 is denoted by (A_0, p_0), an OIR conditional approval scheme with an interim price p_i and a post-marketing trial with sample size n and duration t by $(\mathrm{CA}^{\mathrm{I}}, p_i, n, t)$, an analogous OWR conditional approval scheme by $(\mathrm{CA}^{\mathrm{W}}, p_i, n, t)$, and rejection by R_0. If conditional

Figure 1. Model Timeline



Note. The presubmission stage is assumed to have been completed, leaving the company and payer to work through two potential stages: initial submission, and post-marketing trial and reappraisal.

approval—OIR or OWR—is selected, the ultimate approval of the treatment at price p_1 is denoted by (A_1, p_1). We let R_1 denote the treatment's ultimate rejection, after the post-marketing trial.

3.2. Parameters and Decision Variables for Post-marketing Trial

We define the post-marketing trial in terms of its sample size, n, and duration, t, and assume the trial's finer details may be changed with no effect on our analysis below. Thus, we implicitly assume that the time required to observe patient outcomes is small in comparison with the duration of the market exclusivity period.

3.2.1. Post-marketing Trial Structure. We normalize the time horizon over which the new treatment has market exclusivity to equal one and denote by N the total number of patients who would use the new treatment if it were offered, from the time of initial submission until the end of the market exclusivity period. Thus, if the new treatment is approved for use at the time of initial submission, then the number of patients receiving the new treatment equals N, and under conditional approval with a post-marketing trial, that number would decrease.

To describe the post-marketing trial, we define two decision variables: n, its sample size, measured in patient pairs, and $t \in (0,1)$, the fraction of the market exclusivity period that the post-marketing trial will cover. Of the $2n$ trial subjects, n receive the standard of care and n receive the new treatment. The rate at which patients can be recruited into the post-marketing trial may have a limit, $r_{max} \in (0,1)$, due to capacity or other constraints, so that $2n \leq tr_{max}N$.

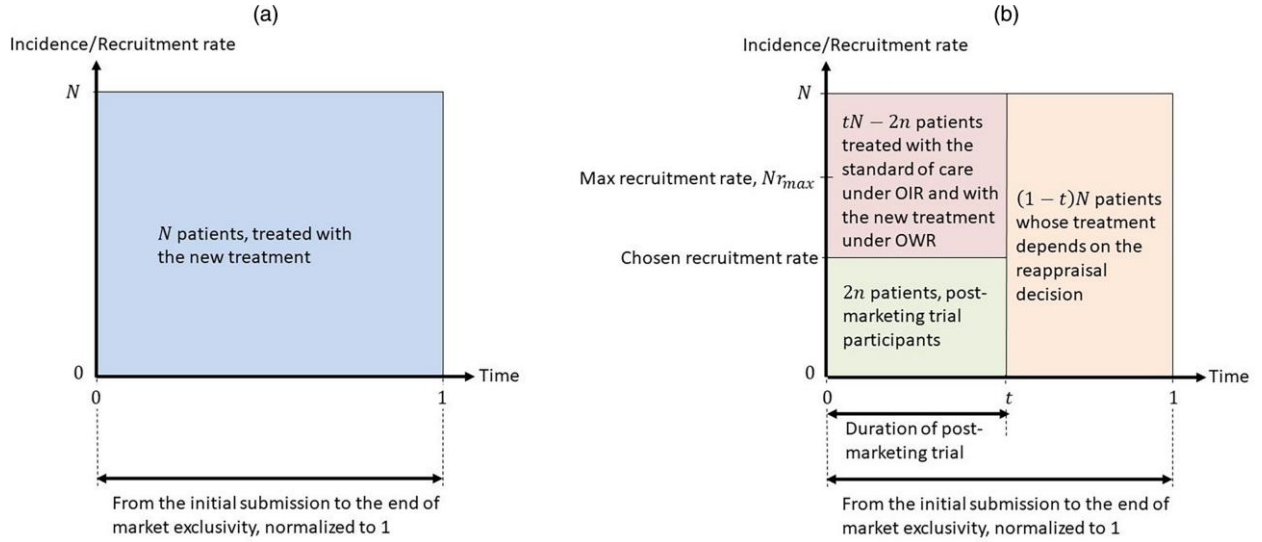
In the OIR scheme of Section 4, those patients who are not recruited into the post-marketing trial over $[0,t)$ continue using the current standard of care. For the OWR scheme studied in Section 5, the $tN - 2n$ patients who are treated during $[0,t)$, but are not in the trial, receive the new treatment. Figure 2 summarizes the numbers of patients treated under different conditions.

Here, with a single publicly funded payer, copayments are often negligible or uniformly applied across treatments (e.g., a flat rate in the United Kingdom), and choice of treatment is often guided by a clinician. Thus, we assume that patients' choices are not impacted by the treatment's price. Our results also apply if a known fraction of patients adopt the conditionally approved new treatment until it receives an approval after the post-marketing trial, a simple algebraic extension of our results.

3.2.2. Post-marketing Trial Outcomes. The post-marketing trial randomizes pairs of patients, one to the new treatment (with subscript $\mathcal{N}$) and the other to the standard of care (with subscript $\mathcal{S}$), and measures differences in health outcomes and costs of care between the two. The random variable X^j models the incremental difference between the new treatment and the standard of care for the jth pair. Each patient's health outcome includes the economic benefit associated with clinical improvement, along with costs that fall into two categories: the price paid for the new health technology and standard of care $(p_{\mathcal{N}}, p_{\mathcal{S}})$ and the value of other relevant patient-level costs of care $(C_{\mathcal{N}}, C_{\mathcal{S}})$, such as administration, follow-up, and the management of complications. We emphasize that $C_{\mathcal{N}}$ and $C_{\mathcal{S}}$ do not include the cost of reimbursement, $(p_{\mathcal{N}}, p_{\mathcal{S}})$.

We denote by $E_{\mathcal{N}}$ (and $E_{\mathcal{S}}$) the *expected* clinical effectiveness of the new treatment (and standard of care,

Figure 2. (Color online) The Number of Patients Treated with the Standard of Care and New Treatment, Represented as Areas



Notes. (a) If the new treatment is immediately approved. (b) If the new treatment is conditionally approved.

respectively) in the patient population, expressed in terms of quality-adjusted life-years and convert QALYs to a financial value using the cost-per-QALY threshold of the healthcare payer, which we denote by λ (e.g., 30,000£/QALY; also see National Institute for Health and Care Excellence 2014).

The population-level expectation of the incremental net monetary benefit of the new treatment per patient, relative to the existing standard, *excluding* the new technology's price (INMB-p), is

$$\theta = \lambda(E_{\mathcal{N}} - E_{\mathcal{S}}) - (C_{\mathcal{N}} - C_{\mathcal{S}}). \tag{1}$$

The expected incremental net monetary benefit (INMB) *including* the new technology's price is

$$\theta - (p_{\mathcal{N}} - p_{\mathcal{S}}).$$

Although the population mean, θ, is unknown, it can be estimated from Phase III clinical-trial data.

We assume that observations are independent and normally distributed, conditional on the unknown population mean, so that $X^j|\theta \sim \texttt{Normal}(\theta, \Sigma_X)$ for each j. The variance in outcomes, Σ_X, is known and models random variation in the differences in outcomes across patient pairs.

3.2.3. Bayesian Inference. We assume that the company and payer have access to the same data and share the same beliefs regarding the INMB-p of the new treatment at the time of initial submission, based on the information available at the end of the Phase III trial. We denote the prior distribution of that common belief by $\theta \sim \texttt{Normal}(\mu_0, \Sigma_0)$, where μ_0 is the mean and Σ_0 is the variance. The choice of (μ_0, Σ_0) might account for statistical issues, such as the reweighing of Phase III trial data to account for potential differences between trial inclusion criteria and the population to be treated postadoption (Mantopoulos et al. 2015) and expert judgement using methods described elsewhere (e.g., O'Hagan et al. 2006).

After (noisy) outcomes $\boldsymbol{X}^n = (X^1, X^2, \ldots, X^n)$ of the n patient pairs in the post-marketing trial are observed, the players use Bayes' rule to update the belief about θ to $\texttt{Normal}(\mu_1, \Sigma_1)$, where

$$\mu_1 = \mu_0 + \frac{\sum_{j=1}^{n} X^j/n - \mu_0}{\Sigma_X/n + \Sigma_0}\Sigma_0, \text{ and } \Sigma_1 = \Sigma_0 - \frac{\Sigma_0\Sigma_0}{\Sigma_X/n + \Sigma_0}. \tag{2}$$

We note that, at the time of initial submission, the patient outcomes to be observed during the post-marketing trial and resulting value of μ_1 are uncertain. Thus, at initial submission, we define the preposterior mean, $M_1 = \mathbb{E}[\mu_1|\boldsymbol{X}^n, \mu_0, n_0]$, as the random variable associated with the posterior mean, μ_1, to be observed at the end of the post-marketing trial, where $n_0 \triangleq \Sigma_X/\Sigma_0$ is *the effective sample size* of the prior distribution. Recalling $\theta \sim \texttt{Normal}(\mu_0, \Sigma_0)$, standard results give

$$M_1|\mu_0, n_0 \sim \texttt{Normal}(\mu_0, \sigma^2_{M_1}) \text{ where } \sigma_{M_1} = \sqrt{\frac{\Sigma_X n}{n_0(n+n_0)}}. \tag{3}$$

3.2.4. Post-marketing Trial Costs. We denote the fixed cost of running a post-marketing trial by f_{DC} and the variable cost of recruiting each patient pair into the trial by v_{DC}, where "DC" stands for "data collection." The NHS states that data collection should not put a burden on the healthcare system (NHS England 2016), and we

assume that the company runs and incurs the full cost of the post-marketing trial. Nevertheless, the interim price at which the payer reimburses the company during the post-marketing trial effectively allows this cost to be shared between the players.

3.3. The Payer's Objective

We assume the payer is risk-neutral (Claxton 1999, Barnsley et al. 2016, Danzon et al. 2018) and seeks to maximize the INMB for its population. We consider associated measures of risk in Section 8.

If the new treatment is approved at submission, the payer gains INMB-p and reimburses p_0 to the company for each patient who receives the new treatment, where p_0 is determined by negotiation. In this case, the payer's *total* expected INMB across the population of N patients is

$$\begin{aligned} V_0(\mathrm{A}_0, p_0) &\triangleq \mathbb{E}[N(\theta - (p_0 - p_{\mathcal{S}}))|\mu_0, n_0] \\ &= N(\mu_0 - p_0 + p_{\mathcal{S}}). \end{aligned} \tag{4}$$

If the new treatment is rejected at the time of initial submission, the payer's total expected INMB is zero (i.e., $V_0(\mathrm{R}_0) \triangleq 0$) because patients continue using the standard of care.

If the new treatment is conditionally approved at the time of initial submission, the payer's total expected INMB from conditional approval depends on whether the new treatment is ultimately approved or rejected after the post-marketing trial ends. If the new treatment is approved, given the updated belief at the end of the post-marketing trial, (μ_1, Σ_1), the payer gains the additional INMB-p and incurs the additional cost of reimbursing the company at p_1 for each patient receiving the new treatment after the post-marketing trial ends. We denote the payer's total expected INMB from approval at price p_1 at the end of the post-marketing trial by

$$\begin{aligned} V_1(\mathrm{A}_1, p_1, t) &\triangleq \mathbb{E}[(1-t)N(\theta - (p_1 - p_{\mathcal{S}}))|\mu_1, \Sigma_1] \\ &= (1-t)N(\mu_1 - p_1 + p_{\mathcal{S}}), \end{aligned} \tag{5}$$

where N is the size of the target population, $(1-t)$ is the fraction of the market exclusivity period that remains at the end of the post-marketing trial, and p_1 is determined by negotiation at reappraisal. If the new treatment is rejected after the conclusion of the post-marketing trial, the total expected INMB is $V_1(\mathrm{R}_1) \triangleq 0$ for OIR schemes and is $V_1(\mathrm{R}_1) \triangleq -f_r$ for OWR schemes.

For an OIR scheme, we combine the two sets of outcomes at the end of the post-marketing trial—acceptance at price p_1 or rejection—to denote the payer's total expected INMB given the updated belief, (μ_1, Σ_1), after a post-marketing trial with duration t as $V_1^*(t)$. In turn, we let $\mathbb{E}[V_1^*(t)|\mu_0, n_0]$ denote the expectation of $V_1^*(t)$ with respect to the players' belief at initial submission.

We then can define the payer's total expected INMB from an OIR scheme, as of the time of initial submission, as a function of the interim price, p_i, the sample size, n, and the post-marketing trial duration, t. This quantity, $V_0(\mathrm{CA}^{\mathrm{I}}, p_i, n, t)$, includes the total expected INMB of the cohort of n patients who receive the new treatment in the post-marketing trial at interim price p_i and the total expected INMB at reappraisal, based on the updated belief at the end of the trial. That is,

$$\begin{aligned} V_0(\mathrm{CA}^{\mathrm{I}}, p_i, n, t) &\triangleq \mathbb{E}\left[\sum_{j=1}^{n} X^j - n(p_i - p_{\mathcal{S}}) + V_1^*(t)|\mu_0, n_0\right] \\ &= n(\mu_0 - p_i + p_{\mathcal{S}}) + \mathbb{E}[V_1^*(t)|\mu_0, n_0]. \end{aligned} \tag{6}$$

The $tN - 2n$ patients who do not participate in the OIR post-marketing trial receive the standard of care, and their INMB is zero. We discuss the analysis of OWR schemes in Section 5 below.

3.4. The Company's Objective

We assume that the company is risk-neutral and aims to maximize its expected profit. We further assume that the fixed cost of production is zero and that variable cost per treatment is $v_{\mathcal{N}}$. This is roughly consistent with the company's using a contract manufacturer to produce the new treatment.

If the new treatment is approved at the time of initial submission, the company incurs the variable production cost $v_{\mathcal{N}}$ and is reimbursed at price p_0 for each patient treated. We denote the company's profit from the treatment's approval at price p_0 at the time of initial submission by

$$\Pi_0(\mathrm{A}_0, p_0) \triangleq N(p_0 - v_{\mathcal{N}}). \tag{7}$$

If the new treatment is rejected, then the company's profit is zero, which we denote as $\Pi_0(\mathrm{R}_0) \triangleq 0$.

If the new treatment is conditionally approved at the time of initial submission, the company's total expected profit from conditional approval depends on whether the new treatment is approved or rejected after the post-marketing trial ends. If the new treatment is approved given the updated belief at the end of the post-marketing trial, (μ_1, Σ_1), the company incurs the variable production cost, $v_{\mathcal{N}}$, and is reimbursed at price p_1 for each patient treated with the new treatment once the post-marketing trial ends. The company's profit from approval at price p_1 following the end of the post-marketing trial is therefore

$$\Pi_1(\mathrm{A}_1, p_1, t) \triangleq (1-t)N(p_1 - v_{\mathcal{N}}). \tag{8}$$

If the new treatment is rejected at the conclusion of the post-marketing trial, the company's additional profit after rejection is $\Pi_1(\mathrm{R}_1) \triangleq 0$.

In analogy with $V_1^*(t)$, we let $\Pi_1^*(t)$ denote the company profit across the two sets of outcomes of renegotiation at the end of the post-marketing trial of an OIR scheme—acceptance at price p_1 or rejection—for a given

updated belief, (μ_1, Σ_1). In turn, we let $\mathbb{E}[\Pi_1^*(t)|\mu_0, n_0]$ be the expectation of the company's postreappraisal profit with respect to the players' belief at initial submission.

To construct the company's expected total profit from an OIR scheme at the time of initial submission, we add the cash flows associated with the post-marketing trial to the expected posttrial profits that follow. During the post-marketing trial, the company pays the fixed cost of running the trial, f_{DC}, plus the variable cost of the trial, v_{DC}, for each of the n patient pairs in the trial. It also earns the interim price, p_i, and incurs the variable production cost, $v_{\mathcal{N}}$, for each of the n patients in the trial who receives the new treatment. Combining these terms gives

$$\Pi_0(\mathrm{CA}^{\mathrm{I}}, p_i, n, t) \triangleq n(p_i - v_{\mathcal{N}}) - f_{DC} - nv_{DC} + \mathbb{E}[\Pi_1^*(t)|\mu_0, n_0]. \tag{9}$$

See Section 5 for a formulation and an analysis of OWR schemes.

4. Analysis of the Two-Stage Bargaining Model with an OIR Scheme

This section analyzes the two-stage bargaining problem for the case, in which the only conditional approval option under consideration is the OIR scheme. In Section 5, we also analyze the OWR scheme.

Our analysis employs backward induction. At each stage of the model, we use an axiomatic, cooperative, Nash bargaining framework that allows for asymmetric outcomes, and we use subgame perfection to roll back later-stage results to earlier periods. (See Online Appendix A and Lippman and McCardle 2012.) In Sections 4.1 and 4.2, we characterize the Nash bargaining solution at the reappraisal and initial submission stages of the game, respectively, and we compare the various prices that are determined through bargaining. In Section 4.3, we summarize the Nash bargaining outcome of the two-stage model, and in Section 4.4, we present comparative statics results.

4.1. The Reappraisal Stage

Consider the reappraisal stage, which begins at the end of the post-marketing trial. By (2), the players' belief regarding the unknown INMB-p of the new treatment is $\texttt{Normal}(\mu_1, \Sigma_1)$. The remaining number of patients to treat before market exclusivity ends is $(1-t)N$. The payer and company negotiate to determine whether the new treatment is approved at some price p_1 or is rejected.

At this stage, our model corresponds to a Nash bargaining problem, in which players negotiate their shares of a joint surplus, and the disagreement outcomes for both players are zero. Online Appendix A presents the details of the bargaining problem, and here, we present a summary of the main result. If the joint surplus is positive, the Nash bargaining solution implies that it is split according to the players' bargaining powers, where the company receives a fraction, β, of the joint surplus, and the payer receives the remaining $1-\beta$. When $\beta = 0.5$, the Nash bargaining problem is symmetric, and when $\beta = 1$, it is equivalent to a Stackelberg game in which the company leads. (See also Online Appendix B.4.) If the joint surplus is negative, then bargaining breaks down, and both players receive the disagreement outcome of zero.

Because the price, p_1, is a transfer between the two players, it only impacts how the surplus is shared, not the size of the joint surplus to be allocated through bargaining. We denote the joint surplus to be shared as $S_1(\mathrm{A}_1, t) \triangleq V_1(\mathrm{A}_1, p_1, t) + \Pi_1(\mathrm{A}_1, p_1, t)$, and from (5) and (8), we have:

$$\begin{aligned} S_1(\mathrm{A}_1, t) &= (1-t)N(\mu_1 - (p_1 - p_{\mathcal{S}})) + (1-t)N(p_1 - v_{\mathcal{N}}) \\ &= (1-t)N(\mu_1 + p_{\mathcal{S}} - v_{\mathcal{N}}). \end{aligned} \tag{10}$$

If $\mu_1 < v_{\mathcal{N}} - p_{\mathcal{S}}$, the joint surplus is negative. In this case, bargaining breaks down, the treatment is rejected, and the payer's and company's expected payouts are zero.

If $\mu_1 > v_{\mathcal{N}} - p_{\mathcal{S}}$, there is a positive joint surplus to be shared, and the Nash bargaining solution implies that the payer and company receive fractions $1-\beta$ and β of the joint surplus, respectively. Therefore, we have $V_1(\mathrm{A}_1, p_1, t) = (1-\beta)S_1(\mathrm{A}_1, t)$ and $\Pi_1(\mathrm{A}_1, p_1, t) = \beta S_1(\mathrm{A}_1, t)$. Using (5), (8), and (10) and then solving for p_1, we find the reappraisal price, p_1^*, at which the payer and company obtain $1-\beta$ and β shares of the joint surplus.

If $\mu_1 + p_{\mathcal{S}} - v_{\mathcal{N}} = 0$, the joint surplus is zero, and the players are indifferent between the bargaining solution and the disagreement outcome. To ensure that the set of bargaining solutions is closed (a technical assumption of Nash bargaining solutions), we assume that, in this case, the bargaining solution prevails. Proposition 1 summarizes the results for Nash bargaining at reappraisal.

Proposition 1. *Suppose that the post-marketing trial is completed and the players' belief regarding the unknown INMB-p, θ, of the new treatment is $\texttt{Normal}(\mu_1, \Sigma_1)$. Then, the joint surplus, the payer's INMB, and the company's expected profit at the Nash bargaining outcome are*

$$\begin{aligned} &S_1^*(t) = \max\{(1-t)N(\mu_1 + p_{\mathcal{S}} - v_{\mathcal{N}}), 0\}, \\ &V_1^*(t) = (1-\beta)S_1^*(t), \quad \Pi_1^*(t) = \beta S_1^*(t). \end{aligned} \tag{11}$$

If $\mu_1 + p_{\mathcal{S}} - v_{\mathcal{N}} \geq 0$, then the Nash bargaining outcome at reappraisal is approval with reappraisal price $p_1^* = v_{\mathcal{N}} + \beta(\mu_1 + p_{\mathcal{S}} - v_{\mathcal{N}})$. Otherwise, the outcome is rejection.

We view p_1^* as cost-plus pricing: the price covers the company's production cost, $v_{\mathcal{N}}$, plus a fraction of each patient's health-economic surplus that is proportional to the company's bargaining power.

4.2. The Initial Submission Stage

At the initial submission stage, the prior mean and variance of the new treatment's INMB-p are μ_0 and Σ_0,

respectively. Using that information, the payer and company negotiate to determine whether the new treatment is immediately approved with a price p_0; conditionally approved with an interim price p_i and a post-marketing trial with sample size n and duration t; or rejected.

Our cooperative bargaining model at the initial submission stage corresponds to a Nash bargaining problem, in which the payer and company have the option to share the joint surplus from immediate approval or the joint surplus from conditional approval, and the disagreement outcomes for both players are zero. Lemma 1 presents the bargaining solution for such a problem.

Lemma 1. *Consider an asymmetric bargaining problem in which two players negotiate to share either the surplus from an OIR scheme or the surplus from immediate approval. If both surpluses are negative, then the disagreement outcome is obtained. Otherwise, a Nash bargaining solution to this problem is obtained by selecting the outcome with the higher surplus and splitting the surplus proportionately, according to the players' bargaining powers.*

As in the analysis for the reappraisal stage, prices do not impact the size of the surplus, only how the surplus is shared, and our analysis proceeds as before. For each outcome, we add the payer's net benefit and the company's profit to construct a joint surplus. The Nash bargaining outcome is the one that maximizes the joint surplus.

4.2.1. Expected Payoffs from Immediate Approval. The decision to immediately approve the new treatment is analogous to that of approving the new treatment at reappraisal. Although the prior mean and variance of the INMB-p at initial submission, (μ_0, Σ_0), differ from those at reappraisal, comparison of (4) to (5) and (7) to (8) shows that the payer's two net benefit functions and that the company's two profit functions have the same forms.

In turn, the joint surplus from immediate approval, which is simply the sum of the net benefit and profit function, is analogous from one period to the next. Proposition 2 summarizes the Nash bargaining solution if the outcome of negotiation is to immediately approve at the initial submission stage.

Proposition 2. *Suppose that the Nash bargaining outcome at initial submission is immediate approval. Then, the immediate approval price is $p_0^* = v_{\mathcal{N}} + \beta(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}})$, and the joint surplus, the payer's total INMB, and the company's expected profit from immediate approval are*

$$S_0(A_0) = N(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}}),\ \ V_0(A_0, p_0^*) = (1-\beta)\, S_0(A_0)$$
$$\text{and}\quad \Pi_0(A_0, p_0^*) = \beta\, S_0(A_0). \tag{12}$$

Note that the immediate-approval price has the same cost-plus structure as the reappraisal price, p_1^*. At the time of initial submission, however, μ_1, is unknown and has a normally distributed preposterior associated with the random variable M_1. Therefore, an explicit comparison of the immediate-approval and reappraisal prices naturally takes the latter as an expectation. Direct evaluation of that expectation allows us to compare p_0^* and p_1^*.

Corollary 1. *Suppose $\mu_0 \geq v_{\mathcal{N}} - p_{\mathcal{S}}$ so that the joint surplus from immediate approval is nonnegative. Then $p_0^* < \mathbb{E}_{M_1}[p_1^* \,|\, M_1 \geq v_{\mathcal{N}} - p_{\mathcal{S}}]$.*

Thus, given $\mu_0 \geq v_{\mathcal{N}} - p_{\mathcal{S}}$, so that a price at initial submission can be negotiated, the expected price at reappraisal will be greater, assuming that it can be negotiated as well. This effect is consistent with the "expected value of information" described in Claxton (2007).

4.2.2. Joint Surplus from Conditional Approval. As before, the joint surplus is the sum of the payer's net benefit and the company's profit from conditional approval, as defined in (6) and (9). Adding the two and recalling the definition of $S_1^*(t)$ from (11), we have

$$S_0(\mathrm{CA}^{\mathrm{I}}, n, t) \triangleq n(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}}) - f_{DC} - n v_{DC} + \mathbb{E}_{M_1}[S_1^*(t) \,|\, \mu_0, n_0], \tag{13}$$

where $S_1^*(t)$ depends on μ_1 and the expectation is taken with respect to M_1, the preposterior distribution of μ_1 at initial submission defined in (3).

We can use (3) to evaluate the expectation in the last term of (13). We first let

$$\psi(x) \triangleq \mathbb{E}[(X - x)^+] = \phi(x) - x(1 - \Phi(x)), \tag{14}$$

denote the standard normal loss function, where $\phi(x)$ and $\Phi(x)$ are the density and cumulative distribution functions of a standard normal random variable $X \sim \texttt{Normal}(0,1)$. Then, substituting M_1 for μ_1 in (11), taking expectations, and applying the definition of $\psi(x)$, we have

$$S_0(\mathrm{CA}^{\mathrm{I}}, n, t) = n(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}}) - f_{DC} - n v_{DC} + (1-t) N \sigma_{M_1} \psi\left(\frac{v_{\mathcal{N}} - p_{\mathcal{S}} - \mu_0}{\sigma_{M_1}}\right). \tag{15}$$

The joint surplus depends on the design parameters of the post-marketing trial, n and t, both directly and through the definition of σ_{M_1} in (3).

4.2.3. Optimal Post-marketing Trial Design. Through the Nash bargaining process, the payer and company both obtain positive fractions of the joint surplus (15), so they share a common interest in maximizing the value of $S_0(\mathrm{CA}^{\mathrm{I}}, n, t)$. They therefore can jointly determine the optimal sample size and duration of the post-marketing trial by solving

$$\max_{n,t} \{S_0(\mathrm{CA}^{\mathrm{I}}, n, t) \mid 0 \leq 2n \leq N r_{max} t\}. \tag{16}$$

In Online Appendix B.3, we show that the optimal sample size n^* and duration t^* are unique and nonzero

whenever conditional approval is the Nash bargaining outcome. We denote the maximized joint surplus as $S_0(\mathrm{CA}^{\mathrm{I}}) \triangleq S_0(\mathrm{CA}^{\mathrm{I}}, n^*, t^*)$.

From (15), we observe that the total number of patients who receive the new treatment decreases with the duration of the post-marketing trial. For any given sample size, n, it is therefore optimal to complete the post-marketing trial as quickly as possible. As a result, (16) can be optimized by setting the duration to $t = 2n/(Nr_{max})$, the shortest feasible time frame in which a given sample of n can be collected, and then optimizing over the sample size.

We define $\sigma^*_{M_1} \triangleq \sqrt{\Sigma_X n^*/(n_0(n^* + n_0))}$. Then, we can rewrite the maximized joint surplus as

$$S_0(\mathrm{CA}^{\mathrm{I}}) = n^*(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}}) - f_{DC} - n^* v_{DC} + (N - 2n^*/r_{max})\sigma^*_{M_1}\psi\left(\frac{v_{\mathcal{N}} - p_{\mathcal{S}} - \mu_0}{\sigma^*_{M_1}}\right). \quad (17)$$

4.2.4. Expected Payoffs from Conditional Approval.

Now, we develop Nash bargaining results that characterize the payer's and company's expected payoffs if the outcome of negotiation at initial submission stage is conditional approval. From (13) and (17), we have $t^* = 2n^*/(Nr_{max})$ and $\mathbb{E}_{M_1}[S^*_1(t^*)|\mu_0, n_0] = (N - 2n^*/r_{max})\sigma^*_{M_1}\psi((v_{\mathcal{N}} - p_{\mathcal{S}} - \mu_0)/\sigma^*_{M_1})$, and recalling that $V^*_1(t) = (1-\beta)S^*_1(t)$ and $\Pi^*_1(t) = \beta S^*_1(t)$ for any realization of μ_1, we can express, as of the time of initial submission, the payer's and company's expected values at reappraisal.

For the optimized n^* and t^*, we can rewrite the payer's expected net benefit (6) as

$$V_0(\mathrm{CA}^{\mathrm{I}}, p_i) = n^*(\mu_0 + p_{\mathcal{S}} - p_i) + (1-\beta)(N - 2n^*/r_{max})\sigma^*_{M_1}\psi\left(\frac{v_{\mathcal{N}} - p_{\mathcal{S}} - \mu_0}{\sigma^*_{M_1}}\right), \quad (18)$$

and the company's expected profit (9) as

$$\Pi_0(\mathrm{CA}^{\mathrm{I}}, p_i) = n^*(p_i - v_{\mathcal{N}}) - f_{DC} - n^* v_{DC} + \beta(N - 2n^*/r_{max})\sigma^*_{M_1}\psi\left(\frac{v_{\mathcal{N}} - p_{\mathcal{S}} - \mu_0}{\sigma^*_{M_1}}\right). \quad (19)$$

Then, setting either $V_0(\mathrm{CA}^{\mathrm{I}}, p_i) = (1-\beta)S_0(\mathrm{CA}^{\mathrm{I}})$ or $\Pi_0(\mathrm{CA}^{\mathrm{I}}, p_i) = \beta S_0(\mathrm{CA}^{\mathrm{I}})$ and solving for p_i, we obtain the following Nash bargaining solution.

Proposition 3. *Suppose that the Nash bargaining outcome at the initial submission is an OIR scheme. Then, the payer's INMB and the company's expected profit from conditional approval are*

$$V_0(CA^I, p_i^*) = (1-\beta)S_0(CA^I) \quad \text{and} \quad \Pi_0(CA^I, p_i^*) = \beta S_0(CA^I),$$

where $S_0(CA^I)$ is defined in (17). In turn, the interim price is $p_i^* = p_0^* + (1-\beta)(v_{DC} + f_{DC}/n^*)$, where $p_0^* = v_{\mathcal{N}} + \beta(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}})$ from Proposition 2.

As with p_0^* and p_1^*, the interim price has a cost-plus structure and equals the price at immediate approval plus a partial reimbursement of the extra costs the company incurs to conduct the post-marketing trial. Note, however, that the share of those costs, $1-\beta$, reflects the *payer's* bargaining power: the payer and company share costs in the same manner that they share gains.

Furthermore, the interim price is always strictly greater than the price that would be approved at initial submission, an increase that, in this case, reflects cost-sharing rather than risk reduction.

Corollary 2. *If p_0^* and p_i^* exist, then $p_0^* < p_i^*$.*

Remark 1. The interim and expected reappraisal prices are not strictly ordered. Their relative magnitudes depend on the initial expected surplus per patient, $(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}})$; the per-patient cost of the post-marketing trial, $(f_{DC}/n^* + v_{DC})$; the parties' relative bargaining powers, β and $1-\beta$; and the degree of uncertainty concerning the INMB-p of the new treatment, n_0. We discuss comparative statics regarding p_i^* in Section 4.4 and numerically study the relationship between p_0^*, p_i^*, and $\mathbb{E}_{M_1}[p_1^*|M_1 \geq v_{\mathcal{N}} - p_{\mathcal{S}}]$ in Section 7.2.

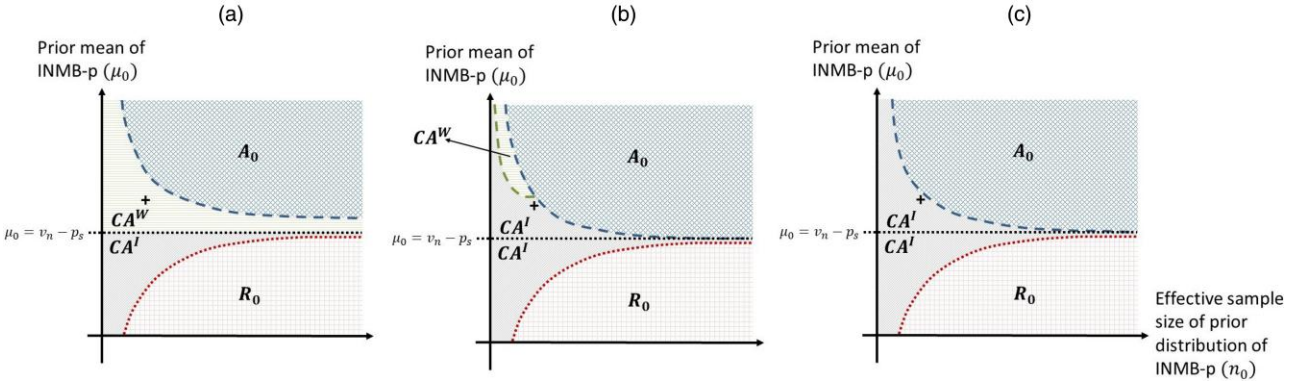
4.3. Solution to the Bargaining Problem

To summarize, for the payer and the company, there are potentially two stages of bargaining on the path to a treatment's approval. In the initial submission stage, the joint surplus to be shared through bargaining is the maximum of the joint surplus from immediate approval, $S_0(\mathrm{A}_0)$, and the joint surplus from conditional approval, $S_0(\mathrm{CA}^{\mathrm{I}})$ (Lemma 1).

- If $S_0(\mathrm{A}_0) > S_0(\mathrm{CA}^{\mathrm{I}})$ and $S_0(\mathrm{A}_0) \geq 0$, the Nash bargaining outcome is immediate approval with price p_0^* set to share the joint surplus in proportion to the players' bargaining powers (Proposition 2).
- If, instead $S_0(\mathrm{CA}^{\mathrm{I}}) > S_0(\mathrm{A}_0)$ and $S_0(\mathrm{CA}^{\mathrm{I}}) \geq 0$, then the Nash bargaining outcome is conditional approval, the company conducts a post-marketing trial with n^* pairs of subjects over time t^*, and the payer reimburses the company at interim price p_i^* that equals the price at immediate approval price plus the payer's share of the cost of the post-marketing trial. (See Proposition 3.)
- If both $S_0(\mathrm{A}_0) < 0$ and $S_0(\mathrm{CA}^{\mathrm{I}}) < 0$, then there is no joint surplus to share, and negotiation breaks down. The treatment is rejected, the payer's expected INMB in the initial submission stage is zero, and the company's expected profit in the initial submission stage is zero.

For completeness, we note that, in the event that the joint surpluses from the two outcomes are nonnegative and equal, we assume that the outcome chosen is immediate approval at price p_0^*. See Figure 3(c) for a visualization of this result on the (μ_0, n_0) plane. (This result is

Figure 3. (Color online) Nash Bargaining Outcomes at the Initial Submission Stage for Different Values of μ_0 and n_0 at Three Levels of the Cost of Reversal, f_r



Notes. Parameter values for the Votrient case study are marked with "+." (a) $f_r = 0$. (b) $f_r = £30 \times 10^7$. (c) $f_r = £100 \times 10^7$.

broader than just for that specific example. See Online Appendix C.2.2.)

A second stage of bargaining occurs if and only if conditional approval dominates at initial submission. In this case, the revised mean at reappraisal, μ_1, becomes known, and the treatment is approved if and only if the resulting $S_1(\mathrm{A}_1, t^*) \geq 0$. If approved, the price p_1^* is set so that the joint surplus is shared according to the players' bargaining powers (Proposition 1).

4.4. Comparative Statics Results

We conduct a comparative statics analysis to understand the sensitivity of Nash-bargaining outcomes and prices to model parameters. Most of the results are intuitive. Therefore, we focus here on a subset of insights for OIR schemes. Additional results and all derivations appear in Online Appendix C. Online Appendix E gives numerical results for parameters that cannot be unambiguously signed.

First, we discuss the sensitivity of the company's payoff to the effective sample size. We note that n_0 does not affect the company's expected profit from immediate approval, and for any given μ_0, the surplus from conditional approval is highest when the effective sample size is as low as possible. Thus, once enough Phase III data are collected to ensure immediate or conditional approval, the company has no incentive beyond the requirements of the Phase III trial to collect further samples.

Second, we examine the sensitivity of prices to the company's bargaining power, β. We know from Proposition 2 that immediate approval can be optimal only when $S_0(\mathrm{A}_0) = N(\mu_0 + p_S - v_N) \geq 0$. Therefore, for all treatments that are immediately approved, the price, $p_0^* = v_N + \beta(\mu_0 + p_S - v_N)$, (weakly) increases with β, and from Proposition 1, an analogous result holds for p_1^*.

In contrast, the interim price, p_i^*, may increase or decrease with the bargaining power of the company. To see this, recall from Proposition 3 that the interim price is $p_i^* = p_0^* + (1-\beta)(v_{DC} + f_{DC}/n^*)$. If $\mu_0 + p_S - v_N > 0$, then p_0^* increases and $(1-\beta)(v_{DC} + f_{DC}/n^*)$ decreases with β, and the direction of change depends on their balance. If the treatment is highly favorable and the cost of the post-marketing trial is small, then the p_0^* term will dominate, so that the interim price increases with β. If the treatment is marginally favorable and the cost of the trial is high, then the last term of p_i^* will dominate, meaning that the interim price decreases with β. When $\mu_0 + p_S - v_N < 0$, so immediate approval is not attractive, both p_0^* and $(1-\beta)(v_{DC} + f_{DC}/n^*)$ decrease with β, and p_i^* unambiguously decreases. The relationship between the company's bargaining power and the interim price is consistent with cooperative bargaining outcomes in which the payer and company share gains and costs.

5. Comparison of the OIR and OWR Conditional Approval Schemes

In this section, we develop expressions for an OWR conditional approval scheme that is the analogue of the OIR scheme analyzed in Section 4. For the case in which both OIR and OWR are under consideration at initial submission, we then compare bargaining outcomes and realized prices for the two schemes.

We begin with the reappraisal stage and recall that, in an OWR scheme, f_r denotes the total cost the payer incurs to reverse public health information and practice in the event that the new treatment is rejected at the reappraisal stage. In this case, the Nash bargaining problem at reappraisal has a disagreement outcome of zero for the company and of $-f_r$ for the payer. There is no such reversal cost for OIR schemes.

The introduction of the reversal cost implies that the joint surplus at reappraisal is

$$S_1^{*,\mathrm{W}}(t) = \max\{(1-t)N(\mu_1 + p_S - v_N),\ -f_r\}, \qquad (20)$$

which for large f_r can have realizations that fall significantly below the floor of zero in the analogous

expression for OIR schemes in (11). In turn, as of the time of initial submission, the joint surplus from an OWR scheme parallels (13):

$$S_0(\mathrm{CA}^{\mathrm{W}}, n, t) \triangleq (Nt - n)(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}}) - f_{DC} - nv_{DC} + \mathbb{E}_{M_1}[S_1^{*,\mathrm{W}}(t) | \mu_0, n_0], \quad (21)$$

and we denote the maximized joint surplus as $S_0(\mathrm{CA}^{\mathrm{W}}) \triangleq \max_{n,t}\{S_0(\mathrm{CA}^{\mathrm{W}}, n, t) | 0 \le 2n \le Nr_{max}t\}$ and the optimal sample size and duration by $n^{*,\mathrm{W}}$ and $t^{*,\mathrm{W}}$.

We note two differences between (13) and (21). In the first term, the cohort of patients who receive the new treatment during the post-marketing trial is typically far larger in the OWR scheme, $(Nt - n)$ rather than n, so the expected total gain or loss from these patients is larger under the OWR scheme. And the final expectation terms can differ significantly for large values of f_r, due to the difference between the floors of the maxima that are embedded within (11) and (20), above.

The characterization of Nash bargaining outcomes then follows the same approach as in Section 4. First, we can show that, for any given sample size, it is optimal to complete the OWR post-marketing trial as quickly as possible, so $t^{*,\mathrm{W}} = 2n^{*,\mathrm{W}}/(Nr_{max})$. Second, when both OIR and OWR are under consideration at initial submission, we can straightforwardly extend the results in Lemma 1 to hold for bargaining that includes three potential surpluses: $S_0(\mathrm{A}_0)$, $S_0(\mathrm{CA}^{\mathrm{I}})$, and $S_0(\mathrm{CA}^{\mathrm{W}})$.

We find that the interim price under the OWR scheme is

$$p_i^{*,\mathrm{W}} = p_0^* + (1-\beta)\frac{n^{*,\mathrm{W}}v_{DC} + f_{DC}}{n^{*,\mathrm{W}}(2/r_{max} - 1)} - \beta\frac{f_r}{n^{*,\mathrm{W}}(2/r_{max} - 1)}, \quad (22)$$

where $n^{*,\mathrm{W}}(2/r_{max} - 1) > 0$ is the total number of patients receiving the new treatment during the post-marketing trial. The first two terms are analogous to those for the interim price in the OIR scheme, p_i^* from Proposition 3: the immediate approval price, $p_0^* = v_{\mathcal{N}} + \beta(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}})$ from Proposition 2, plus a partial reimbursement of the costs that the company incurs to conduct the post-marketing trial. The third and final term reflects the company's share of the reversal cost that the payer would incur if the treatment were rejected at reappraisal. The first term, p_0^*, increases with β for $(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}}) > 0$, and the second and third terms decrease as β increases. How $p_i^{*,\mathrm{W}}$ changes with β depends on the relative magnitudes of the three terms' costs and revenues.

We also show that the reappraisal price under an OWR scheme has a cost-plus structure, similar to its OIR counterpart, with an extra term proportional to the reversal cost:

$$p_1^{*,\mathrm{W}} = v_{\mathcal{N}} + \beta(\mu_1 + p_{\mathcal{S}} - v_{\mathcal{N}}) + \beta\frac{f_r}{N - 2n^{*,\mathrm{W}}/r_{max}}, \quad (23)$$

where $N - 2n^{*,\mathrm{W}}/r_{max} > 0$ is the total number of patients remaining to be treated after the conclusion of the post-marketing trial. The first two terms are equal to the reappraisal price under the OIR scheme, p_1^* in Proposition 1. The final term allows the company to recover the share of the reversal cost paid through the interim price in the event that the new treatment is approved at reappraisal, in which case the reversal cost is not incurred.

We now compare the prices under the OWR scheme, $p_1^{*,\mathrm{W}}$ and $p_i^{*,\mathrm{W}}$, to the immediate approval price, p_0^*. An analogue to Corollary 1 can be shown for $p_1^{*,\mathrm{W}}$: the expected reappraisal price after an OWR scheme strictly exceeds the immediate approval price. The result for the interim price under the OWR scheme differs from that of its OIR counterpart, however. The OWR scheme's interim price includes partial reimbursement of the company's costs from the post-marketing trial, as well as partial compensation for the potential reversal cost that the payer may incur, whereas the OIR scheme's interim price includes only the former. Therefore, the relationship between the OWR scheme's interim price and the immediate approval price depends on the balance between these two effects. If the payer's share of the total post-marketing-trial cost exceeds the company's share of the reversal cost, $(1-\beta)(n^{*,\mathrm{W}}v_{DC} + f_{DC}) > \beta f_r$, an analogue to Corollary 2 can be shown: the interim price of an OWR scheme strictly exceeds the immediate approval price. Otherwise, the interim price of an OWR scheme falls below the immediate approval price.

The similarity of (13) and (21) also allows us to provide a sharp comparison of the preferability of the two schemes in certain cases. If $S_0(\mathrm{CA}^{\mathrm{I}}) = S_0(\mathrm{CA}^{\mathrm{W}})$, we break ties by choosing OIR.

Proposition 4.

i. *If* $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} < 0$, *then* $S_0(CA^I) > S_0(CA^W)$.

ii. *If* $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} = 0$, *then* $S_0(CA^I) = S_0(CA^W)$ *for* $f_r = 0$ *and* $S_0(CA^I) > S_0(CA^W)$ *for* $f_r > 0$.

iii. *If* $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} > 0$, *then there is an* $R > 0$ *such that* $S_0(CA^I) < S_0(CA^W)$ *for* $f_r < R$, $S_0(CA^I) = S_0(CA^W)$ *for* $f_r = R$, *and* $S_0(CA^I) > S_0(CA^W)$ *for* $f_r > R$.

To interpret Proposition 4, we recall that the expected surplus at initial submission for both schemes is the sum of the expected surplus during the post-marketing trial and that obtained at reappraisal. When the expected per-patient surplus at initial submission is negative, $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} < 0$, OWR's use of the new treatment for $Nt - n > n$ patients drives its total expected health-economic value below that of OIR, and the presence of reversal costs, $-f_r \le 0$, only makes the disparity worse.

In contrast, when $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} > 0$, an OWR scheme might be preferable to an OIR scheme under some conditions. In the absence of a reversal cost, $f_r = 0$, the new treatment's availability to a larger number of patients during the post-marketing trial makes OWR more

attractive than OIR. When there is a positive reversal cost, $f_r > 0$, this advantage that OWR may enjoy during the post-marketing trial may be more than outweighed by a lower expectation at reappraisal. In this case, we show that there is an upper threshold on the reversal cost, R, that determines which scheme is preferable. In Section 7.2, we explore the relationship between joint surpluses from OWR and OIR schemes for different values of the cost of reversal.

Details of the analysis and comparative statics results are in Online Appendices B.2 and C, respectively.

6. Impact of Cost-Effectiveness Constraints on the Interim Price

Although the UK Government's pricing guidelines (UK Department of Health and Social Care and Association of the British Pharmaceutical Industry 2018) support a bargaining approach to price determination, other guidance of NHS England (2016) suggests that the interim price should be lowered, if needed, to satisfy relevant cost-effectiveness thresholds. Such a limit has the potential to conflict with the interim price obtained via Nash bargaining, especially if the initial appraisal of expected effectiveness is low, data collection or production costs are high, or both. Here, we assess how constraints on the interim price can affect bargaining outcomes, first for OIR schemes and then for OWR schemes.

We let $\overline{p}_i$ denote an exogenously defined cap on the interim price and recall that the interim price for OIR schemes characterized in Proposition 3 is p_i^*. If $\overline{p}_i \geq p_i^*$, then the interim price obtained by bargaining does not violate the cap. If $\overline{p}_i < p_i^*$, however, then the Nash-bargaining price violates the cap, and the uniqueness of p_i^* implies that the two cannot be reconciled without some adjustment: either the cap or the details of our Nash bargaining model must be modified.

In fact, the players can effectively relax the details of our Nash bargaining model through the use of a contracting mechanism that guides the conditional approval process. We note that both the immediate costs of the post-marketing trial, $f_{DC} + nv_{DC}$, and the distribution of the subsequent benefits, $M_1 + p_S - v_N$, are common knowledge to the players, as is the ultimate realization once the trial completes, $\mu_1 + p_S - v_N$. Therefore, the costs and expected gains associated with conditional approval can be contracted upon in advance. (For example, see Hart and Moore 1988.)

Suppose that Nash bargaining at initial submission obtains the interim price, p_i^*, and $[\beta, (1-\beta)]$ shares of expected gains, as defined in Proposition 3. If $\overline{p}_i < p_i^*$, the players can use the capped interim price, $\overline{p}_i$, and still preserve the $[\beta, (1-\beta)]$ split of expected gains defined in Proposition 3 by explicitly adjusting the split of expected gains at reappraisal to compensate the company for the revenues lost during the post-marketing trial. Formally, they use the capped interim price, $\overline{p}_i$, and alternative fractions, $[\beta_1, (1-\beta_1)]$, to define analogues to (18) and (19) as follows:

$$V_0(\mathrm{CA}^{\mathrm{I}}, \overline{p}_i, n, t, \beta_1) = n(\mu_0 - \overline{p}_i + p_S) + (1-\beta_1)\mathbb{E}_{M_1}[S_1^*(t) \mid \mu_0, n_0], \text{ and} \tag{24}$$

$$\Pi_0(\mathrm{CA}^{\mathrm{I}}, \overline{p}_i, n, t, \beta_1) = n(\overline{p}_i - v_N) - f_{DC} - nv_{DC} + \beta_1 \mathbb{E}_{M_1}[S_1^*(t) \mid \mu_0, n_0], \tag{25}$$

and adding (24) and (25), they obtain $S_0(\mathrm{CA}^{\mathrm{I}}, n, t)$. Preserving the $[\beta, (1-\beta)]$ split implies:

$$V_0(\mathrm{CA}^{\mathrm{I}}, \overline{p}_i, n^*, t^*, \beta_1) = (1-\beta) S_0(\mathrm{CA}^{\mathrm{I}}) \quad \text{and}$$
$$\Pi_0(\mathrm{CA}^{\mathrm{I}}, \overline{p}_i, n^*, t^*, \beta_1) = \beta S_0(\mathrm{CA}^{\mathrm{I}}). \tag{26}$$

The players use (24)–(26) to identify and contract upon a β_1^* that is consistent with an outcome that divides the total expected surplus at initial submission according to $[\beta, (1-\beta)]$. If, in turn, OIR is the Nash bargaining outcome at initial submission, then at reappraisal, the players substitute β_1^* for β in (11) to determine p_1^*. If $\overline{p}_i \geq p_i^*$, then $\beta_1^* = \beta$ because no adjustment to the Nash solution is required. If $\overline{p}_i < p_i^*$, however, (24)–(26) imply that $\beta_1^* > \beta$: a lower interim price paid to the company is balanced by higher expected price at reimbursement.

Because cooperative bargaining is conserved at initial submission, the company's and the payer's incentives remain aligned, and they maintain the common objective of designing the post-marketing trial to maximize the expected joint surplus from the OIR scheme. Thus, they continue to agree to choose the same post-marketing trial parameters n^* and $t^* = 2n^*/(Nr_{max})$ identified in Section 4.2.3.

At the same time, when $\overline{p}_i < p_i^*$ and $\beta < \beta_1^* \leq 1$, the contracting mechanism matches the expected gains obtained through the less restrictive, bargaining-based interim price, p_i^*, by shifting the allocation of costs and rewards over time. In particular, the company bears a higher share of post-marketing-trial costs, but enjoys only a chance at earning higher rewards because these gains are obtained only should the new treatment ultimately be approved. Thus, the approach shifts financial risk from the payer to the company, and we refer to the scheme as a *risk-sharing contract*.

Furthermore, if $\overline{p}_i$ is far below p_i^*, then β_1^* might exceed one. In that case, the payer obtains a *negative* share of the gains at reappraisal. Proposition 5 shows when this is a concern, and Corollary 3 indicates how the cap can be set to avoid the problem.

Proposition 5. *Consider the case in which* $S_0(CA^I) \geq S_0(CA^W)$ *and* $S_0(CA^I) > 0$.

i. *If* $\overline{p}_i \geq p_i^*$, *then the interim price is* p_i^* *and* $\beta_1^* = \beta$.

ii. *If* $p_i^* > \overline{p}_i \geq p_i^* - (1-\beta)\mathbb{E}_{M_1}[S_1^*(t^*)|\mu_0, n_0]/n^*$, *then* $\beta < \beta_1^* \leq 1$,

iii. *If* $p_i^* - (1-\beta)\mathbb{E}_{M_1}[S_1^*(t^*)|\mu_0, n_0]/n^* > \overline{p}_i$, *then* $\beta_1^* > 1$ *and* $(1-\beta_1^*)\mathbb{E}_{M_1}[S_1^*(t^*)|\mu_0, n_0] < 0$.

Corollary 3. *If* $S_0(CA^I) \geq 0$ *and* $\beta < 1$, *then* $\overline{p}_i = \mu_0 + p_S$ *always satisfies case* (ii) *of Proposition 5.*

Recall from the first term of (6) that the new treatment is cost-effective when its expected INMB is nonnegative: $\mu_0 - p_i + p_S \geq 0$. Therefore, Corollary 3's cap of $\overline{p}_i = \mu_0 + p_S$ guarantees that the new treatment will be (marginally) cost-effective at the interim price and that a risk-sharing contract is implementable, so that the incentives of the players can be realigned. If the price cap is selected to be much lower than $\mu_0 + p_S$, however, as in case (iii) of Proposition 5, then even with the availability of a risk-sharing contract, cooperation may break down.

If OIR maximizes the joint surplus under the original Nash bargaining scheme, but $p_i^* > \overline{p}_i$ and $\beta_1^* > 1$, then one or both of the players may be unwilling to pursue the surplus-maximizing course of action. The payer may balk at incurring losses at reappraisal or the company may refuse to enter an OIR scheme under the capped interim price. When it comes to the design of the post-marketing trial, the payer and the company's incentives may differ, and it is not immediately clear how the sample size and the duration of the post-marketing trial would be determined.

If OWR is preferred to OIR, one can prove analogous results. Let $\beta_1^{*,W}$ be the readjusted fraction to be used when OWR is the Nash negotiation outcome, and let $\tilde{N} \triangleq Nt^{*,W} - n^{*,W}$.

Proposition 6. *Consider the case in which* $S_0(CA^W) > S_0(CA^I)$ *and* $S_0(CA^W) > 0$.

i. *If* $\overline{p}_i \geq p_i^{*,W}$, *then the interim price is* $p_i^{*,W}$ *and* $\beta_1^{*,W} = \beta$.

ii. *If* $p_i^{*,W} > \overline{p}_i \geq p_i^{*,W} - (1-\beta)\mathbb{E}_{M_1}[S_1^{*,W}(t^{*,W})|\mu_0, n_0]/\tilde{N} + \beta f_r/\tilde{N}$, *then* $\beta < \beta_1^{*,W} \leq 1$,

iii. *If* $p_i^{*,W} - (1-\beta)\mathbb{E}_{M_1}[S_1^{*,W}(t^{*,W})|\mu_0, n_0]/\tilde{N} + \beta f_r/\tilde{N} > \overline{p}_i$, *then* $\beta_1^{*,W} > 1$ *and* $(1-\beta_1^{*,W})\mathbb{E}_{M_1}[S_1^{*,W}(t^{*,W})|\mu_0, n_0] < 0$.

Corollary 4. *If* $S_0(CA^W) \geq 0$ *and* $\beta < 1$, *then* $\overline{p}_i = \mu_0 + p_S$ *always satisfies case* (ii) *of Proposition 6.*

Thus, the imposition of an interim price cap can potentially transform conditional approval from the preferred option into to an unacceptable alternative, reducing the expected joint surplus that would have been obtainable via Nash bargaining and destroying societal value. In the case of a treatment for which $S_0(\mathrm{A}_0) < 0$ and either $S_0(\mathrm{CA}^{\mathrm{I}}) > 0$ or $S_0(\mathrm{CA}^{\mathrm{W}}) > 0$, the imposition of such a cap may block the approval of a treatment that ultimately may have made it to market through an OIR or OWR scheme.

We note that a cap with $\overline{p}_i \geq \mu_0 + p_S$ would not change the preference for OIR versus OWR when conditional approval is optimal. We also note that in cases (i) and (ii) of Propositions 5 and 6, and therefore under the hypothesis of Corollaries 3 and 4 as well, the negotiated prices if the treatment is accepted on reappraisel will be cost-effective at the CPQ threshold, λ, from (1).

7. Case Study: Votrient

We present a numerical case study that illustrates our Nash bargaining model, many of the issues raised for OIR and OWR schemes in Sections 4 and 5, and the interim price caps in Section 6. In Section 7.1, we use data from previous approval processes to parameterize our case-study example. In Section 7.2, we explore how Nash bargaining outcomes, the optimal sample size and duration of the post-marketing trial, and prices change with the cost of reversal when both OIR and OWR options are available for conditional approval. In Section 7.3, we illustrate the potential negative impact of the interim-price constraints addressed in Section 6, as well as the feasibility of our risk-sharing approach for mitigating adverse consequences. Together, Section 7.2 and Section 7.3 underscore that the role of the interim price in conditional approval scheme design is one of cost-sharing and is not aligned with current practices, which link interim price with initial estimates of a cost-effective price.

Our example is based, in part, on data from an OWR risk-sharing agreement between the NHS and GSK for Votrient (pazopanib).[1] Votrient, which was developed by GSK, is a tyrosine kinase inhibitor that is used in the treatment of advanced renal cell carcinoma. As a small-molecule treatment, Votrient does not require a specific new manufacturing infrastructure, and it can be produced for GSK by contract manufacturers. The example is illustrative and not intended to advocate for any specific medical treatment.

In 2011, the National Institute for Health and Care Excellence (NICE) conditionally approved Votrient with an OWR scheme, in which GSK would provide a future price update linked to the outcome of a trial called COMPARZ (National Institute for Health and Care Excellence 2011). Votrient entered the UK market while COMPARZ collected further data on its effectiveness relative to that of the current standard of care, Sutent (sunitinib). In 2013, NICE announced that, the cost-effectiveness of Votrient was re-evaluated based on the evidence collected in COMPARZ, and the UK health system approved Votrient for use at its initially approved price.

7.1. Parameter Values

Table 1 summarizes the parameter values used for the Votrient case study, together with their data sources.

Table 1. Parameter Values Used for the Votrient Case Study of Section 7

Parameter	Value	Source
λ	£30,000	NICE (2014)
μ_0	£2,049	Derived from NICE (2011)
Σ_X	£^{2}796,890^2	Derived from NICE (2011)
n_0	290	Derived from NICE (2011) and a noninformative prior assumption
p_S	£20,089	Derived from NICE (2009) and Motzer et al. (2009)
N	21,200	NICE (2011)
r_{max}	0.2	Derived from NICE (2011) and ClinicalTrials.gov (2010)
v_N	£1,205	Derived following the calculation method in Hill et al. (2016)
f_{DC}	£10×10^6	Derived from Sertkaya et al. (2014)
v_{DC}	£6,226	Derived from Sertkaya et al. (2014) and Moore et al. (2018)

Along with these estimates, our examples cover a range of values for the "bargaining power" parameter, $\beta \in \{0.1, 0.2, \ldots, 0.9, 1\}$, and for the cost of reversal parameter, $f_r \in \{0, 10^7, 2 \times 10^7, \ldots, 99 \times 10^7, 100 \times 10^7\}$. Online Appendix D.1 provides details of how we derive the parameter values summarized in Table 1 from regulatory and industry sources.

7.2. Impact of the Cost of Reversal in OWR Schemes

To explore the relationships studied in Section 5, we numerically analyze how our example's Nash bargaining solution, post-marketing trial sample size, and prices change with the cost of reversal. We begin with the Nash bargaining solution.

The joint surpluses from immediate approval and rejection directly follow from their definitions: $S_0(\mathrm{A}_0) =$ £444 million and $S_0(\mathrm{R}_0) =$ £0. To find $S_0(\mathrm{CA}^{\mathrm{I}})$ and $S_0(\mathrm{CA}^{\mathrm{W}})$, we recall that both $S_0(\mathrm{CA}^{\mathrm{I}}, n, t)$ and $S_0(\mathrm{CA}^{\mathrm{W}}, n, t)$ decrease as t increases for any given n. Therefore, we calculate $S_0(\mathrm{CA}^{\mathrm{I}}, n, t)$ for $n \in \{1, 2, \ldots, Nr_{max}/2\}$ and let $t = 2n/(Nr_{max})$. We find that $n^* = 219$, $t^* = 0.1033$, and $S_0(\mathrm{CA}^{\mathrm{I}}) =$ £477 million for the case-study parameter values. We also find the n that achieves the highest $S_0(\mathrm{CA}^{\mathrm{W}}, n, t)$ for each f_r and call the OWR scheme's optimal trial size $n^{*,\mathrm{W}}$.

Figure 3 has three panels. Each depicts the Nash bargaining outcomes at initial submission for different values of μ_0 and n_0, and the three differ in their reversal costs. In each panel, treatments with high prior mean beliefs regarding INMB-p with and high effective sample sizes obtain immediate approval, whereas analogous treatments with low prior mean beliefs are immediately rejected. Conditional approval (OIR or OWR) is used either when the prior mean implies that the joint surplus from immediate approval is close to zero or when the effective number of samples is low, both cases in which $\mathbb{E}_{M_1}[p_1^* | M_1 \geq v_N - p_S]$ is much larger than p_0^* and for which the expected value of information is high.

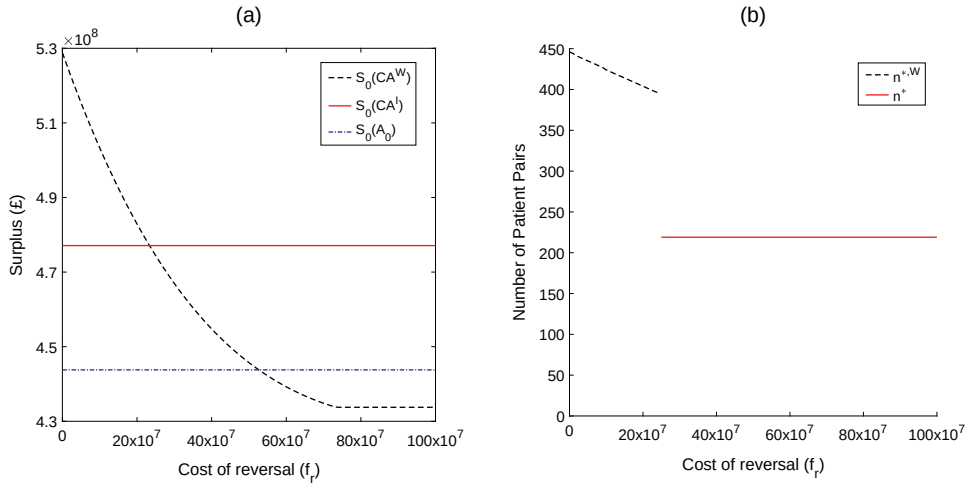
In Figure 3(a), the reversal cost is zero. For small n_0, for which CA schemes are optimal, the results are consistent with Proposition 4: the OWR scheme is the Nash outcome when $\mu_0 + p_S - v_N > 0$, and the OIR scheme is the outcome otherwise. In Figure 3(b), the reversal cost is positive, the region for OWR is smaller compared with that in Figure 3(a), and an OWR scheme is the Nash outcome for treatments with relatively high μ_0 and low n_0. In Figure 3(c), the reversal cost is high enough that an OWR scheme is never the Nash outcome.

Recall that Votrient received conditional approval through an OWR scheme, and on each of the panels, we mark the COMPARZ trial's (μ_0, n_0) coordinates with a "+" sign. From Figure 3, (a) and (b), we see that, given a low to moderate cost of reversal, an OWR scheme would have been optimal for Votrient. In contrast, from Figure 3(c), we see that, for a high cost of reversal, an OIR approach would have been preferable. Because Votrient was approved at the end of COMPARZ, it did not incur reversal costs, and we do not know what its f_r might have been. But the results reported in Figure 3 suggest that, in the context of our model, the decision to pursue an OWR scheme in COMPARZ appears to have been reasonable.

We can also explore the optimal choice of OIR/OWR and post-marketing trial design as a function of f_r. Figure 4(a) presents joint surpluses at initial submission for a range of reversal costs. If the cost of reversal is zero, then, as in Proposition 4, an OWR scheme obtains the highest joint surplus because Votrient's per-patient joint surplus is positive ($\mu_0 + p_S - v_N =$ £20,933 > 0). As the cost of reversal increases, however, the joint surplus of the OWR scheme decreases and drops below those for the OIR scheme and for immediate approval, which do not have reversal costs and remain constant. We see that the Nash bargaining outcome for Votrient is an OWR scheme if $f_r <$ £24×10^7 and is an OIR scheme otherwise.

In Figure 4(b), we see that the optimal sample size is higher for an OWR scheme, as compared with an OIR scheme, and the optimal sample size for the OWR scheme decreases in f_r. The post-marketing trial for an OIR scheme would run over about 10% of the drug's market exclusivity period and include about 2.1% ($2 \times n^*/N \times 100\%$) of the target population. In contrast the post-marketing trial for an OWR scheme would run

Figure 4. (Color online) The Effect of the Cost of Reversal on the Joint Surplus and Optimal Post-marketing Trial Size



Notes. (a) Joint surplus from an OWR scheme, and OIR scheme, and immediate approval. (b) Optimal number of patient pairs under OWR ($n^{*,\mathrm{W}}$) and OIR (n^*) schemes.

over about 19%–21% of the drug's market exclusivity period and include roughly 3.2%–4.7% of the target population. In comparison, COMPARZ was planned to take about 20% of the exclusivity period and included 4.1% ($876/N \times 100\%$) of the target population.

Finally, we consider the prices that would arise under different bargaining outcomes. Table 2 presents the prices associated with immediate approval, which is never the Nash negotiation outcome for the parameter values of Votrient case study; the OIR scheme, which is the Nash outcome if $f_r > £24 \times 10^7$; and the OWR scheme, which is the Nash outcome if $f_r < £24 \times 10^7$. We denote the event of the new treatment being approved upon reappraisal after an OIR scheme by $\mathcal{A}_1 \triangleq \{M_1 \geq v_{\mathcal{N}} - p_{\mathcal{S}}\}$ and after an OWR scheme by $\mathcal{A}_1^{\mathrm{W}} \triangleq \{M_1 \geq v_{\mathcal{N}} - p_{\mathcal{S}} - f_r/(N - 2n^{*,\mathrm{W}}/r_{max})\}$, and we report the expected reappraisal price conditional on approval at reappraisal. Table 2 assumes that $f_r = 0$. Online Appendix D.2 discusses qualitative observations for other values of $f_r > 0$, including those for which OIR is preferred.

Looking across each row for a given β, we see that the interim price and the expected reappraisal price (conditional on approval) are both higher than the immediate approval price, as is consistent with Corollaries 1 and 2 for OIR and the analysis in Online Appendix B.2 for OWR. The relationship between the interim price and the expected reappraisal price depends on the value of β for both the OIR and OWR scheme, however.

Table 2 also shows that the interim price under the OIR scheme is higher than that under the OWR scheme for each value of $\beta < 1$. We recall that the interim price under both OIR and OWR includes a partial reimbursement of the extra cost the company incurs to conduct a post-marketing trial. Under an OWR scheme with $f_r = 0$, this reimbursement is spread across $Nt^{*,\mathrm{W}} - n^{*,\mathrm{W}} = 4,014$ patients who use the new treatment during the post-marketing trial. Comparatively, under an OIR scheme, the reimbursement for the post-marketing trial is spread across only $n^* = 219$ patients. This leads to a significant difference between the OIR and OWR schemes' interim prices, because these per-patient prices reflect fixed costs, f_{DC}, that are allocated over patient cohorts that have significantly different sizes. Indeed, the interim price p_i^* for the OIR scheme can far exceed the cost-effectiveness threshold in this setting, particularly for low values of β. ICER estimates for Votrient

Table 2. Votrient Case Study: Bargaining Prices (in £) for Different Values of the Bargaining Power Parameter

	Immediate approval	OIR		OWR with $f_r = 0$	
Bargaining power	p_0^*	p_i^*	$\mathbb{E}_{M_1}[p_1^* \mid \mathcal{A}_1]$	$p_i^{*,\mathrm{W}}$	$\mathbb{E}_{M_1}[p_1^{*,\mathrm{W}} \mid \mathcal{A}_1^{\mathrm{W}}]$
$\beta = 0.1$	3,298	49,998	4,585	6,163	5,012
$\beta = 0.3$	7,485	43,807	11,344	9,713	12,625
$\beta = 0.5$	11,672	37,616	18,103	13,263	20,238
$\beta = 0.7$	15,858	31,425	24,862	16,813	27,852
$\beta = 0.9$	20,045	25,234	31,621	20,363	35,465
$\beta = 1.0$	22,138	22,138	35,001	22,138	39,272

Note. OWR is preferred to OIR here, because $f_r = 0$ for OWR in this table.

at p_i^* range from 75,522£/QALY to 439,700£/QALY, depending on the value of β, and all are above the 30,000£/QALY threshold often adopted by NICE.

For the special case of $\beta = 1$, in which cooperative bargaining degenerates to a Stackelberg game (see Online Appendix B.4 for a proof), Table 2 shows that the interim price under the OIR and OWR schemes are equal to the immediate approval price. That price is lower than the expected reappraisal price, conditioned on approval, with either scheme.

Conversely, Table 2 shows that the expected reappraisal price under the OWR scheme is higher than that under the OIR scheme for all values of β. Given the same mean μ_0 and Σ_0 in both schemes, as well as a zero reversal cost for OWR, the OWR scheme's larger sample sizes imply a systematically higher VoI and, in turn, higher expected prices at reappraisal.

Table 2 also shows that the effect of bargaining power on prices is consistent with the comparative statics results in Section 4.4 and Online Appendix C. Whereas immediate approval and expected reappraisal prices increase with β for both OIR and OWR, interim prices behave differently for the two schemes. For OIR, the interim price decreases as β increases, a reflection of the fact that large fixed trials costs are spread over only a small group of $n^* = 219$ subjects who will be charged the interim price, so that per-subject trial cost dominates the more modest increase in p_0^* that accompanies an increase in β. In contrast, the number of patients receiving the new treatment under OWR is 20-fold higher ($Nt^{*,\mathrm{W}} - n^{*,\mathrm{W}} = 4,014$), and the increase in p_0^* that accompanies β instead dominates the decrease in price associated with per-patient allocation of post-marketing trial costs.

7.3. Impact of Cost-Effectiveness Constraints on the Interim Price

In Section 6, we noted that cost-effectiveness considerations can motivate the payer to constrain interim prices and that these caps can result in infeasible Nash bargaining outcomes for the interim price. Here, we numerically illustrate the potential consequences of using caps on the interim price, and we use the solution approach proposed in Section 6 to show how surplus sharing can be adjusted at reappraisal to accommodate these constraints. For illustrative purposes, we focus on the OIR scheme and assume that the bargaining power of the company is $\beta = 0.5$, but the insights hold for other values of β and for the OWR scheme.

The cap on the interim price we study in this section is $\overline{p}_i = \mu_0 + p_S$ and is motivated by NHS England (2016). The price sets the INMB to zero so that the treatment is cost-effective at the cost-per-QALY threshold λ. At the same time, the company pays the full cost of the post-marketing trial and the full production cost. For the parameter values calculated for the case study, $\overline{p}_i = £22,138$.

We start by illustrating the consequences of putting a cap on the interim price. As explained in Section 6, a cap can break the Nash bargaining framework unless the bargaining process is modified. To show *how* it breaks, we assume that bargaining at the reappraisal stage proceeds without any adjustments, so that the expected surplus at reappraisal is split between players in proportion to their bargaining powers, $[\beta, 1-\beta]$. We calculate the company's expected profit under the cap from (25), $\Pi_0(\mathrm{CA}^{\mathrm{I}}, \overline{p}_i, n^*, t^*, \beta)$, and we divide by the expected joint surplus, $S_0(\mathrm{CA}^{\mathrm{I}})$, to find the *effective share* of the gain the company would receive if the interim price cap is implemented without any other adjustments to the bargaining process.

Figure 5(a) presents a contour plot of the company's effective share under the cap, $\overline{p}_i$, for various prior means and effective prior sample sizes. The dashed lines represent the boundary between conditional approval, immediate approval (A_0) and rejection (R_0) outcomes. Therefore the contour lines are only relevant between the dashed lines where the Nash outcome is conditional approval.

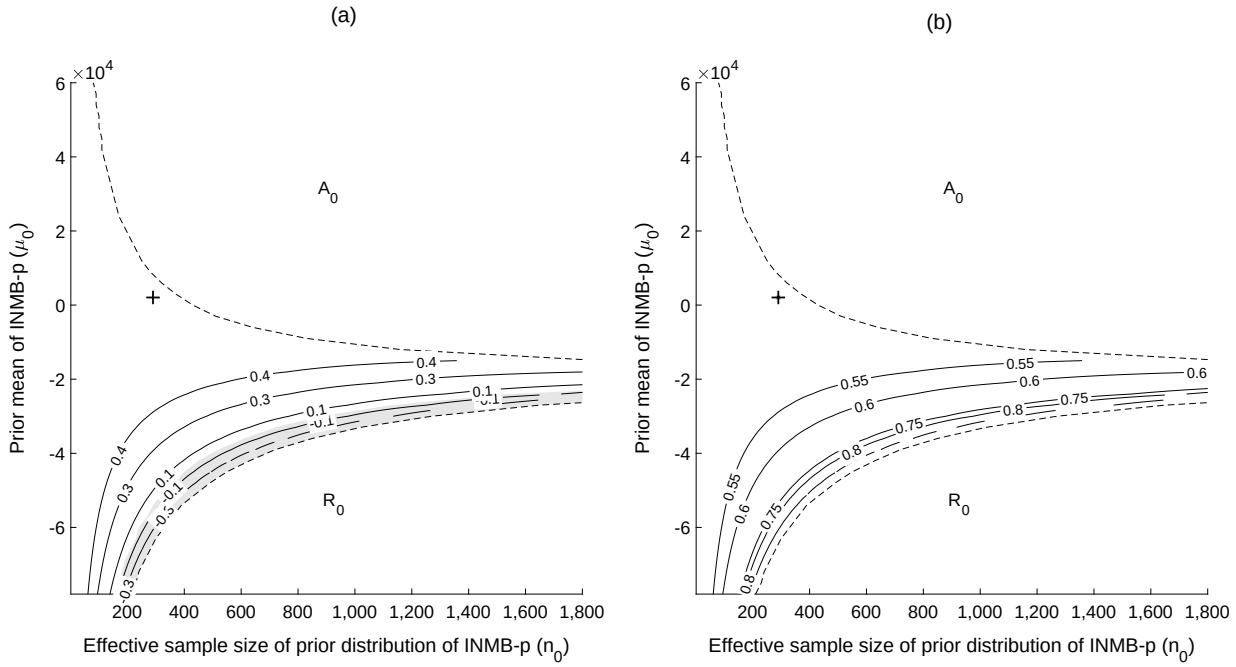
Figure 5(a) shows that, as expected, the company's effective share of the joint surplus under the cap falls below its bargaining power, $\beta = 0.5$, for all values of μ_0 and n_0, if advance contracting is not used. For the Votrient case study, the company's share is 0.486. (See "+" on Figure 5(a).) More generally, the company's share decreases as the prior mean decreases and as the effective sample size increases. In the shaded region that is closest to the boundary between conditional approval and rejection, the company's effective share of the surplus is negative.

Thus, in these cases, *the company would not enter into a conditional approval scheme*. Because the surplus at initial submission is negative, these treatments also would not be immediately approved at initial submission, and, as a result, they would be rejected.

Now, we explore the advance contracting mechanism proposed in Section 6 as a remedy for that breakdown. Figure 5(b) presents an analogous contour plot of β_1^* when advance contracting is used for different values of μ_0 and n_0. For the Votrient case study, $\beta_1^* = 0.507$. For treatments with lower prior means and higher effective samples sizes compared with the case study—which are also the closest to the boundary between conditional approval and rejection—the value of β_1^* is higher and is close to 0.9. This implies that the payer would share about 0.9 of the gain at the reappraisal with the company, even though the bargaining power of the company is only 0.5.

We tested different values of β to understand the range of possible values of β_1^*. For the Votrient case study, $\beta_1^* =$

Figure 5. Effect of Constraints on Interim Prices That May Be Inconsistent with Nash Bargaining Outcomes



Notes. Parameter values for Votrient case study are marked with "+." (Here, $\beta = 0.5$ and $f_r = 100 \times 10^7$, so that OWR is not preferred to OIR in this figure.) (a) The company's effective share of joint surplus under a cap on interim price without advance contracting. (b) The value of β_1^* obtained from advance contracting for different values of u_0 and n_0.

0.024 when $\beta = 0.01$, $\beta_1^* = 0.507$ when $\beta = 0.5$, and $\beta_1^* = 0.9901$ when $\beta = 0.99$. We see that the gap between β_1^* and β gets smaller as β increases. This means that the risk-sharing-based readjustment to β decreases with the company's bargaining power.

8. Probability of Cost-Effectiveness and Competitive Response

We now consider how CA schemes affect the payer's risks, as well as how competition from an incumbent manufacturer may affect the outcome of negotiation. In Section 8.1, we characterize the probability that a new treatment is cost-effective at the prices that arise from cooperative bargaining. This is an important measure of risk that follows from parameter uncertainty about the treatment's effectiveness and costs, due to limited data, and it has been used in practice (e.g., Barton et al. 2008, Danzon et al. 2018). In Section 8.2, we turn our attention to the probability of cost-effectiveness of an entire CA scheme. There are significant costs beyond the price of the treatment that are associated with implementing CA schemes, and here, we say a CA scheme is cost-effective if its total cost is less than the expected gain in health economic value achieved at the completion of the scheme. In Section 8.3, we consider the potential influence that price reductions offered by an incumbent manufacturer may have on the outcome of negotiations between the payer and the company.

8.1. Probability That a New Treatment Is Cost-Effective

A new treatment is considered cost-effective compared with the standard of care if its INMB, based on an expected population-wide benefit, exceeds zero (e.g., Claxton et al. 2005, Barton et al. 2008, Danzon et al. 2018). That INMB, in turn, depends on the negotiated price of the adopted treatment and on data available regarding its health benefits and other treatment costs. Because data are limited, there is uncertainty regarding the INMB. National Institute for Health and Care Excellence (2014, p. 119) highlights the need to explore the impact of parameter uncertainty on the results of the economic analysis. We analyze the probability of the new treatment being cost-effective, or, equivalently, the probability that the INMB is greater than zero, at the different prices that emerge from a bargaining process, given uncertainty regarding the treatment's effectiveness and cost.

We let $CE(p) \triangleq \{\theta - (p - p_S) > 0\}$ denote the event that the new treatment is cost-effective—that is, its INMB is positive at a given price, p. We then define a treatment's probability of cost-effectiveness at price p as the probability that the event $CE(p)$ realizes given the uncertainty about the INMB, $\theta \sim \texttt{Normal}(\mu_0, \Sigma_0)$, and, given that the price, p, can be negotiated. For example, the probability of cost-effectiveness at the immediate approval price, p_0^*, is $\mathbb{P}(CE(p_0^*) | \mu_0 \geq v_N - p_S)$, where the condition $\mu_0 \geq v_N - p_S$ ensures that an immediate approval price can be negotiated.

If $\mu_0 = v_{\mathcal{N}} - p_{\mathcal{S}}$, the negotiated immediate-approval price is cost-effective with a probability of 50%. However, if $\mu_0 > v_{\mathcal{N}} - p_{\mathcal{S}}$, we find that the probability that the negotiated immediate approval price results in a cost-effective treatment decreases in the company's bargaining power, β, and is 50% when the company has all of the bargaining power ($\beta = 1$). Thus, the risk neutrality assumption does *not* imply a probability of cost-effectiveness of 50%, a contrast with Danzon et al. (2018). This result extends to the reappraisal prices negotiated after an OIR or an OWR scheme with zero reversal cost. However, if the OWR scheme has significant reversal costs, then the probability of cost-effectiveness at the final reappraisal price might fall below 50% even when the payer has some bargaining power. We demonstrate these results in Online Appendix F.1.

We also show in Online Appendix F.1 that, for our case study, even though the information collected through conditional approval may lead to higher expected prices at reappraisal, as compared with the immediate approval price, these reappraisal prices may also be associated with higher probabilities of cost-effectiveness compared with the analogous probability for the immediate approval price.

8.2. Probability of a Conditional Approval Scheme Being Cost-Effective

We now study the probability of a CA scheme itself is cost-effective—that is, whether the expected gains in health-economic value achieved exceed the total cost associated with the scheme, including the treatment price, fixed and variable data collection costs, and potential reversal cost.

As an analogue to a treatment being cost-effective relative to the standard of care, we define the cost-effectiveness of a CA scheme in comparison with other negotiation outcomes. As a result, we have three probabilities of relative cost-effectiveness associated with each CA scheme: as compared with the competing CA scheme (OIR or OWR), immediate approval, and rejection. For example, to characterize the probability of cost-effectiveness of an OIR scheme, we track the unconditional probability that, as of the time of initial submission, the payer's total INMB under the OIR scheme is greater than that of each of the three alternatives—the OWR scheme, immediate approval, and rejection—and this results in three probabilities that are associated with the OIR scheme.

The main high-level insight from our analysis in Online Appendix F.2 is that, when the company's bargaining power is high, a CA scheme might have a low probability of being cost-effective, even if it is, in expectation, desirable. For our case study, we calculate the probability that the Nash outcome with the highest expected surplus (which is either an OIR or an OWR scheme, depending on the value chosen for the reversal cost) is cost-effective when compared with immediate approval, and this probability can be lower than 0.5. And the probability that the Nash outcome is cost-effective when compared with immediate rejection falls below 0.5 when the bargaining power of the company is high (e.g., $\beta > 0.8$ for $f_r = 0$ and $\beta > 0.6$ for $f_r = 30 \times 10^7$ in our case study).

We also observed that an increasing reversal cost leads to a decrease in the expected value of an OWR scheme, resulting in OIR becoming relatively more desirable. But even with high reversal costs, the probability that an OWR scheme is cost-effective relative to OIR can remain above 0.5.

8.3. What If a Competing Incumbent Lowers its Price?

As a response to the company's submission of the new treatment, the producer of a key component of the standard of care, who we call *the incumbent*, may attempt to maintain its position as technology provider by reducing its price. Such a discount reduces the INMB of the new treatment and, in turn, can change the payer's and company's bargaining outcome. For simplicity, we focus on the case in which only the OIR scheme is under consideration. Here, we sketch the high-level impact of the incumbent's action, which we analyze in more detail in Online Appendix F.3.

The mechanism by which a price reduction by the incumbent can alter the payer's and company's negotiation is a shift in the payer's disagreement outcome. Specifically, in the original OIR scheme analyzed in Section 3, the payer's rejection of the new treatment leads to disagreement outcomes of zero for both players. If the payer elects to take a discount from the incumbent and reject the new treatment, its disagreement outcome increases by the total value implied by the discount, whereas the company's disagreement value remains zero. Therefore, when the outcome is either immediate approval or rejection, the payer is able to appropriate the entire value obtained from the discount.

In turn, a discount implies that the value of μ_1 needed for the new treatment to be approved at reappraisal is higher under competition compared with the one under the original model. And at initial submission, the region for immediate approval in Figure 3(c) would be smaller under competition. If approved, the immediate approval and reappraisal prices are both weakly lower under competition.

9. Discussion and Conclusions

Conditional approval schemes can mitigate a healthcare payer's risk of approving a treatment that might be cost-ineffective or of rejecting a treatment that might be cost-effective, while potentially giving patients early access to promising new health technologies. They represent important tools to inform reimbursement

approval and pricing decisions in practice, but areas of concern with their implementation include two features we have studied in this paper: strategic behavior in payer-company price negotiations; and uncertainty in the health-economic value of the new technology.

For an interesting subset of CA schemes—for example, those in which costs to a drug developer are largely variable—our stylized model of immediate acceptance, immediate rejection, or the choice of an OIR or OWR scheme, along with associated prices, suggests two important implications for their analysis and practice, and it provides a new view on a third.

One, although strategic negotiation of the interim price per treatment has not been rigorously studied as such in the past, the interim price per treatment that is used during the CA scheme's post-marketing trial period is critical to the option's negotiation process and viability. Given the assumptions of our model, it is not appropriate to set the interim price based on the estimated cost-effectiveness target for the new treatment, as in the early betaferon risk-sharing scheme (UK Department of Health 2002, Boggild et al. 2009) and in more recent UK Cancer Drugs Fund guidance (NHS England 2016). Instead, it should be considered to be a cost-sharing mechanism for the CA scheme.

Two, interim-price caps that are in line with these UK examples may disincentivize firms from bringing some new treatments to market unless an additional risk-sharing mechanism is introduced. The mechanism we propose compensates a company affected by an interim-price cap with a higher price should the treatment ultimately be approved for reimbursement.

Three, our analysis of CA schemes underscores the observation that the use of value-based principles, paying more for better health outcomes, may require an explicit incorporation of price negotiation into health technology assessments. To wit, in many cases, the ICER assumes that cost and health effectiveness can be estimated separately, but value-based principles used within CA schemes imply that cost and price may both be influenced by health outcomes.

There are other interesting settings that might be studied by relaxing some of our assumptions: new health technologies, such as devices and diagnostics whose approval processes may be similar to, but different from, drug approval pathways; sequences of new treatments; treatments that have high fixed costs to the company associated with approval; price-sensitive demand; risk aversion; CA schemes that consider multiple subpopulations; different fixed costs to the payer to launch an OIR or OWR scheme or at approval; other market exclusivity models; a reversal cost that is correlated with the duration of or number of patients in the post-marketing trial or with posterior cost-effectiveness; surpluses that occur once market exclusivity ends; broader options for the post-marketing trial's design; and nuances among treatments for acute care versus chronic diseases. The extension of our model to health systems funded by a mix of public programs, private insurance, and out-of-pocket payments (as in the United States) may require the solution to multiple, simultaneous bargaining problems between the company and many payers. Different modeling may be useful to asses Medicare's push to lower prices for already-marketed drugs without considering QALYs.

That said, even if some of the paper's modeling assumptions are modified and some specific mathematical results change, it may be that some of its general implications may still hold. These questions point to interesting areas for further research.

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Endnote

[1] We use brand names in this section. Active ingredients are mentioned in parentheses.

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