Conditional Approval and Value-Based Pricing for New Health Technologies

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Health technology assessments often inform decisions made by public payers, such as the UK's NHS, 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-QALY (CPQ). 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 models this distinction but 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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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 (EMA 2022, MHRA 2023). Emanuel et al. (2020) review the purchasing processes of six countries and find that all except the US 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 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., OECD 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 UK, for example, the relevant CPQ threshold might be 30,000£/QALY (NICE 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. While this point of view that 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 DOH 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 US's Centers for Medicare & Medicaid Services (CMS 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, (c) the process of implementing a given CA scheme itself is cost effective.

In §1, 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 §2, 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 §3, 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 §4, 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 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 §3 and §4 regarding the interim prices that are used during the post-marketing trial. While 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 §5 that caps on the interim price, such as those recommended in current UK Cancer Drugs Fund (CDF) 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 §6, 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 §5.

In §7, 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 §7 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 UK and other socialized health systems, so we focus on the case of one company and one payer. It is less well suited for the US, 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 §8.

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

1. 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.

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 tradeoffs. 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 §7.

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 de-listing 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).

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 Dept. of Health and Social Care and the Association of the British Pharmaceutical Industry (UK DHSC and ABPI 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, NICE 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.

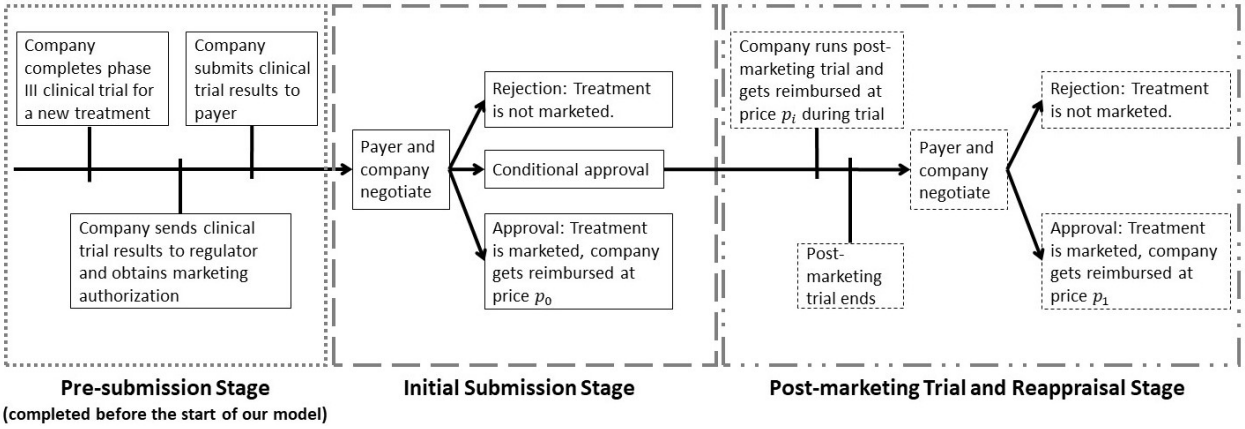
Berdud et al. (2023) also use a stylized Nash bargaining model for a finite set of new treatments to study how to split surpluses between payer and drug producers, but they assume that ICERs are known and do not model uncertainty about them. Other work also uses a Nash bargaining framework to characterize 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.

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 (Gavious et al. 2014, Zhang et al. 2011, 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, Olsder et al. 2022, Adida 2021, Xu et al. 2022). Our paper and those papers are complements.

2. 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

Figure 1 Model timeline. The pre-submission 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.



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 summarizes its notation.

2.1. 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 NICE (2021). In a *pre-submission 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 (OIR) scheme in §3 limits the use of the new treatment during the post-marketing trial to patients who are trial subjects. The only-with-research scheme (OWR, also called approval with research) in §4 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 §3 and §4, 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 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.

2.2. Parameters and Decision Variables for Post-Marketing Trial

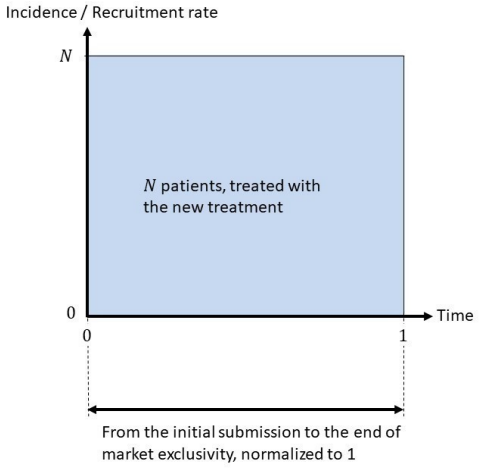
We define the post-marketing trial in terms of its sample size, n, and duration, t and assume the trial's finer details may be changed with no effect on our analysis, below. Thus, we implicitly assume that the time required to observe patient outcomes is small in comparison with the duration of the market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

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.

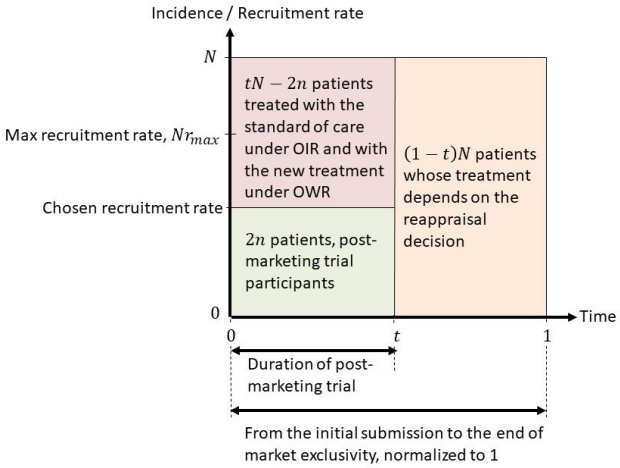
To describe the post-marketing trial, we define two decision variables: n, its sample size, measured in patient pairs, and $t \in (0, 1)$, the fraction of the market exclusivity period that the post-marketing

Figure 2 The number of patients treated with the standard of care and new treatment, represented as areas.

(a) If the new treatment is immediately approved.



(b) If the new treatment is conditionally approved.



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 $2n \leq t r_{max} N$.

In the OIR scheme of §3, 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 §4, 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, co-payments are often negligible or uniformly applied across treatments (e.g., a flat rate in the UK), 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.

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, respectively) in the patient population, expressed in terms of quality-adjusted life-years

(QALYs) and convert QALYs to a financial value using the cost-per-QALY (CPQ) threshold of the healthcare payer, which we denote by λ (e.g., 30,000£/QALY; also see NICE 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

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

While 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 $X^j \mid \theta \sim \texttt{Normal}\,(\theta, \Sigma_X)$ for each j. The variance in outcomes, Σ_X, is known and models random variation in the differences in outcomes across patient pairs.

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 post-adoption (Mantopoulos et al. 2015) and expert judgement using methods described elsewhere (e.g., O'Hagan et al. 2006).

After (noisy) outcomes $\vec{X}^n = (X^1, X^2, \ldots, X^n)$ 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, $M_1 = \mathbb{E}[\mu_1 \mid \vec{X}^n, \mu_0, n_0]$, 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

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

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.

2.3. 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 §7.

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

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

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

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

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 $\mathbb{E}\left[V_1^*(t) \,|\, \mu_0, n_0\right]$ 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,

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

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 §4 below.

2.4. 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

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

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

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

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 $\mathbb{E}\left[\Pi_1^*(t) \mid \mu_0, n_0\right]$ be the expectation of the company's post-reappraisal 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 post-trial 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

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

See §4 for a formulation and an analysis of OWR schemes.

3. 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 §4, we also analyze the OWR scheme.

Our analysis employs backwards 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 Appendix A and Lippman and McCardle 2012.) In §3.1 and §3.2, 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 §3.3, we summarize the Nash bargaining outcome of the two-stage model, and in §3.4 we present comparative statics results.

3.1. 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. 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 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:

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

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. Prop. 1 summarizes the results for Nash bargaining at reappraisal.

PROP. 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*

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

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.

3.2. 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.

3.2.1. Expected Payoffs from Immediate Approval. The decision to immediately approve the new treatment is analogous to that of approving the new treatment at reappraisal. While 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. Prop. 2 summarizes the Nash bargaining solution if the outcome of negotiation is to immediately approve at the initial submission stage.

PROP. 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*

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

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 pre-posterior 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 non-negative. Then* $p_0^* < \mathbb{E}_{M_1}\left[p_1^* \mid M_1 \geq v_{\mathcal{N}} - p_{\mathcal{S}}\right]$.

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).

3.2.2. 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

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

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).

3.2.3. 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

$$\max_{n,t} \left\{ S_0(\mathrm{CA}^{\mathrm{I}}, n, t) \;\middle|\; 0 \le 2n \le N r_{max} t \right\}. \tag{16}$$

In 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 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 $t = 2n/(N r_{max})$, 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

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

3.2.4. 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 $t^* = 2n^*/(N r_{max})$ and $\mathbb{E}_{M_1}\left[S_1^*(t^*) \,|\, \mu_0, n_0\right] = (N - 2n^*/r_{max})\sigma^*_{M_1}\psi\left((v_{\mathcal{N}} - p_{\mathcal{S}} - \mu_0)/\sigma^*_{M_1}\right)$, 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

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

and the company's expected profit (9) as

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

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

PROP. 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*

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

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 Prop. 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 §3.4 and numerically study the relationship between p_0^*, p_i^*, and $\mathbb{E}_{M_1}[p_1^* \mid M_1 \geq v_\mathcal{N} - p_\mathcal{S}]$ in §6.2.

3.3. 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 (Prop. 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 Prop. 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 non-negative and equal, we assume that the outcome chosen is immediate approval at price p_0^*. See Figure 3c below for a visualization of this result on the (μ_0, n_0) plane. (This result is broader than just for that specific example. See 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 an 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 (Prop. 1).

3.4. 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 Appendix C. 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 Prop. 2 that immediate approval can be optimal only when $S_0(\mathrm{A}_0) = N(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}}) \geq 0$.

Therefore, for all treatments that are immediately approved, the price, $p_0^* = v_{\mathcal{N}} + \beta(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}})$, (weakly) increases with β, and from Prop. 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 Prop. 3 that the interim price is $p_i^* = p_0^* + (1-\beta)(v_{DC} + f_{DC}/n^*)$. If $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} > 0$, 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 cost of the trial is high, then the last term of p_i^* will dominate, meaning that the interim price decreases with β. When $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} < 0$, 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.

4. 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 §3. 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

$$S_1^{*,\mathrm{W}}(t) \;=\; \max\{(1-t)N(\mu_1 + p_{\mathcal{S}} - v_{\mathcal{N}}), -f_r\}, \tag{20}$$

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):

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

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 §3. 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

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

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 Prop. 3: the immediate approval price, $p_0^* = v_{\mathcal{N}} + \beta(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}})$ from Prop. 2, plus a partial reimbursement of the costs 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 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:

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

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 Prop. 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 the payer may incur, while 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 $S_0(\mathrm{CA^I})=S_0(\mathrm{CA^W})$, we break ties by choosing OIR.

PROP. 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 Prop. 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, $-f_r\leq 0$ 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 §6.2 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 Appendices B.2 and C, respectively.

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

While the UK Government's pricing guidelines (UK DHSC and ABPI 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 Prop. 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, $M_1 + p_{\mathcal{S}} - v_{\mathcal{N}}$, are common knowledge to the players, as is the ultimate realization once the trial completes, $\mu_1 + p_{\mathcal{S}} - v_{\mathcal{N}}$. 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 Prop. 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 Prop. 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)-(19) as follows:

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

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

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

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

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 §3.2.3.

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, since 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 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. Prop. 5 shows when this is a concern, and Corollary 3 indicates how the cap can be set to avoid the problem.

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

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

COROLLARY 3. *If* $S_0(CA^I) \geq 0$ *and* $\beta < 1$, *then* $\overline{p}_i = \mu_0 + p_{\mathcal{S}}$ *always satisfies Case (ii) of Prop. 5.*

Recall from the first term of (6) that the new treatment is cost effective when its expected INMB is non-negative: $\mu_0 - p_i + p_{\mathcal{S}} \geq 0$. Therefore, Corollary 3's cap of $\overline{p}_i = \mu_0 + p_{\mathcal{S}}$, 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 $\mu_0 + p_{\mathcal{S}}$, however, as in Case (iii) of Prop. 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 $\beta_1^{*,\mathrm{W}}$ be the readjusted fraction to be used when OWR is the Nash negotiation outcome and let $\tilde{N} \triangleq Nt^{*,\mathrm{W}} - n^{*,\mathrm{W}}$.

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

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

COROLLARY 4. *If* $S_0(CA^W) \geq 0$ *and* $\beta < 1$, *then* $\overline{p}_i = \mu_0 + p_{\mathcal{S}}$ *always satisfies Case (ii) of Prop. 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 $\overline{p}_i \geq \mu_0 + p_{\mathcal{S}}$ would not change the preference for OIR versus OWR when conditional approval is optimal. We also note that in cases i. and ii. of Props. 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).

6. 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 §3–§4, and the interim price caps in §5. In §6.1, we use data from previous approval processes to parameterize our case-study example. In §6.2, 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 §6.3, we illustrate the potential negative impact of the interim-price constraints addressed in §5, as well as the feasibility of our risk-sharing approach for mitigating adverse consequences. Together, §6.2 and §6.3 underscore that the role of the interim price in conditional approval (CA) 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, 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 (NICE 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.

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

Table 1 Parameter values used for the Votrient case study of §6.

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 non-informative prior assumption
$p_{\mathcal{S}}$	£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)
$v_{\mathcal{N}}$	£1,205	Derived following the calculation method in Hill et al. (2016)
f_{DC}	$£10 \times 10^6$	Derived from Sertkaya et al. (2014)
v_{DC}	£6,226	Derived from Sertkaya et al. (2014) and Moore et al. (2018)

6.1. Parameter Values

Table 1 summarizes the parameter values used for the Votrient case study, together with their data sources. 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, $f_r \in \{0, 10^7, 2 \times 10^7, \ldots, 99 \times 10^7, 100 \times 10^7\}$. Appendix D.1 provides details of how we derive the parameter values summarized in Table 1 from regulatory and industry sources.

6.2. Impact of the Cost of Reversal in OWR Schemes

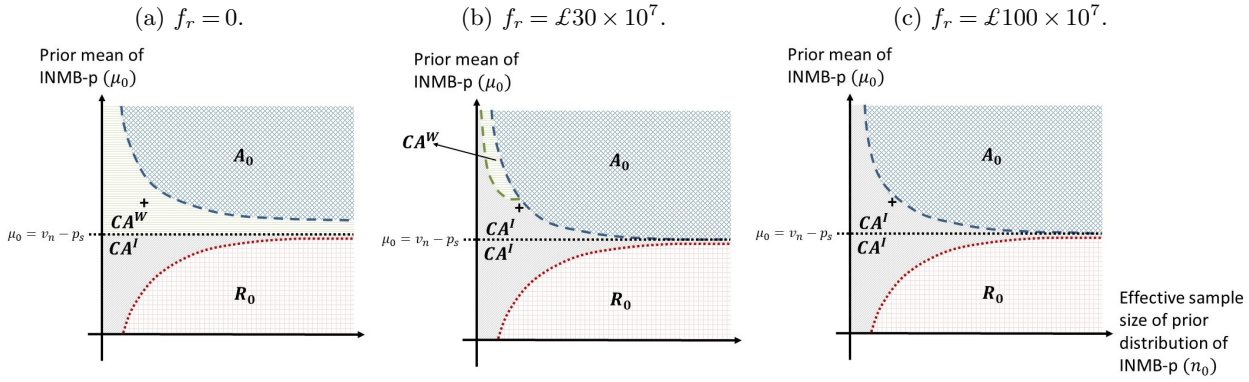
To explore the relationships studied in §4, we numerically analyze how our example's Nash bargaining solution, post-marketing trial sample size, and prices change with the cost of reversal. We begin with the Nash bargaining solution.

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, while 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 $\mathbb{E}_{M_1}[p_1^* \mid M_1 \geq v_{\mathcal{N}} - p_{\mathcal{S}}]$ is much larger than p_0^* and for which the expected value of information (VoI) is high.

In Figure 3a, the reversal cost is zero. For small n_0, for which CA schemes are optimal, the results are consistent with Prop. 4: the OWR scheme is the Nash outcome when $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} > 0$

Figure 3 **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. Parameter values for the Votrient case study are marked with '+'.**



and the OIR scheme is the outcome otherwise. In Figure 3b, the reversal cost is positive, the region for OWR is smaller compared to that in Figure 3a, and an OWR scheme is the Nash outcome for treatments with relatively high μ_0 and low n_0. In Figure 3c, the reversal cost is high enough that an OWR scheme is never the Nash outcome.

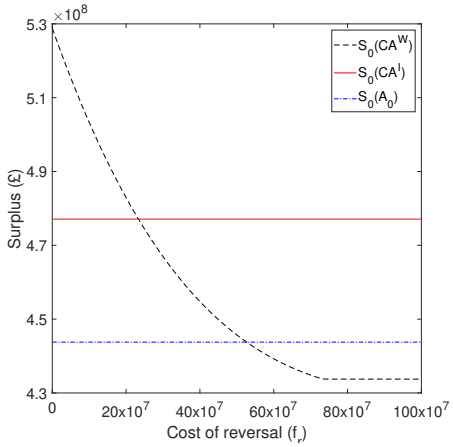
Recall that Votrient received conditional approval through an OWR scheme, and on each of the panels we mark the COMPARZ trial's (μ_0, n_0) coordinates with a '+' sign. From Figures 3a and 3b, we see that, given a low to moderate cost of reversal, an OWR scheme would have been optimal for Votrient. In contrast, from Figure 3c 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 4a presents joint surpluses at initial submission for a range of reversal costs. If the cost of reversal is zero then, as in Prop. 4, an OWR scheme obtains the highest joint surplus, since Votrient's per-patient joint surplus is positive ($\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} = £20{,}933 > 0$). 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 $f_r < £24 \times 10^7$ and is an OIR scheme otherwise.

In Figure 4b we see that the optimal sample size is higher for an OWR scheme as compared to 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

Figure 4 The effect of the cost of reversal on the joint surplus and optimal post-marketing trial size.

(a) Joint surplus from an OWR scheme, an OIR scheme and immediate approval.



(b) Optimal number of patient pairs under OWR ($n^{*,\mathrm{W}}$) and OIR (n^*) schemes.

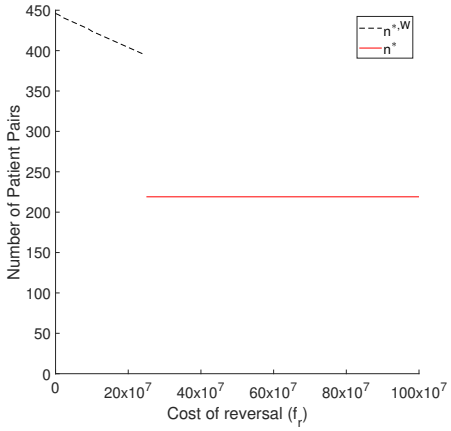


Table 2 Votrient Case Study: Bargaining prices (in £) for different values of the bargaining power parameter. (OWR is preferred to OIR here, because $f_r = 0$ for OWR in this table).

Bargaining	Immediate Approval	OIR		OWR with $f_r = 0$	
power	p_0^*	p_i^*	$\mathbb{E}_{M_1}[p_1^* \mid \mathcal{A}_1]$	$p_i^{*,\mathrm{W}}$	$\mathbb{E}_{M_1}[p_1^{*,\mathrm{W}} \mid \mathcal{A}_1^W]$
$\beta = 0.1$	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

trial for an OWR scheme would run 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 $\mathcal{A}_1^W \triangleq \{M_1 \geq v_{\mathcal{N}} - p_{\mathcal{S}} - f_r/(N - 2n^{*,\mathrm{W}}/r_{max})\}$, and we report the expected reappraisal price conditional on approval at reappraisal. Table 2 assumes that $f_r = 0$. 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 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 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 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 §3.4 and Appendix C. While 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.

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

In §5 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 §5 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 $\overline{p}_i = \mu_0 + p_{\mathcal{S}}$ 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 §5, 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 5a 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.

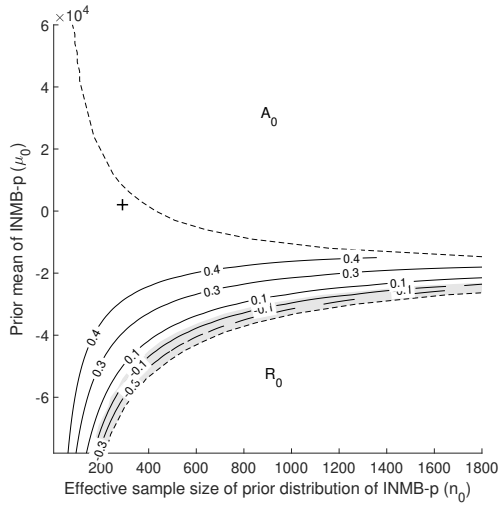
Figure 5a shows that, as expected, the company's effective share of the joint surplus under the cap falls below its bargaining power, $\beta = 0.5$, for all values of μ_0 and n_0, if advance contracting is not used. For the Votrient case study, the company's share is 0.486. (See '+' on Figure 5a.) More 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.

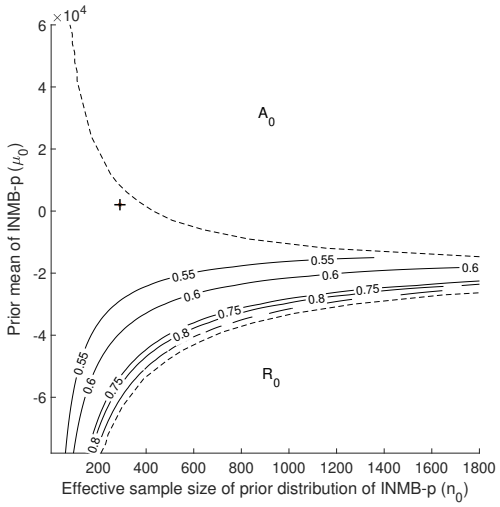
Now we explore the advance contracting mechanism proposed in §5 as a remedy for that breakdown. Figure 5b presents an analogous contour plot of β_1^* when advance contracting is used for different values of μ_0 and n_0. For the Votrient case study, $\beta_1^* = 0.507$. For treatments with lower prior means and higher effective samples sizes compared to the case study – which are also the closest to the boundary between conditional approval and rejection – the value of β_1^* is higher and

Figure 5 Effect of constraints on interim prices that may be inconsistent with Nash bargaining outcomes. 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 values of β_1^* obtained from advance contracting for different values of μ_0 and n_0.



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 Votrient case study, $\beta_1^* = 0.024$ 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.

7. 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 §7.1 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 §7.2 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 §7.3 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.

7.1. Probability that a New Treatment is Cost-effective

A new treatment is considered cost-effective compared to 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. NICE (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 $CE(p) \triangleq \{\theta - (p - p_{\mathcal{S}}) > 0\}$ denote the event that the new treatment is cost-effective, i.e., 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 $\mathbb{P}(CE(p_0^*)|\mu_0 \geq v_{\mathcal{N}} - p_{\mathcal{S}})$, where the condition $\mu_0 \geq v_{\mathcal{N}} - p_{\mathcal{S}}$ 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 Appendix F.1.

We also show in 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 to the immediate approval price, these reappraisal prices may also be associated with higher probabilities of cost effectiveness compared to the analogous probability for the immediate approval price.

7.2. Probability of a Conditional Approval (CA) Scheme Being Cost-effective.

We now study the probability of a CA scheme itself is cost-effective, i.e., 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 to other negotiation outcomes. As a result, we

have three probabilities of relative cost-effectiveness associated with each CA scheme: as compared to 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 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 to immediate approval, and this probability can be lower than 0.5. And the probability that the Nash outcome is cost-effective when compared to 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.

7.3. 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 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, while 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 to the one under the original model. And at initial submission, the region for immediate approval in Figure 3c would be smaller under competition. If approved, the immediate approval and reappraisal prices are both weakly lower under competition.

8. Discussion and Conclusions

Conditional approval (CA) 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 DOH 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 US) 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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Online Companion: Appendices

Table EC.1 includes a table that summarizes the notation for our model. Appendix A recalls elements of the Nash bargaining problem that will be relevant to our model and its analysis. Appendix B provides the mathematical results that support the claims made in §3, §4 and §5, as well as the connection between the two-stage Nash bargaining model with $\beta = 1$ and a Stackelberg game with a price-setting company. Appendix C presents comparative statics results that assess the effect of key parameters on the Nash bargaining outcome of our two-stage model, on the optimal sample sizes of the post-marketing trial, and on the prices that arise from bargaining. Appendix D shows how parameter values were chosen for the Votrient case study presented in §6 and presents additional numerical results based on the case study. Appendix E extends Appendices C and D by providing numerical comparative statics for our case study and for parameters whose comparative statics are not unambiguously signed. Appendix F presents supporting analysis and additional insights regarding the discussion on assumptions in §7.

Appendix A: Summary of Nash Bargaining As It Applies to Our Model

We present an introduction to the asymmetric, two-person Nash bargaining problem. This introduction enables a more self-contained discussion of our model and its analysis. Nash's formulation of the problem is based on the assumption that the payoffs of the two players at the end of the bargaining process should depend only on (1) the payoffs they would expect if they fail to reach an agreement at the end of bargaining, and (2) the set of payoffs that are jointly feasible for the two players in the process of bargaining. Nash's original formulation of the bargaining problem involves two players whose positions in the bargaining game are symmetric. We focus on the asymmetric case which involves two players with asymmetric bargaining power. See Myerson (1997) for further discussion on Nash bargaining, and see Lippman and McCardle (2012) for the use of subgame perfection to embed Nash bargaining within a multi-stage game.

Let $\mathcal{F}$ to denote the feasible set of the bargaining game, which consists of a set of possible payoffs of players attainable through agreement. Let d represent the disagreement payoffs the players obtain if they fail to reach agreement. A two-person bargaining problem consists of a pair $(\mathcal{F}, d)$, where $\mathcal{F}$ is a closed and convex subset of $\mathbb{R}^2$, $d = (d_1, d_2)$ is a vector in $\mathbb{R}^2$, and the set $\mathcal{F} \cap \{(x_1, x_2) : x_1 \geq d_1 \text{ and } x_2 \geq d_2\}$ is bounded. If the two players fail to reach an agreement, player $i = 1, 2$ receives d_i, and if the two players agree on a point $(x_1, x_2) \in \mathcal{F}$, then player $i = 1, 2$ receives x_i.

If the set $\mathcal{F} \cap \{(x_1, x_2) : x_1 \geq d_1 \text{ and } x_2 \geq d_2\}$ is empty for a bargaining problem, we say that bargaining fails, and both payers receive their disagreement payoffs. We continue with the cases in which the bargaining problem satisfies the non-emptiness condition.

The assumption that $\mathcal{F}$ is convex can be justified by allowing the players to agree on implementing jointly randomized strategies. The assumption that $\mathcal{F}$ is closed is a natural topological requirement. The non-emptiness and boundedness conditions mean that some feasible payoff through agreement is at least as good as disagreement for both players, but unbounded gains over the disagreement point are not possible.

The solution to a bargaining problem, $(\mathcal{F}, d)$, is a function, denoted by $\phi(\mathcal{F}, d)$, that maps any two-person bargaining problem to a set of payoffs in $\mathbb{R}^2$. We let $\phi_i(\mathcal{F}, d)$ denote the ith component of $\phi(\mathcal{F}, d)$ and represent the payoff received by player $i = 1, 2$ based on the solution function.

Table EC.1 Principal Notation.

Symbol	*Definition*
N	Total number of patients who would switch to the new treatment if it were approved for use at the time of initial submission
X^j	Incremental net monetary benefit, excluding the price of the new treatment, relative to the standard of care, for patient pair j
θ	Expected incremental net monetary benefit per patient, excluding the price (INMB-p) of treatment, for the given population
Σ_X	Variance of noisy observations of differences in INMB-p from patient pairs
μ_0	Mean of the prior belief regarding the INMB-p per patient of the new treatment in the population, based on information at the time of initial submission
Σ_0	Variance of the prior belief regarding the INMB-p per patient of the new treatment in the population, based on information at the time of initial submission
n_0	Effective sample size of the prior belief regarding the INMB-p of the new treatment in the population, based on information at the time of initial submission
μ_1	Mean of the updated belief, at the end of the post-marketing trial, regarding the INMB-p per patient of the new treatment in the population
Σ_1	Variance of the updated belief, at the end of the post-marketing trial, regarding the INMB-p per patient of the new treatment in the population
t	Fraction of the market exclusivity period used for the post-marketing trial
n	Sample size (number of patient pairs) in the post-marketing trial
r_{max}	Upper limit on the proportion of patients that can be recruited into the post-marketing trial in a unit of time
f_{DC}	Fixed cost of running the post-marketing trial for further data collection ('DC')
v_{DC}	Variable cost per patient pair recruited during the post-marketing trial
f_r	Reversal cost if the new treatment is withdrawn at the end of an OWR scheme
$v_{\mathcal{N}}$	Variable, per-patient production cost of the new treatment
β	The company's Nash 'bargaining power'
$p_{\mathcal{S}}$	Per-patient price of the standard of care
p_0	Immediate-approval price of the new treatment at the time of initial submission
p_i	Interim price of the new treatment during the post-marketing trial
p_1	Price of the new treatment determined at the end of the post-marketing trial
$\mathcal{A}_1$	Event that the new treatment is approved at reappraisal after an OIR scheme, given $\{M_1 \geq v_{\mathcal{N}} - p_{\mathcal{S}}\}$
$\mathcal{A}_1^W$	Event that the new treatment is approved at reappraisal after an OWR scheme, given $\{M_1 \geq v_{\mathcal{N}} - p_{\mathcal{S}} - f_r/(N - 2n^{*,\mathrm{W}}/r_{max})\}$

Nash identified this solution function by taking an axiomatic approach. These axioms are a list of properties that a reasonable bargaining solution function needs to satisfy:

Axiom 1. Strong Efficiency. The solution to any two-person bargaining problem should be feasible and Pareto efficient. Formally, $\phi(\mathcal{F}, d)$ is in $\mathcal{F}$, and, for any $(x_1, x_2) \in \mathcal{F}$, if $x_1 \geq \phi_1(\mathcal{F}, d)$ and $x_2 \geq \phi_2(\mathcal{F}, d)$, then $x_1 = \phi_1(\mathcal{F}, d)$ and $x_2 = \phi_2(\mathcal{F}, d)$.

Axiom 2. Individual Rationality. The participation constraint of each player should be satisfied. Formally, $\phi_1(\mathcal{F}, d) \geq d_1$ and $\phi_2(\mathcal{F}, d) \geq d_2$.

Axiom 3. Scale Covariance. An increasing affine utility transformation that maintains ordering over preferences should not alter the outcome of the bargaining process. Formally, for any numbers $\lambda_1, \lambda_2, \gamma_1$ and γ_2 such that $\lambda_1 > 0$ and $\lambda_2 > 0$, if $G = \{(\lambda_1 x_1 + \gamma_1, \lambda_2 x_2 + \gamma_2) : (x_1, x_2) \in \mathcal{F}\}$ and $w = (\lambda_1 d_1 + \gamma_1, \lambda_2 d_2 + \gamma_2)$, then $\phi(G, w) = (\lambda_1 \phi_1(\mathcal{F}, d) + \gamma_1, \lambda_2 \phi_2(\mathcal{F}, d) + \gamma_2)$.

Axiom 4. Independence of Irrelevant Alternatives. Eliminating feasible alternatives that would not have been chosen, other than the disagreement point, should not affect the solution. Formally, for any closed convex set G, if $G \subseteq F$ and $\phi(\mathcal{F}, d) \in G$, then $\phi(G, d) \in G$.

Let β and $1-\beta$ denote the bargaining power of player 1 and 2, respectively. Then there is a unique solution function, $\phi(\mathcal{F}, d)$, that satisfies Axioms 1-4 above, and this solution function maximizes the following generalized Nash product for every two person bargaining problem, $(\mathcal{F}, d)$,

$$\phi(\mathcal{F}, d) \in \underset{(x_1,x_2)\in\mathcal{F}, x_1\geq d_1, x_2\geq d_2}{\arg\max} (x_1 - d_1)^{\beta}(x_2 - d_2)^{1-\beta}. \tag{EC.1}$$

A Nash bargaining problem is often used to model situations in which the two players attempt to reach an agreement on how to split a value, A, which can be random. In such situations, we write the feasible set of the problem as $\mathcal{F} = \{(\alpha A, (1-\alpha)A) : 0 \leq \alpha \leq 1\}$ and the disagreement outcome as $d = (d_1, d_2)$. Note that this also implies that $x_1 + x_2 = A$ for all $(x_1, x_2) \in \mathcal{F}$.

For such a bargaining problem, if $A \geq d_1 + d_2$, the solution to (EC.1) is $\phi(\mathcal{F}, d) = (d_1 + \beta(A - d_1 - d_2), d_2 + (1-\beta)(A - d_1 - d_2))$. In words, the Nash bargaining solution implies a split of the total joint surplus, $A - d_1 - d_2$, between two players that is proportional to their bargaining powers, and the share of the surplus is added to the disagreement outcome of each player: $x_1 = d_1 + \beta(A - d_1 - d_2)$ and $x_2 = d_2 + (1-\beta)(A - d_1 - d_2)$. If $A < d_1 + d_2$, there is no pair of feasible payoffs through agreement that is at least as good as disagreement for both players, bargaining fails, and both payers receive the payoffs at the disagreement point.

Appendix B: Proofs of Mathematical Claims

This appendix proves the mathematical claims made in the main text, except the ones for the discussion of assumptions in §7. See Appendix F for the supporting analysis for §7.

Appendix B.1 proves claims made in §3. Appendix B.2 similarly supports the results in §4. Appendix B.3 discusses the trade-offs associated with optimal sample size and duration of the post-marketing trial of OIR and OWR schemes and proves the existence of a unique, non-zero optimal sample size. Appendix B.4 introduces the Stackelberg game in which the company acts first as the price-setter and the payer then make an approval decision given the submitted price, and it proves the equivalence of the two-stage Nash bargaining model with $\beta = 1$ and the Stackelberg game. Appendix B.5 proves mathematical claims in §5.

B.1. Proofs of Mathematical Claims in §3

The proofs of propositions are presented throughout the text in §3. Here we present the derivations of the rest of the results.

Proof of Lemma 1. Consider the asymmetric bargaining problem in which the payer and the company negotiate to share the surplus from one of two possible bargaining outcomes, denoted by $S_0(\mathrm{A}_0)$ and $S_0(\mathrm{CA}^{\mathrm{I}})$, where β and $1-\beta$ denote the company's and payer's respective bargaining power.

Here, the constituent parameters of $S_0(\mathrm{A}_0)$, defined in (12), are all finite. Similarly, the boundedness of the loss function, (14), along with that of the other scaler parameters in the definition of $S_0(\mathrm{CA}^{\mathrm{I}})$ in (15), implies that $S_0(\mathrm{CA}^{\mathrm{I}})$ is finite as well. Thus, both surpluses are finite constants.

We can write the feasible set of the problem as $\mathcal{F}_0 = \{(\alpha S_0(\mathrm{A}_0), (1-\alpha)S_0(\mathrm{A}_0)) : 0 \leq \alpha \leq 1\} \cup \{(\alpha S_0(\mathrm{CA}^{\mathrm{I}}), (1-\alpha)S_0(\mathrm{CA}^{\mathrm{I}})) : 0 \leq \alpha \leq 1\}$ and the disagreement outcome as $d_0 = (0, 0)$.

We need to show that $\mathcal{F}_0$ is a convex and closed subset of $\mathbb{R}^2$. Given $0 \le \alpha \le 1$ and finite constants $S_0(\mathrm{A}_0)$ and $S_0(\mathrm{CA}^{\mathrm{I}})$, if follows that $\{(\alpha S_0(\mathrm{A}_0), (1-\alpha)S_0(\mathrm{A}_0)) : 0 \le \alpha \le 1\}$ and $\{(\alpha S_0(\mathrm{CA}^{\mathrm{I}}), (1-\alpha)S_0(\mathrm{CA}^{\mathrm{I}})) : 0 \le \alpha \le 1\}$ are convex and closed subsets of $\mathbb{R}^2$. As is common in the Nash bargaining literature, we allow the players to randomise their actions across the two disjoint sets of $\mathcal{F}_0$ (Myerson 1997), though we later show that randomized outcomes are never used in equilibrium. Under this assumption, $\mathcal{F}_0$ contains a convex combination of two convex and closed sets and therefore is also closed and convex.

As long as either $S_0(\mathrm{A}_0) \ge 0$ or $S_0(\mathrm{CA}^{\mathrm{I}}) \ge 0$ holds, $\mathcal{F}_0 \cap \{(x_1, x_2) : x_1 \ge 0 \text{ and } x_2 \ge 0\}$ is nonempty. If $S_0(\mathrm{A}_0) < 0$ and $S_0(\mathrm{CA}^{\mathrm{I}}) < 0$, there is no feasible solution to the bargaining problem, bargaining breaks down, and both players receive their respective disagreement outcomes (as in Appendix A). Otherwise the boundedness of $S_0(\mathrm{A}_0)$ and $S_0(\mathrm{CA}^{\mathrm{I}})$ imply that $\mathcal{F}_0 \cap \{(x_1, x_2) : x_1 \ge 0 \text{ and } x_2 \ge 0\}$ is bounded as well.

Then, we apply the Nash bargaining solution to the bargaining problem $(\mathcal{F}_0, d_0)$. If $S_0(\mathrm{CA}^{\mathrm{I}}) < S_0(\mathrm{A}_0)$, then $x_1 + x_2 \le S_0(\mathrm{A}_0)$ for all $(x_1, x_2) \in \mathcal{F}_0$ and the solution is $\phi(\mathcal{F}_0, d_0) = (\beta S_0(\mathrm{A}_0), (1-\beta)S_0(\mathrm{A}_0))$. If $S_0(\mathrm{CA}^{\mathrm{I}}) > S_0(\mathrm{A}_0)$, then $x_1 + x_2 \le S_0(\mathrm{CA}^{\mathrm{I}})$ for all $(x_1, x_2) \in \mathcal{F}_0$, and the solution is $\phi(\mathcal{F}_0, d_0) = (\beta S_0(\mathrm{CA}^{\mathrm{I}}), (1-\beta)S_0(\mathrm{CA}^{\mathrm{I}}))$. We break ties, $S_0(\mathrm{CA}^{\mathrm{I}}) = S_0(\mathrm{A}_0)$, by selecting $S_0(\mathrm{A}_0)$.

To summarize, the Nash bargaining solution implies that two players share the value that results in a larger joint surplus, $\max\{S_0(\mathrm{A}_0), S_0(\mathrm{CA}^{\mathrm{I}})\}$, and that the split of the total joint surplus between two players is proportional to their bargaining powers. □

Proof of Corollary 1. For $\mu_0 \ge v_{\mathcal{N}} - p_{\mathcal{S}}$,

$$\mathbb{E}_{M_1}\left[p_1^* \mid M_1 \ge v_{\mathcal{N}} - p_{\mathcal{S}}\right] = \frac{\int_{v_{\mathcal{N}} - p_{\mathcal{S}}}^{\infty} \left[v_{\mathcal{N}} + \beta(M_1 + p_{\mathcal{S}} - v_{\mathcal{N}})\right] dF(M_1)}{\mathbb{P}\left(M_1 > v_{\mathcal{N}} - p_{\mathcal{S}}\right)}$$
$$> v_{\mathcal{N}} + \beta \int_{-\infty}^{\infty} (M_1 + p_{\mathcal{S}} - v_{\mathcal{N}})\, dF(M_1) = v_{\mathcal{N}} + \beta(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}}) = p_0^*,$$

where M_1, defined in (2), has cumulative distribution function $F(M_1)$. □

Proof of Corollary 2. Follows directly from the definitions of p_0^* and p_i^*. □

B.2. Proofs of Mathematical Claims in §4

B.2.1. Analysis of The Reappraisal Stage when an OWR Scheme is Implemented. With the inclusion of a non-negative cost of reversal, $f_r \ge 0$, our cooperative bargaining model at the reappraisal stage corresponds to a Nash bargaining problem in which the disagreement outcome for the company is zero while the disagreement payoff for the payer is $-f_r$. As in Appendix A the Nash solution of such a bargaining problem is as follows. If the joint surplus that will be obtained with agreement is greater than the joint surplus at the disagreement outcome, the Nash bargaining solution implies that the difference between the two will be split proportionately, according to the players' bargaining powers, with the relevant share added to the disagreement payoff of each player. We use superscript 'W' to indicate that these results are associated with an OWR scheme, which might have a positive cost of reversal.

The joint surplus that will be obtained with agreement at reappraisal is $S_1(\mathrm{A}_1, t)$ and is defined in (10). If there is a disagreement, the joint surplus would be $-f_r$. The Nash solution implies that an agreement is reached only if

$$S_1(\mathrm{A}_1, t) = (1-t)N(\mu_1 + p_{\mathcal{S}} - v_{\mathcal{N}}) \ge -f_r, \quad \text{which holds if} \quad \mu_1 \ge v_{\mathcal{N}} - p_{\mathcal{S}} - f_r/((1-t)N).$$

If $\mu_1 < v_{\mathcal{N}} - p_{\mathcal{S}} - f_r/((1-t)N)$, bargaining breaks down, the treatment is rejected, the payer's and company's expected payouts are $-f_r$ and zero, respectively. If instead $\mu_1 \geq v_{\mathcal{N}} - p_{\mathcal{S}} - f_r/((1-t)N)$, and the Nash bargaining solution implies that

$$V_1^{\mathrm{W}}(\mathrm{A}_1, p_1, t) = -f_r + (1-\beta)(S_1(\mathrm{A}_1, t) - (-f_r)), \quad \Pi_1^{\mathrm{W}}(\mathrm{A}_1, p_1, t) = \beta(S_1(\mathrm{A}_1, t) - (-f_r)).$$

Using (5) and (8) and solving for p_1, we find $p_1^{*,\mathrm{W}}$, the reappraisal price for the Nash bargaining outcome. Prop. EC.1 summarizes the Nash bargaining outcome at the reappraisal stage for an OWR scheme with a non-negative cost of reversal.

PROP. EC.1. *Suppose that the post-marketing trial of an only with research scheme with the cost of reversal, $f_r \geq 0$, is completed and the players' belief regarding the unknown INMB-p 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*

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

If $\mu_1 \geq v_{\mathcal{N}} - p_{\mathcal{S}} - f_r/((1-t)N)$, the Nash bargaining outcome at the reappraisal stage is approval with the reappraisal price $p_1^{*,W} = v_{\mathcal{N}} + \beta(\mu_1 + p_{\mathcal{S}} - v_{\mathcal{N}}) + \beta f_r/((1-t)N)$. Otherwise, the Nash bargaining outcome at the reappraisal stage is rejection.

Comparing the reappraisal price under an OWR scheme to the immediate approval price, we have

COROLLARY EC.1. *Suppose $\mu_0 > v_{\mathcal{N}} - p_{\mathcal{S}}$ so that the joint surplus from immediate approval is non-negative. Then $p_0^* < \mathbb{E}_{M_1}\left[p_1^{*,W} \mid M_1 \geq v_{\mathcal{N}} - p_{\mathcal{S}} - f_r/((1-t)N)\right]$.*

Proof of Corollary EC.1. For $\mu_0 \geq v_{\mathcal{N}} - p_{\mathcal{S}}$,

$$\begin{aligned} \mathbb{E}_{M_1}\left[p_1^{*,\mathrm{W}} \mid M_1 \geq v_{\mathcal{N}} - p_{\mathcal{S}} - f_r/((1-t)N)\right] &= \frac{\int_{v_{\mathcal{N}} - p_{\mathcal{S}} - f_r/((1-t)N)}^{\infty} \left[v_{\mathcal{N}} + \beta(M_1 + p_{\mathcal{S}} - v_{\mathcal{N}} + f_r/((1-t)N))\right] dF(M_1)}{\mathbb{P}\left(M_1 > v_{\mathcal{N}} - p_{\mathcal{S}} - f_r/((1-t)N)\right)} \\ &> v_{\mathcal{N}} + \beta \int_{-\infty}^{\infty} (M_1 + p_{\mathcal{S}} - v_{\mathcal{N}})\, dF(M_1) + f_r/((1-t)N) \\ &> v_{\mathcal{N}} + \beta \int_{-\infty}^{\infty} (M_1 + p_{\mathcal{S}} - v_{\mathcal{N}})\, dF(M_1) \ = \ v_{\mathcal{N}} + \beta(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}}) \ = \ p_0^*, \end{aligned}$$

where M_1, defined in (2), has cumulative distribution function $F(M_1)$. □

Thus, given that a price at the initial submission can be negotiated, the expected price at the reappraisal will be greater, assuming it can be negotiated as well.

B.2.2. Analysis of The Initial Submission Stage when an OWR scheme is the Nash Outcome.

Now we find the prices and player payoffs in the event that the Nash bargaining outcome at initial submission is conditional approval with an OWR scheme. We use superscript 'W' to indicate that these results are associated with an OWR scheme which might have a positive cost of reversal.

Joint Surplus from an OWR Scheme. We define the payer's total expected INMB from an OWR scheme, as of the time of initial submission, as

$$V_0(\mathrm{CA}^{\mathrm{W}}, p_i, n, t) \triangleq (tN-n)(\mu_0 - p_i + p_{\mathcal{S}}) + \mathbb{E}_{M_1}\left[V_1^{*,\mathrm{W}}(t) \mid \mu_0, n_0\right], \tag{EC.2}$$

where p_i, n, and t are determined by negotiation, and $V_1^{*,\mathrm{W}}(t)$ is defined in Prop. EC.1 and depends on μ_1. The expectation is taken with respect to M_1, the preposterior distribution of μ_1 at initial submission. (See equations (3) and (11).) Note that under an OWR scheme, n patients receive the standard of care as a part of the post-marketing trial, and $tN-n$ patients receive the new treatment during the post-marketing data collection.

Similarly, the company's total expected profit from OWR, as of the time of initial submission, is

$$\Pi_0(\mathrm{CA}^{\mathrm{W}}, p_i, n, t) \triangleq (tN-n)(p_i - v_{\mathcal{N}}) - f_{DC} - nv_{DC} + \mathbb{E}_{M_1}\left[\Pi_1^{*,\mathrm{W}}(t) \mid \mu_0, n_0\right], \tag{EC.3}$$

where $\Pi_1^{*,\mathrm{W}}(t)$ is defined in Prop. EC.1.

As in §3.2.2, we obtain the joint surplus from an OWR scheme by adding (EC.2) and (EC.3).

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

where $S_1^{*,\mathrm{W}}(t)$ is defined in Prop. EC.1. By substituting M_1 for μ_1, taking expectations, and applying the definition of $\psi(x)$ we have

$$\begin{aligned} S_0(\mathrm{CA}^{\mathrm{W}}, n, t) \;=\; & (tN-n)(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}}) - f_{DC} - nv_{DC} \\ & - f_r + (1-t)N\sigma_{M_1}\psi\left(\frac{v_{\mathcal{N}} - p_{\mathcal{S}} - f_r/((1-t)N) - \mu_0}{\sigma_{M_1}}\right). \end{aligned} \tag{EC.4}$$

Designing the Post-Marketing Trial for an OWR scheme. As in §3.2.3, the payer and the company share a common interest in maximizing the joint surplus by solving the following optimization problem

$$\max_{n,t}\left\{S_0(\mathrm{CA}^{\mathrm{W}}, n, t) \mid 0 \le 2n \le Nr_{max}t\right\}. \tag{EC.5}$$

From (EC.4), we observe that increasing the duration of the post-marketing trial, t, has two opposing effects on the joint surplus. On one hand, more patients are treated with the new treatment during data collection as t increases. On the other hand, the number of patients that can be treated with the new treatment after the reappraisal decision decreases. To see how these two forces play out, we take the first derivative of (EC.4) with respect to t:

$$\begin{aligned} \frac{\partial S_0(\mathrm{CA}^{\mathrm{W}}, n, t)}{\partial t} \;=\; & N(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}}) - N\sigma_{M_1}\psi\left(\frac{v_{\mathcal{N}} - p_{\mathcal{S}} - f_r/((1-t)N) - \mu_0}{\sigma_{M_1}}\right) \\ & + (1-t)N\sigma_{M_1}\left[\Phi\left(\frac{v_{\mathcal{N}} - p_{\mathcal{S}} - f_r/((1-t)N) - \mu_0}{\sigma_{M_1}}\right) - 1\right]\left[\frac{-f_r}{(1-t)^2 N\sigma_{M_1}}\right] \\ =\; & N(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}}) - N\sigma_{M_1}\psi\left(\frac{v_{\mathcal{N}} - p_{\mathcal{S}} - f_r/((1-t)N) - \mu_0}{\sigma_{M_1}}\right) \\ & + \left[1 - \Phi\left(\frac{v_{\mathcal{N}} - p_{\mathcal{S}} - f_r/((1-t)N) - \mu_0}{\sigma_{M_1}}\right)\right]\frac{f_r}{(1-t)} \\ =\; & N(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} + f_r/((1-t)N)) - N\sigma_{M_1}\psi\left(\frac{v_{\mathcal{N}} - p_{\mathcal{S}} - f_r/((1-t)N) - \mu_0}{\sigma_{M_1}}\right) \\ & - \Phi\left(\frac{v_{\mathcal{N}} - p_{\mathcal{S}} - f_r/((1-t)N) - \mu_0}{\sigma_{M_1}}\right)\frac{f_r}{(1-t)}. \end{aligned}$$

The first derivative above is non-positive because $x \leq \psi(-x)$ implies $N(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} + f_r/((1-t)N)) \leq N\sigma_{M_1}\psi\left(\frac{v_{\mathcal{N}} - p_{\mathcal{S}} - f_r/((1-t)N) - \mu_0}{\sigma_{M_1}}\right)$ and $\Phi\left(\frac{v_{\mathcal{N}} - p_{\mathcal{S}} - f_r/((1-t)N) - \mu_0}{\sigma_{M_1}}\right)\frac{f_r}{(1-t)} \geq 0$. We conclude that the joint surplus from an OWR scheme decreases with t for a given n. Then (EC.5) 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 denote the optimal sample size and duration under an OWR scheme by $n^{*,\mathrm{W}}$ and $t^{*,\mathrm{W}}$, and we write the maximized joint surplus as

$$\begin{aligned} S_0(\mathrm{CA}^{\mathrm{W}}) &\triangleq S_0(\mathrm{CA}^{\mathrm{W}}, n^{*,\mathrm{W}}, t^{*,\mathrm{W}}) \\ &= n^{*,\mathrm{W}}(2/r_{max} - 1)(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}}) - f_{DC} - n^{*,\mathrm{W}} v_{DC} \\ &\quad - f_r + (N - 2n^{*,\mathrm{W}}/r_{max})\sigma^{*,\mathrm{W}}_{M_1}\psi\left(\frac{v_{\mathcal{N}} - p_{\mathcal{S}} - f_r/((N - 2n^{*,\mathrm{W}}/r_{max})) - \mu_0}{\sigma^{*,\mathrm{W}}_{M_1}}\right), \end{aligned} \tag{EC.6}$$

where $\sigma^{*,\mathrm{W}}_{M_1} \triangleq \sqrt{\Sigma_X n^{*,\mathrm{W}}/(n_0(n^{*,\mathrm{W}} + n_0))}$. In Appendix B.3, we show that the optimal sample size $n^{*,\mathrm{W}}$ and duration $t^{*,\mathrm{W}}$ are unique and nonzero whenever the OWR scheme is the Nash bargaining outcome.

Expected Payoffs from an OWR Scheme. By using (EC.2), (EC.3) and (EC.6), setting either $V_0(\mathrm{CA}^{\mathrm{W}}, p_i, n^{*,\mathrm{W}}, t^{*,\mathrm{W}}) = (1-\beta)S_0(\mathrm{CA}^{\mathrm{W}})$ or $\Pi_0(\mathrm{CA}^{\mathrm{W}}, p_i, n^{*,\mathrm{W}}, t^{*,\mathrm{W}}) = \beta S_0(\mathrm{CA}^{\mathrm{W}})$ and solving for p_i, we obtain the Nash bargaining outcome summarized in Prop. EC.2.

Prop. EC.2. *Suppose that the Nash bargaining outcome at the initial submission stage is an OWR conditional approval scheme with the cost of reversal, $f_r \geq 0$. Then the payer's INMB and the company's expected profit from conditional approval are*

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

where $S_0(CA^W)$ is defined in (EC.6). In turn, the interim price is

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

The first two terms of $p_i^{*,\mathrm{W}}$ are analogous to the interim price under the OIR scheme, p_i^*: the immediate approval price, p_0^*, plus a partial reimbursement of the extra costs 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 might incur if the treatment is rejected at the reappraisal. The difference between $p_i^{*,\mathrm{W}}$ and p_i^* stem from (i) the number of patients who receive the new treatment during the post-marketing data collection differ between OIR and OWR schemes, (ii) the optimal sample sizes for the post-marketing trials of OIR and OWR schemes are different, and (iii) the compensation for the reversal cost associated with the OWR scheme in the event of rejection after the post-marketing trial.

Furthermore, we have a result that is similar to Corollary 2 and that follows from the definition of $p_i^{*,\mathrm{W}}$:

Corollary EC.2. *Suppose that p_0^* and $p_i^{*,W}$ exist. If $(1-\beta)(n^{*,W} v_{DC} + f_{DC}) > \beta f_r$, then $p_0^* < p_i^{*,W}$. Otherwise, $p_0^* \geq p_i^{*,W}$.*

B.2.3. Nash Bargaining Solution when both OIR and OWR Conditional Approval Schemes are Feasible. We now discuss the Nash bargaining outcome at the initial submission stage when an OWR scheme is a feasible bargaining outcome in addition to an OIR scheme, immediate approval, and rejection. Extending the result in Lemma 1 to also account for OWR is straightforward. Therefore, in the initial submission stage, the joint surplus to be shared through bargaining is the maximum of the joint surplus from immediate approval, $S_0(\mathrm{A}_0)$, the joint surplus from an OIR scheme, $S_0(\mathrm{CA}^{\mathrm{I}})$, and the joint surplus from an OWR scheme, $S_0(\mathrm{CA}^{\mathrm{W}})$.

Prop. 4 summarizes the analytical results about the choice between OIR and OWR schemes. We present the proof below.

Proof of Prop. 4. We recall the definitions of $S_0(\mathrm{CA}^{\mathrm{I}})$ and $S_0(\mathrm{CA}^{\mathrm{W}})$ from (17) and (EC.6), respectively.

First, for claim i., we show that the joint surplus obtained from an OIR scheme is always higher than the one from an OWR scheme when $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} < 0$.

$$\begin{aligned}
S_0(\mathrm{CA}^{\mathrm{I}}) &\geq n^{*,\mathrm{W}}(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}}) - f_{DC} - n^{*,\mathrm{W}} v_{DC} + (N - 2n^{*,\mathrm{W}}/r_{max})\sigma^{*,\mathrm{W}}_{M_1}\psi\left(\frac{v_{\mathcal{N}} - p_{\mathcal{S}} - \mu_0}{\sigma^{*,\mathrm{W}}_{M_1}}\right) \\
&> n^{*,\mathrm{W}}(2/r_{max} - 1)(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}}) - f_{DC} - n^{*,\mathrm{W}} v_{DC} \\
&\quad + (N - 2n^{*,\mathrm{W}}/r_{max})\sigma^{*,\mathrm{W}}_{M_1}\psi\left(\frac{v_{\mathcal{N}} - p_{\mathcal{S}} - \mu_0}{\sigma^{*,\mathrm{W}}_{M_1}}\right) \\
&\geq n^{*,\mathrm{W}}(2/r_{max} - 1)(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}}) - f_{DC} - n^{*,\mathrm{W}} v_{DC} \\
&\quad - f_r + (N - 2n^{*,\mathrm{W}}/r_{max})\sigma^{*,\mathrm{W}}_{M_1}\psi\left(\frac{v_{\mathcal{N}} - p_{\mathcal{S}} - f_r/((N - 2n^{*,\mathrm{W}}/r_{max})) - \mu_0}{\sigma^{*,\mathrm{W}}_{M_1}}\right) \\
&= S_0(\mathrm{CA}^{\mathrm{W}}).
\end{aligned}$$

The first inequality holds for any arbitrary sample size, including $n^{*,\mathrm{W}}$, because $S_0(\mathrm{CA}^{\mathrm{I}})$ is optimized over the sample size. The second inequality follows because $2/r_{max} - 1 > 1$ and $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} < 0$. The third follows from the fact that $\psi(\cdot)$ is decreasing at a rate lower than 1. The equality follows from the definition of $S_0(\mathrm{CA}^{\mathrm{W}})$.

Second, for part of claim ii., we consider the case of $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} = 0$ and $f_r = 0$. The optimization problems (16) and (EC.5) are equal to each other, therefore $S_0(\mathrm{CA}^{\mathrm{I}}) = S_0(\mathrm{CA}^{\mathrm{W}})$.

Third, for the remainder of claim ii., we show $S_0(\mathrm{CA}^{\mathrm{I}}) > S_0(\mathrm{CA}^{\mathrm{W}})$ when $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} = 0$ and $f_r > 0$:

$$\begin{aligned}
S_0(\mathrm{CA}^{\mathrm{I}}) &= -f_{DC} - n^* v_{DC} + (N - 2n^*/r_{max})\sigma^*_{M_1}\psi(0) \\
&\geq -f_{DC} - n^{*,\mathrm{W}} v_{DC} + (N - 2n^{*,\mathrm{W}}/r_{max})\sigma^{*,\mathrm{W}}_{M_1}\psi(0) \\
&> -f_{DC} - n^{*,\mathrm{W}} v_{DC} - f_r + (N - 2n^{*,\mathrm{W}}/r_{max})\sigma^{*,\mathrm{W}}_{M_1}\psi\left(\frac{-f_r/((N - 2n^{*,\mathrm{W}}/r_{max}))}{\sigma^{*,\mathrm{W}}_{M_1}}\right) \\
&= S_0(\mathrm{CA}^{\mathrm{W}}).
\end{aligned}$$

The first equality follows because we assumed $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} = 0$. The inequality in the second line holds for any arbitrary sample size, including $n^{*,\mathrm{W}}$, because $S_0(\mathrm{CA}^{\mathrm{I}})$ is optimized over the sample size. The third line follows because $\psi(\cdot)$ is decreasing at a rate lower than 1. And the final equality follows from the definition of $S_0(\mathrm{CA}^{\mathrm{I}})$ when $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} = 0$.

Finally, for claim iii., we show that there is a threshold-type rule when $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} > 0$. It follows from the definition of $S_0(\mathrm{CA}^{\mathrm{I}})$ that the joint surplus from the OIR scheme is independent of f_r. To show the joint surplus from the OWR scheme strictly decreases with f_r, we use the envelope theorem and we take the first derivative of $S_0(\mathrm{CA}^{\mathrm{W}})$ with respect to f_r:

$$\begin{aligned}\frac{\partial S_0(\mathrm{CA}^{\mathrm{W}})}{\partial f_r} = \frac{\partial S_0(\mathrm{CA}^{\mathrm{W}}, n, t)}{\partial f_r} &= -1 + (1-t)N\sigma_{M_1}\left(\frac{-1}{((1-t)N)\sigma_{M_1}}\right)\left(\Phi\left(\frac{v_{\mathcal{N}} - p_{\mathcal{S}} - f_r/((1-t)N) - \mu_0}{\sigma_{M_1}}\right) - 1\right) \\ &= -\Phi\left(\frac{v_{\mathcal{N}} - p_{\mathcal{S}} - f_r/((1-t)N) - \mu_0}{\sigma_{M_1}}\right) < 0.\end{aligned}$$

We next show that $S_0(\mathrm{CA}^{\mathrm{W}}) > S_0(\mathrm{CA}^{\mathrm{I}})$ when $f_r = 0$.

$$\begin{aligned}S_0(\mathrm{CA}^{\mathrm{W}}) &\geq n^*(2/r_{max} - 1)(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}}) - f_{DC} - n^* v_{DC} + (N - 2n^*/r_{max})\sigma^*_{M_1}\psi\left(\frac{v_{\mathcal{N}} - p_{\mathcal{S}} - \mu_0}{\sigma^*_{M_1}}\right) \\ &> n^*(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}}) - f_{DC} - n^* v_{DC} + (N - 2n^*/r_{max})\sigma^*_{M_1}\psi\left(\frac{v_{\mathcal{N}} - p_{\mathcal{S}} - \mu_0}{\sigma^*_{M_1}}\right) \\ &= S_0(\mathrm{CA}^{\mathrm{I}}).\end{aligned}$$

The first inequality holds for any arbitrary sample size, including n^*, because $S_0(\mathrm{CA}^{\mathrm{W}})$ is optimized over the sample size. The second inequality follows because $2/r_{max} - 1 > 1$ and $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} > 0$, and the equality follows from the definition of $S_0(\mathrm{CA}^{\mathrm{I}})$.

Then, if $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} > 0$, there is a $R > 0$ such that $S_0(\mathrm{CA}^{\mathrm{I}}) < S_0(\mathrm{CA}^{\mathrm{W}})$ for $f_r < R$; $S_0(\mathrm{CA}^{\mathrm{I}}) = S_0(\mathrm{CA}^{\mathrm{W}})$ for $f_r = R$; and $S_0(\mathrm{CA}^{\mathrm{I}}) > S_0(\mathrm{CA}^{\mathrm{W}})$ for $f_r > R$. We note that, for the special case of $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} > 0$ and $f_r = 0$, we have $S_0(\mathrm{CA}^{\mathrm{I}}) < S_0(\mathrm{CA}^{\mathrm{W}})$. □

B.3. The Optimal Sample Size and Duration of OIR and OWR Schemes

We now characterize the solution of the optimal trial size and duration for the OIR and OWR conditional approval schemes, from the optimization problems in (16) and (EC.5), respectively. We will show that when an OIR or OWR scheme is the outcome of the negotiation, there is a unique, non-zero optimal trial size and duration.

The existence of optimal solutions for (16) and (EC.5) follows from the Weierstrass extreme value theorem. The functions being maximized, $S_0(\mathrm{CA}^{\mathrm{I}}, n, t)$ and $S_0(\mathrm{CA}^{\mathrm{W}}, n, t)$, are real-valued and continuous. And the feasible sets of both problems, $\{0 \leq 2n \leq N r_{max} t\}$, are closed and bounded. Therefore, $S_0(\mathrm{CA}^{\mathrm{I}}, n, t)$ and $S_0(\mathrm{CA}^{\mathrm{W}}, n, t)$ must attain a maximum in the set $\{0 \leq 2n \leq N r_{max} t\}$ at least once.

In 3.2.3 and B.2.2, we showed that it is optimal to complete the trial as quickly as possible for both OIR and OWR schemes. Therefore, we can set $t = 2n/(N r_{max})$ for any n. The optimization problem for an OIR scheme becomes $\max_n \left\{S_0(\mathrm{CA}^{\mathrm{I}}, n, 2n/(N r_{max})) \,|\, 0 \leq 2n \leq N r_{max}\right\}$, and the one for the OWR scheme becomes $\max_n \left\{S_0(\mathrm{CA}^{\mathrm{W}}, n, 2n/(N r_{max}) \,|\, 0 \leq 2n \leq N r_{max}\right\}$.

We discuss three trade-offs involved with choosing the optimal n before presenting the technical analysis. (1) Higher n implies that a higher number of patients are treated with the new treatment during the post-marketing trial (both for OIR and OWR schemes). For treatments with a positive expected INMB, $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} > 0$, a higher n increases the joint surplus because more patients have access to a treatment that provides positive benefit in expectation. For treatments with a negative expected INMB, $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} < 0$, a

higher n decreases the joint surplus because more patients are exposed to a treatment that does not provide a positive benefit in expectation. (2) Higher n increases the total cost of the post-marketing trial due to the variable data collection cost and, as a result, decreases the joint surplus. (3) The expected value of information to be gained from the post-marketing trial, not including sampling costs, increases with n.

OIR Scheme. We start by showing that the optimal sample size is non-zero if the OIR scheme is the bargaining outcome. If we have $\mu_0+p_{\mathcal{S}}-v_{\mathcal{N}}\geq 0$ and we set $n=0$, $S_0(\mathrm{CA}^{\mathrm{I}},0,0)=-f_{DC}+N(\mu_0+p_{\mathcal{S}}-v_{\mathcal{N}})<S_0(\mathrm{A}_0)$. And if we have $\mu_0+p_{\mathcal{S}}-v_{\mathcal{N}}<0$ and we set $n=0$, $S_0(\mathrm{CA}^{\mathrm{I}},0,0)=-f_{DC}<S_0(\mathrm{R}_0)$. Therefore, if the optimal sample size is zero, then the OIR scheme is not the bargaining outcome.

We continue with the case of $n>0$. To simplify the equations, we let $y\triangleq v_{\mathcal{N}}-p_{\mathcal{S}}-\mu_0$. The first derivative of $S_0(\mathrm{CA}^{\mathrm{I}},n,2n/(Nr_{max}))$ with respect n is

$$\begin{aligned}\frac{\partial S_0(\mathrm{CA}^{\mathrm{I}},n,2n/(Nr_{max}))}{\partial n}=&-y-v_{DC}-\frac{2}{r_{max}}\sigma_{M_1}\psi\left(\frac{y}{\sigma_{M_1}}\right)+\left(N-\frac{2n}{r_{max}}\right)\frac{\partial\sigma_{M_1}}{\partial n}\psi\left(\frac{y}{\sigma_{M_1}}\right)\\&+\left(N-\frac{2n}{r_{max}}\right)\sigma_{M_1}\frac{\partial\psi\left(y/\sigma_{M_1}\right)}{\partial n}.\end{aligned}$$

Recall the definition of the standard loss function, $\psi(y/\sigma_{M_1})=\phi(y/\sigma_{M_1})-(y/\sigma_{M_1})(1-\Phi(y/\sigma_{M_1}))$, then:

$$\frac{\partial\psi\left(y/\sigma_{M_1}\right)}{\partial n}=\left(1-\Phi\left(\frac{y}{\sigma_{M_1}}\right)\right)\frac{y}{\sigma_{M_1}^2}\frac{\partial\sigma_{M_1}}{\partial n},\text{ and }\frac{\partial\sigma_{M_1}}{\partial n}\psi\left(\frac{y}{\sigma_{M_1}}\right)+\sigma_{M_1}\frac{\partial\psi\left(y/\sigma_{M_1}\right)}{\partial n}=\frac{\partial\sigma_{M_1}}{\partial n}\phi\left(\frac{y}{\sigma_{M_1}}\right).$$

Therefore, we obtain the first derivative as

$$\frac{\partial S_0(\mathrm{CA}^{\mathrm{I}},n,2n/(Nr_{max}))}{\partial n}=-y-v_{DC}-\frac{2}{r_{max}}\sigma_{M_1}\psi\left(\frac{y}{\sigma_{M_1}}\right)+\left(N-\frac{2n}{r_{max}}\right)\frac{\partial\sigma_{M_1}}{\partial n}\phi\left(\frac{y}{\sigma_{M_1}}\right).\tag{EC.7}$$

We now derive the second derivative of $S_0(\mathrm{CA}^{\mathrm{I}},n,2n/(Nr_{max}))$ with respect n. We have

$$\begin{aligned}\frac{\partial^2 S_0(\mathrm{CA}^{\mathrm{I}},n,2n/(Nr_{max}))}{\partial n^2}=&-\frac{2}{r_{max}}\frac{\partial\sigma_{M_1}}{\partial n}\psi\left(\frac{y}{\sigma_{M_1}}\right)-\frac{2}{r_{max}}\sigma_{M_1}\frac{\partial\psi\left(y/\sigma_{M_1}\right)}{\partial n}-\frac{2}{r_{max}}\frac{\partial\sigma_{M_1}}{\partial n}\phi\left(\frac{y}{\sigma_{M_1}}\right)\\&+\left(N-\frac{2n}{r_{max}}\right)\frac{\partial^2\sigma_{M_1}}{\partial n^2}\phi\left(\frac{y}{\sigma_{M_1}}\right)+\left(N-\frac{2n}{r_{max}}\right)\frac{\partial\sigma_{M_1}}{\partial n}\frac{\partial\phi\left(y/\sigma_{M_1}\right)}{\partial n}\\=&-\frac{4}{r_{max}}\frac{\partial\sigma_{M_1}}{\partial n}\phi\left(\frac{y}{\sigma_{M_1}}\right)+\left(N-\frac{2n}{r_{max}}\right)\frac{\partial^2\sigma_{M_1}}{\partial n^2}\phi\left(\frac{y}{\sigma_{M_1}}\right)\\&+\left(N-\frac{2n}{r_{max}}\right)\frac{y^2}{\sigma_{M_1}^3}\phi\left(\frac{y}{\sigma_{M_1}}\right)\left(\frac{\partial\sigma_{M_1}}{\partial n}\right)^2,\end{aligned}$$

where the second equality follows from

$$\frac{\partial\phi\left(y/\sigma_{M_1}\right)}{\partial n}=\frac{y^2}{\sigma_{M_1}^3}\phi\left(\frac{y}{\sigma_{M_1}}\right)\frac{\partial\sigma_{M_1}}{\partial n},\text{ and }\frac{\partial\sigma_{M_1}}{\partial n}\psi\left(\frac{y}{\sigma_{M_1}}\right)+\sigma_{M_1}\frac{\partial\psi\left(y/\sigma_{M_1}\right)}{\partial n}=\frac{\partial\sigma_{M_1}}{\partial n}\phi\left(\frac{y}{\sigma_{M_1}}\right).$$

Using the following two equations

$$\frac{\partial\sigma_{M_1}}{\partial n}=\frac{\Sigma_X}{2\sigma_{M_1}(n+n_0)^2}\ ,\ \frac{\partial^2\sigma_{M_1}}{\partial n^2}=-\sigma_{M_1}\frac{n_0(4n+n_0)}{4n^2(n+n_0)^2},\tag{EC.8}$$

and rearranging the terms, we get

$$\begin{aligned}&\frac{\partial^2 S_0(\mathrm{CA}^{\mathrm{I}},n,2n/(Nr_{max}))}{\partial n^2}\\&=\phi\left(\frac{y}{\sigma_{M_1}}\right)\frac{-n^2(2n_0^2y^2+6n_0\Sigma_X+4Nr_{max}\Sigma_X)+n(-2n_0^3y^2+n_0^2Nry^2-n_0Nr_{max}\Sigma_X)+n_0^3Nr_{max}y^2}{4r_{max}n^2(n_0+n)^3\sigma_{M_1}}.\end{aligned}$$

The value in the denominator, $4r_{max}n^2(n_0+n)^3\sigma_{M_1}$, and $\phi(y/\sigma_{M_1})$ are positive for all $n>0$. In the nominator, we have a second-degree polynomial in n that is concave and whose discriminant is positive. Then, there are two roots for the polynomial. We can further show that one root is always negative and the other root is positive when $y=v_{\mathcal{N}}-p_{\mathcal{S}}-\mu_0\neq 0$ and is zero when $y=v_{\mathcal{N}}-p_{\mathcal{S}}-\mu_0=0$.

Now, we can analyze the sign of $\partial^2 S_0(\mathrm{CA^I},n,2n/(Nr_{max}))/\partial n^2$. If $\mu_0+p_{\mathcal{S}}-v_{\mathcal{N}}=0$, then $\partial^2 S_0(\mathrm{CA^I},n,2n/(Nr_{max}))/\partial n^2<0$ for $n>0$. If $\mu_0+p_{\mathcal{S}}-v_{\mathcal{N}}\neq 0$, there is a threshold $n_T>0$ such that $\partial^2 S_0(\mathrm{CA^I},n,2n/(Nr_{max}))/\partial n^2>0$ when $0<n<n_T$, $\partial^2 S_0(\mathrm{CA^I},n,2n/(Nr_{max}))/\partial n^2=0$ when $n=n_T$ and $\partial^2 S_0(\mathrm{CA^I},n,2n/(Nr_{max}))/\partial n^2<0$ when $n_T<n$.

To summarize, if $\mu_0+p_{\mathcal{S}}-v_{\mathcal{N}}=0$, then $S_0(\mathrm{CA^I},n,2n/(Nr_{max}))$ is concave in $0<n\leq Nr_{max}/2$, and the maximum is achieved either at $n=0$ or $n\in(0,Nr_{max}/2]$. And if $\mu_0+p_{\mathcal{S}}-v_{\mathcal{N}}\neq 0$, then $S_0(\mathrm{CA^I},n,2n/(Nr_{max}))$ is convex for $0<n<n_T$ and concave for $n_T<n\leq Nr_{max}$. Because the maximum of a convex function is at the extremes, the maximum is achieved either at $n=0$, $n=n_T$ or at a unique $n\in(n_T,Nr_{max}/2]$ where $n_T>0$.

We already showed that the OIR scheme is not optimal if the maximum is achieved at $n=0$. We can also show that the maximum is never achieved at $n=n_T$. We consider the following two cases separately: $\partial S_0(\mathrm{CA^I},n,2n/(Nr_{max}))/\partial n$ evaluated at $n=n_T$ is non-zero and $\partial S_0(\mathrm{CA^I},n,2n/(Nr_{max}))/\partial n$ evaluated at $n=n_T$ is zero. In the first case, the first derivative is non-zero therefore $n=n_T$ is not a local maximum. In the second case, the sign of the second derivative implies that the first derivative is increasing for $n<n_T$ and decreasing for $n>n_T$. Then, the first derivative would be negative in the neighborhood of n_T, and $n=n_T$ is not a local maximum.

As a result, if $\mu_0+p_{\mathcal{S}}-v_{\mathcal{N}}=0$ and the OIR scheme is the bargaining outcome, the optimal sample size is unique and satisfies $0<n\leq Nr_{max}/2$. And if $\mu_0+p_{\mathcal{S}}-v_{\mathcal{N}}\neq 0$ and the OIR scheme is the bargaining outcome, the optimal sample size is unique and satisfies $n\in(n_T,Nr_{max}/2]$ where $n_T>0$.

OWR Scheme. We first show that the optimal sample size is not $n=0$ or $n=Nr_{max}/2$ if the OWR scheme is the bargaining outcome. We note that the OWR scheme might be optimal only when $\mu_0+p_{\mathcal{S}}-v_{\mathcal{N}}\geq 0$ (see Prop. 4), and therefore we focus only on this case. If we set $n=0$, $S_0(\mathrm{CA^W},0,0)=-f_{DC}+N(\mu_0+p_{\mathcal{S}}-v_{\mathcal{N}})<S_0(\mathrm{A}_0)$. If we set $n=Nr_{max}/2$, then $S_0(\mathrm{CA^W},Nr_{max}/2,1)=(N-Nr_{max}/2)(\mu_0+p_{\mathcal{S}}-v_{\mathcal{N}})-f_{DC}-v_{DC}Nr_{max}/2<S_0(\mathrm{A}_0)$. Therefore, if the optimal sample size is zero or $Nr_{max}/2$, then the conditional approval with an OWR scheme is not the bargaining outcome.

We next consider the case of $f_r=0$. If $f_r=0$, the only difference between $S_0(\mathrm{CA^I},n,2n/(Nr_{max})$ and $S_0(\mathrm{CA^W},n,2n/(Nr_{max})$ is in the first term, n vs. $n(2/r_{max}-1)$, and both of these terms disappear in the second derivative. Therefore, the argument for the non-zero, unique optimal made for the OIR scheme holds for the OWR scheme if $f_r=0$.

We continue with the case of $f_r>0$ and $0<n<Nr_{max}/2$. We let $g(n)\triangleq v_{\mathcal{N}}-p_{\mathcal{S}}-\mu_0-f_r/(N-2n/r_{max})$ to simplify the equations. The first derivative of $S_0(\mathrm{CA^W},n,2n/(Nr_{max}))$ with respect n is

$$\frac{\partial S_0(\mathrm{CA^W},n,2n/(Nr_{max}))}{\partial n}=\left(\frac{2}{r_{max}}-1\right)(\mu_0+p_{\mathcal{S}}-v_{\mathcal{N}})-v_{DC}-\frac{2}{r_{max}}\sigma_{M_1}\psi\left(\frac{g(n)}{\sigma_{M_1}}\right)$$
$$+\left(N-\frac{2n}{r_{max}}\right)\frac{\partial\sigma_{M_1}}{\partial n}\psi\left(\frac{g(n)}{\sigma_{M_1}}\right)+\left(N-\frac{2n}{r_{max}}\right)\sigma_{M_1}\frac{\partial\psi\left(g(n)/\sigma_{M_1}\right)}{\partial n}. \tag{EC.9}$$

And the second derivative of $S_0(\mathrm{CA}^{\mathrm{W}}, n, 2n/(Nr_{max}))$ with respect n is

$$\begin{aligned}\frac{\partial^2 S_0(\mathrm{CA}^{\mathrm{W}}, n, 2n/(Nr_{max}))}{\partial n^2} &= -\frac{4}{r_{max}}\frac{\partial \sigma_{M_1}}{\partial n}\psi\left(\frac{g(n)}{\sigma_{M_1}}\right) - \frac{4}{r_{max}}\sigma_{M_1}\frac{\partial \psi\left(g(n)/\sigma_{M_1}\right)}{\partial n} \\ &+ \left(N - \frac{2n}{r_{max}}\right)\frac{\partial^2 \sigma_{M_1}}{\partial n^2}\psi\left(\frac{g(n)}{\sigma_{M_1}}\right) + 2\left(N - \frac{2n}{r_{max}}\right)\frac{\partial \sigma_{M_1}}{\partial n}\frac{\partial \psi(g(n)/\sigma_{M_1})}{\partial n} \\ &+ \left(N - \frac{2n}{r_{max}}\right)\sigma_{M_1}\frac{\partial^2 \psi\left(g(n)/\sigma_{M_1}\right)}{\partial n^2}. \end{aligned} \tag{EC.10}$$

From the definition of the standard normal loss function, we have:

$$\begin{aligned}\frac{\partial \psi\left(g(n)/\sigma_{M_1}\right)}{\partial n} &= -\left(1 - \Phi\left(\frac{g(n)}{\sigma_{M_1}}\right)\right)\frac{\partial (g(n)/\sigma_{M_1})}{\partial n}, \\ \frac{\partial^2 \psi\left(g(n)/\sigma_{M_1}\right)}{\partial n^2} &= \phi\left(\frac{g(n)}{\sigma_{M_1}}\right)\left(\frac{\partial (g(n)/\sigma_{M_1})}{\partial n}\right)^2 - \left(1 - \Phi\left(\frac{g(n)}{\sigma_{M_1}}\right)\right)\frac{\partial^2 (g(n)/\sigma_{M_1})}{\partial n^2}.\end{aligned}$$

And from the definitions of $g(n)$ and σ_{M_1}, we have

$$\begin{aligned}\frac{\partial (g(n)/\sigma_{M_1})}{\partial n} &= \frac{\sigma_{M_1}}{\sigma_{M_1}^2}\frac{\partial g(n)}{\partial n} - \frac{g(n)}{\sigma_{M_1}^2}\frac{\partial \sigma_{M_1}}{\partial n}, \\ \frac{\partial^2 (g(n)/\sigma_{M_1})}{\partial n^2} &= -\frac{1}{\sigma_{M_1}^2}g(n)\frac{\partial^2 \sigma_{M_1}}{\partial n^2} - 2\frac{1}{\sigma_{M_1}^2}\frac{\partial \sigma_{M_1}}{\partial n}\frac{\partial g(n)}{\partial n} + 2\frac{g(n)}{\sigma_{M_1}^3}\left(\frac{\partial \sigma_{M_1}}{\partial n}\right)^2 + \frac{1}{\sigma_{M_1}}\frac{\partial^2 g(n)}{\partial n^2}.\end{aligned}$$

Plugging these four equalities into (EC.10), we get

$$\begin{aligned}\frac{\partial^2 S_0(\mathrm{CA}^{\mathrm{W}}, n, 2n/(Nr_{max}))}{\partial n^2} &= -\frac{4}{r_{max}}\frac{\partial \sigma_{M_1}}{\partial n}\psi\left(\frac{g(n)}{\sigma_{M_1}}\right) + \frac{4}{r_{max}}\sigma_{M_1}\left(1 - \Phi\left(\frac{g(n)}{\sigma_{M_1}}\right)\right)\left(\frac{\sigma_{M_1}}{\sigma_{M_1}^2}\frac{\partial g(n)}{\partial n} - \frac{g(n)}{\sigma_{M_1}^2}\frac{\partial \sigma_{M_1}}{\partial n}\right) \\ &+ \left(N - \frac{2n}{r_{max}}\right)\frac{\partial^2 \sigma_{M_1}}{\partial n^2}\psi\left(\frac{g(n)}{\sigma_{M_1}}\right) - 2\left(N - \frac{2n}{r_{max}}\right)\frac{\partial \sigma_{M_1}}{\partial n}\left(1 - \Phi\left(\frac{g(n)}{\sigma_{M_1}}\right)\right)\left(\frac{\sigma_{M_1}}{\sigma_{M_1}^2}\frac{\partial g(n)}{\partial n} - \frac{g(n)}{\sigma_{M_1}^2}\frac{\partial \sigma_{M_1}}{\partial n}\right) \\ &+ \left(N - \frac{2n}{r_{max}}\right)\sigma_{M_1}\phi\left(\frac{g(n)}{\sigma_{M_1}}\right)\left(\frac{\sigma_{M_1}}{\sigma_{M_1}^2}\frac{\partial g(n)}{\partial n} - \frac{g(n)}{\sigma_{M_1}^2}\frac{\partial \sigma_{M_1}}{\partial n}\right)^2 \\ &- \left(N - \frac{2n}{r_{max}}\right)\sigma_{M_1}\left(1 - \Phi\left(\frac{g(n)}{\sigma_{M_1}}\right)\right)\left(-\frac{1}{\sigma_{M_1}^2}g(n)\frac{\partial^2 \sigma_{M_1}}{\partial n^2} - 2\frac{1}{\sigma_{M_1}^2}\frac{\partial \sigma_{M_1}}{\partial n}\frac{\partial g(n)}{\partial n} + 2\frac{g(n)}{\sigma_{M_1}^3}\left(\frac{\partial \sigma_{M_1}}{\partial n}\right)^2 + \frac{1}{\sigma_{M_1}}\frac{\partial^2 g(n)}{\partial n^2}\right) \\ &= -\frac{4}{r_{max}}\frac{\partial \sigma_{M_1}}{\partial n}\phi\left(\frac{g(n)}{\sigma_{M_1}}\right) + \frac{4}{r_{max}}\left(1 - \Phi\left(\frac{g(n)}{\sigma_{M_1}}\right)\right)\frac{\partial g(n)}{\partial n} + \left(N - \frac{2n}{r_{max}}\right)\frac{\partial^2 \sigma_{M_1}}{\partial n^2}\phi\left(\frac{g(n)}{\sigma_{M_1}}\right) \\ &+ \left(N - \frac{2n}{r_{max}}\right)\sigma_{M_1}\phi\left(\frac{g(n)}{\sigma_{M_1}}\right)\left(\frac{\sigma_{M_1}}{\sigma_{M_1}^2}\frac{\partial g(n)}{\partial n} - \frac{g(n)}{\sigma_{M_1}^2}\frac{\partial \sigma_{M_1}}{\partial n}\right)^2 - \left(N - \frac{2n}{r_{max}}\right)\left(1 - \Phi\left(\frac{g(n)}{\sigma_{M_1}}\right)\right)\frac{\partial^2 g(n)}{\partial n^2}\end{aligned}$$

Next, we use the following equalities:

$$\frac{\partial g(n)}{\partial n} = -\frac{2f_r}{r_{max}\left(N - 2n/r_{max}\right)^2}\ ,\ \frac{\partial^2 g(n)}{\partial n^2} = -\frac{8f_r}{r_{max}^2\left(N - 2n/r_{max}\right)^3}, \tag{EC.11}$$

and obtain the following:

$$\begin{aligned}\frac{\partial^2 S_0(\mathrm{CA}^{\mathrm{W}}, n, 2n/(Nr_{max}))}{\partial n^2} &= -\frac{4}{r_{max}}\frac{\partial \sigma_{M_1}}{\partial n}\phi\left(\frac{g(n)}{\sigma_{M_1}}\right) - \frac{4}{r_{max}}\left(1 - \Phi\left(\frac{g(n)}{\sigma_{M_1}}\right)\right)\frac{2f_r}{r_{max}\left(N - 2n/r_{max}\right)^2} \\ &+ \left(N - \frac{2n}{r_{max}}\right)\frac{\partial^2 \sigma_{M_1}}{\partial n^2}\phi\left(\frac{g(n)}{\sigma_{M_1}}\right) + \left(N - \frac{2n}{r_{max}}\right)\sigma_{M_1}\phi\left(\frac{g(n)}{\sigma_{M_1}}\right)\left(\frac{\sigma_{M_1}}{\sigma_{M_1}^2}\frac{\partial g(n)}{\partial n} - \frac{g(n)}{\sigma_{M_1}^2}\frac{\partial \sigma_{M_1}}{\partial n}\right)^2 \\ &+ \left(N - \frac{2n}{r_{max}}\right)\left(1 - \Phi\left(\frac{g(n)}{\sigma_{M_1}}\right)\right)\frac{8f_r}{r_{max}^2\left(N - 2n/r_{max}\right)^3} \\ &= -\frac{4}{r_{max}}\frac{\partial \sigma_{M_1}}{\partial n}\phi\left(\frac{g(n)}{\sigma_{M_1}}\right) + \left(N - \frac{2n}{r_{max}}\right)\frac{\partial^2 \sigma_{M_1}}{\partial n^2}\phi\left(\frac{g(n)}{\sigma_{M_1}}\right) + \left(N - \frac{2n}{r_{max}}\right)\sigma_{M_1}\phi\left(\frac{g(n)}{\sigma_{M_1}}\right)\left(\frac{1}{\sigma_{M_1}}\frac{\partial g(n)}{\partial n} - \frac{g(n)}{\sigma_{M_1}^2}\frac{\partial \sigma_{M_1}}{\partial n}\right)^2 \\ &= \phi\left(\frac{g(n)}{\sigma_{M_1}}\right)\left(-\frac{4}{r_{max}}\frac{\partial \sigma_{M_1}}{\partial n} + \left(N - \frac{2n}{r_{max}}\right)\frac{\partial^2 \sigma_{M_1}}{\partial n^2} + \left(N - \frac{2n}{r_{max}}\right)\left(\frac{\partial g(n)}{\partial n} - \frac{g(n)}{\sigma_{M_1}}\frac{\partial \sigma_{M_1}}{\partial n}\right)^2\right)\end{aligned}$$

We plug (EC.8) and (EC.11) into the above equation, use $y \triangleq v_{\mathcal{N}} - p_{\mathcal{S}} - \mu_0$ and rearrange terms to obtain:

$$\frac{\partial^2 S_0(\mathrm{CA^W}, n, 2n/(Nr_{max}))}{\partial n^2} = \phi\left(\frac{y - f_r/((N-2n/r_{max}))}{\sigma_{M_1}}\right)\frac{an^5+bn^4+cn^3+dn^2+en+h}{4n^2 r_{max}(n_0+n)^3\sigma_{M_1}(Nr_{max}-2n)^3},$$

where

$$\begin{aligned}
a &= 16n_0^2y^2 - 32n_0f_r r_{max}y + 48n_0\Sigma_X + 16f_r^2r_{max}^2 + 32\Sigma_X N r_{max},\\
b &= 16n_0^3y^2 - 80n_0^2f_r r_{max}y - 32n_0^2 N r_{max}y^2 + 64n_0f_r^2r_{max}^2 + 32n_0f_r N r_{max}^2 y - 64n_0\Sigma_X N r_{max} - 48\Sigma_X N^2 r_{max}^2,\\
c &= -48n_0^3f_r r_{max}y - 32n_0^3 N r_{max}y^2 + 84n_0^2f_r^2r_{max}^2 + 88n_0^2f_r N r_{max}^2 y + 24n_0^2N^2r_{max}^2y^2 - 8n_0f_r^2 N r_{max}^3\\
&\quad - 8n_0f_r N^2 r_{max}^3 y + 24n_0\Sigma_X N^2 r_{max}^2 + 24\Sigma_X N^3 r_{max}^3,\\
d &= 36n_0^3f_r^2r_{max}^2 + 56n_0^3f_r N r_{max}^2 y + 24n_0^3N^2r_{max}^2y^2 - 20n_0^2f_r^2 N r_{max}^3 - 28n_0^2f_r N^2 r_{max}^3 y - 8n_0^2N^3r_{max}^3y^2\\
&\quad - 4\Sigma_X N^4 r_{max}^4,\\
e &= -12n_0^3f_r^2 N r_{max}^3 - 20n_0^3f_r N^2 r_{max}^3 y - 8n_0^3N^3r_{max}^3y^2 + n_0^2f_r^2N^2r_{max}^4 + 2n_0^2f_r N^3 r_{max}^4 y + n_0^2N^4r_{max}^4y^2\\
&\quad - n_0\Sigma_X N^4 r_{max}^4,\\
h &= n_0^3f_r^2N^2r_{max}^4 + 2n_0^3f_r N^3 r_{max}^4 y + n_0^3N^4r_{max}^4y^2.
\end{aligned}$$

The value in the denominator, $4n^2r_{max}(n_0+n)^3\sigma_{M_1}(Nr_{max}-2n)^3$, and $\phi(g(n)/\sigma_{M_1})$ are positive for all $0 < n < Nr_{max}/2$. In the nominator, we have a fifth-degree polynomial. We found that this polynomial has two positive real roots. Then, there are two thresholds such that $n_{T2}^W \in (0, Nr_{max})$, $n_{T3}^W \in (0, Nr_{max})$, and $n_{T2}^W < n_{T3}^W$. We have $\partial^2 S_0(\mathrm{CA^W}, n, 2n/(Nr_{max}))/\partial n^2 > 0$ if $0 \le n < n_{T2}^W$, $\partial^2 S_0(\mathrm{CA^W}, n, 2n/(Nr_{max}))/\partial n^2 < 0$ if $n_{T2}^W < n < n_{T3}^W$, $\partial^2 S_0(\mathrm{CA^W}, n, 2n/(Nr_{max}))/\partial n^2 > 0$ if $n_{T3}^W < n \le Nr_{max}/2$, and $\partial^2 S_0(\mathrm{CA^W}, n, 2n/(Nr_{max}))/\partial n^2 = 0$ if $n = n_{T2}^W$ or $n = n_{T3}^W$. In other words, $S_0(\mathrm{CA^W}, n, 2n/(Nr_{max}))$ is convex for $0 \le n < n_{T2}^W$, is concave for $n_{T2}^W < n < n_{T3}^W$, and convex for $n_{T3}^W < n \le Nr_{max}/2$. Therefore, the maximum is achieved either at $n = 0$, $n \in [n_{T2}^W, n_{T3}^W]$, or $n = Nr_{max}/2$.

We discussed above why the optimal sample size cannot be zero or $Nr_{max}/2$ if the OWR scheme is optimal. We can also show that the maximum is never achieved at $n = n_{T2}^W$ or $n = n_{T3}^W$, using an argument similar to the one for the OIR scheme. Therefore, if the OWR scheme is the bargaining outcome, we have a unique optimal, non-zero sample size that satisfies $n^* \in (n_{T2}^W, n_{T3}^W)$ if $f_r > 0$ and $n^* \in (n_T^W, Nr_{max}/2)$ if $f_r = 0$.

B.4. Equivalence of the Bargaining Model with $\beta = 1$ and a Stackelberg Game

Consider a Stackelberg model in which the company acts first as a price-setter and the payer then makes an approval decision given the submitted price. In this section, we prove that the approval outcomes and prices obtained under the Stackelberg model, described in §B.4.1, are equivalent to the ones we obtain from the two-stage Nash bargaining model, described in §2, when $\beta = 1$.

B.4.1. Timeline of a Stackelberg Model. We now describe the timeline of events for a Stackelberg model. As in the timeline of the Nash bargaining model in §2, the company completes a phase III clinical trial for a new treatment and obtains marketing authorization from a regulatory authority in a pre-submission stage.

At the beginning of the initial submission stage, the company decides whether to submit the new treatment to the payer and at which price. We let NS_0 denote the outcome of the company not submitting the new

treatment to the payer. If the company submits the new treatment to the payer, the company presents the trial results to the payer and submits an offer which contains the following three sets of values: an immediate approval price, p_0, an OIR conditional approval scheme which involves an interim price p_i and a post-marketing trial with sample size n and duration t, and an analogous OWR conditional approval scheme.

Given the new treatment's trial results and the submitted offer, the payer makes the reimbursement decision, which has four potential outcomes: (1) the new treatment is immediately approved at price p_0, which is denoted by (A_0, p_0), (2) the new treatment is conditionally approved under an OIR scheme with an interim price p_i and a post-marketing trial with sample size n and duration t, which is denoted by $(\mathrm{CA}^{\mathrm{I}}, p_i, n, t)$, (3) the new treatment is conditionally approved under an OWR scheme with an interim price p_i^W and a post-marketing trial with sample size n and duration t, which is denoted by $(\mathrm{CA}^{\mathrm{W}}, p_i^W, n, t)$, or (4) the new treatment is rejected, which is denoted by R_0.

If the payer decides to conditionally approve the new treatment through an OIR or OWR scheme, the company conducts the post-marketing trial and pays for its nominal cost, and the payer reimburses the company at the interim price during the trial, p_i under an OIR scheme and p_i^W under an OWR scheme.

After the post-marketing trial concludes, the company decides either to withdraw the new treatment from the payer's consideration or to continue with the submission and present a new offer which consists of a reappraisal price p_1. We let NS_1 denote the outcome of the company withdrawing the submission. The payer makes the reimbursement decision, which has two potential outcomes: (1) the new treatment is approved at price p_1, which is denoted by (A_1, p_1), and (2) the new treatment is rejected, which is denoted by R_1.

The players' payoffs under different outcomes are as in §2. The only two outcomes that are not explicitly defined in §2 are the company not making a submission at the initial submission and the company withdrawing the submission at the reappraisal. In a bargaining setting, these two outcomes would be contained by the bargaining breaking down, therefore, the payoffs are the same as the ones under the rejection outcome.

B.4.2. Analysis of the Stackelberg Model with an OIR Scheme. This section parallels §3 and analyzes the Stackelberg model for the case in which the conditional approval option is only in research (OIR). Our analysis employs backwards induction.

Payer's Reimbursement Decision at The Reappraisal Stage. Suppose that the company submits a reappraisal price p_1 at the conclusion of the post-marketing trial. If the payer approves the new treatment at that price, its total expected INMB from approval is given by $V_1(\mathrm{A}_1, p_1, t)$ in (5). If the payer rejects the new treatment, however, the total expected INMB is $V_1(\mathrm{R}_1) = 0$.

The payer approves the new treatment at price p_1 if $V_1(\mathrm{A}_1, p_1, t) \geq V_1(\mathrm{R}_1)$. (We break ties by choosing approval as in §3). Because $V_1(\mathrm{A}_1, p_1, t) = (1-t)N(\mu_1 - p_1 + p_{\mathcal{S}})$ and $V_1(\mathrm{R}_1) = 0$, the treatment is approved if $\mu_1 + p_{\mathcal{S}} \geq p_1$, and is rejected otherwise.

Company's Submission and Pricing Decisions at The Reappraisal Stage. If the company submits reappraisal price p_1 and the new treatment is approved at that price, then the company's expected profit at the end of the post-marketing trial is $\Pi_1(\mathrm{A}_1, p_1, t)$ in (8). If the company decides to withdraw the submission, or if the new treatment is rejected at the submitted price, the company's additional profit after rejection at the end of the post-marketing trial is $\Pi_1(\mathrm{R}_1) = \Pi_1(\mathrm{NS}_1) \triangleq 0$.

Because $\Pi_1(\mathrm{A}_1, p_1, t)$ increases with p_1, and because the payer would reject the treatment if $p_1 > \mu_1 + p_{\mathcal{S}}$, we find that $p_1 = \mu_1 + p_{\mathcal{S}}$ maximizes the company's profit from continuing with the submission. Therefore, the company submits the new treatment with the reappraisal price $p_1^{Seq,*} = \mu_1 + p_{\mathcal{S}}$ if $\Pi_1(\mathrm{A}_1, p_1^{Seq,*}, t) \geq 0$, which implies $\mu_1 + p_{\mathcal{S}} - v_{\mathcal{N}} \geq 0$. Otherwise, the company withdraws the submission. (We break the ties by choosing to submit the treatment.) Here, optimal values that are associated with the sequential Stackelberg model may be denoted with a superscript ^{Seq}.

PROP. EC.3. *Consider the the reappraisal stage of the Stackelberg model outlined in §B.4.1. If* $\mu_1 + p_{\mathcal{S}} - v_{\mathcal{N}} \geq 0$ *at the conclusion of the post-marketing trial, the company would submit the reappraisal price* $p_1^{Seq,*} = \mu_1 + p_{\mathcal{S}}$*, and the payer would approve the new treatment. The players' payoffs would be*

$$\Pi_1(A_1, p_1^{Seq,*}, t) = (1-t)N(\mu_1 + p_{\mathcal{S}} - v_{\mathcal{N}}) \text{ and } V_1(A_1, p_1^{Seq,*}, t) = 0. \tag{EC.12}$$

Otherwise, the company withdraws the submission at the conclusion of the post-marketing trial, and $\Pi_1(NS_1) = 0$ *and* $V_1(NS_1) = 0$.

REMARK EC.1. Prop. EC.3 is equivalent to Prop. 1 when $\beta = 1$.

Payer's Reimbursement Decision at The Initial Submission Stage. Suppose the company presents the trial results to the payer and submits an offer that contains an initial submission price, p_0, an interim price, p_i, and the sample size and duration of the post-marketing trial to be conducted if the payer chooses an OIR scheme, (n, t). We now analyze the best response of the payer to the company's submission.

If the payer immediately approves the new treatment at price p_0, the payer's *total* expected INMB across the population of N patients is given by $V_0(\mathrm{A}_0, p_0)$ in (4). If the payer rejects the new treatment, the payer's total expected INMB is zero (i.e., $V_0(\mathrm{R}_0) \triangleq 0$).

If the payer accepts the OIR scheme proposed by the company, 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. Combining the two sets of outcomes at the end of the post-marketing trial, which are outlined in Prop. EC.3, we denote the payer's total expected INMB after a post-marketing trial with duration t as $V_1^*(t) = 0$. We then have the payer's total expected INMB from an OIR scheme as $V_0(\mathrm{CA}^{\mathrm{I}}, p_i, n, t) = n(\mu_0 - p_i + p_{\mathcal{S}})$, which follows from (6).

The payer selects the outcome that would maximize its INMB, $\max\{V_0(\mathrm{A}_0, p_0), V_0(\mathrm{CA}^{\mathrm{I}}, p_i, n, t), V_0(\mathrm{R}_0)\}$ given the submission made by the company. We break ties by selecting in the order of immediate approval, conditional approval, and rejection. Then, the payer immediately approves the new treatment at the initial submission, i.e. $V_0(\mathrm{A}_0) = \max\{V_0(\mathrm{A}_0, p_0), V_0(\mathrm{CA}^{\mathrm{I}}, p_i, n, t), V_0(\mathrm{R}_0)\}$, if

$$\mu_0 + p_{\mathcal{S}} \geq p_0 \text{ and } (N-n)(\mu_0 + p_{\mathcal{S}}) \geq Np_0 - np_i.$$

And, the payer conditionally approves the new treatment with an OIR scheme at the initial submission, i.e. $V_0(\mathrm{CA}^{\mathrm{I}}, p_i, n, t) = \max\{V_0(\mathrm{CA}^{\mathrm{I}}, p_i, n, t), V_0(\mathrm{R}_0)\} > V_0(\mathrm{A}_0, p_0)$, if

$$\mu_0 + p_{\mathcal{S}} \geq p_i \text{ and } (N-n)(\mu_0 + p_{\mathcal{S}}) < Np_0 - np_i.$$

Finally, the payer rejects the new treatment at the initial submission, i.e. $V_0(\mathrm{R}_0) > \max\{V_0(\mathrm{A}_0, p_0), V_0(\mathrm{CA}^{\mathrm{I}}, p_i, n, t)\}$, if

$$\mu_0 + p_{\mathcal{S}} < p_0 \text{ and } \mu_0 + p_{\mathcal{S}} < p_i.$$

Figure EC.1 summarizes the payer's best response to a submission from the company in this model.

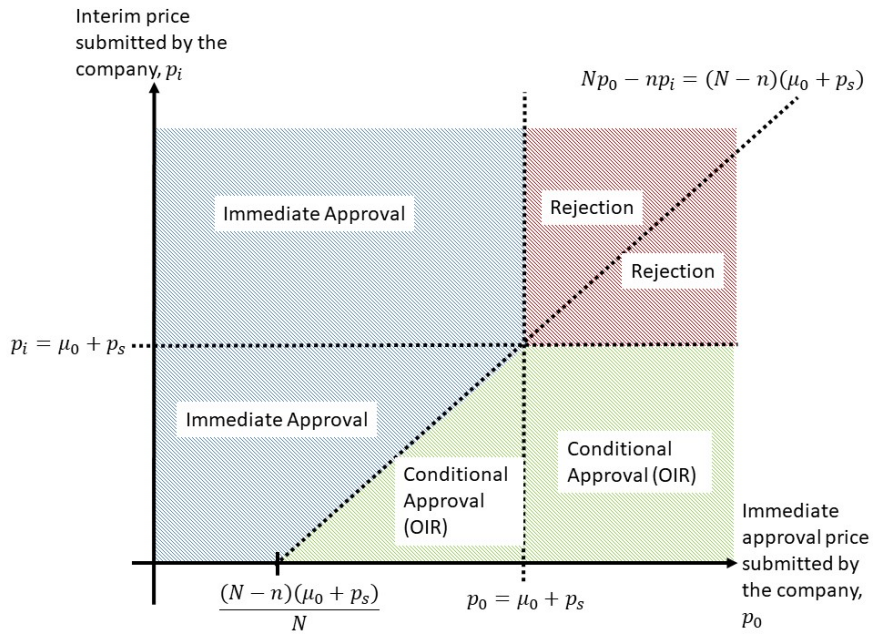
Company's Submission and Pricing Decisions at The Initial Submission Stage. We analyze the company's optimal submission and pricing decisions given the payer's best response in Figure EC.1.

If the company does not submit the new treatment or the new treatment is rejected at initial submission, the company's profit is zero, $\Pi_0(\mathrm{NS}_0) \triangleq \Pi_0(\mathrm{R}_0) = 0$. If the company submits the new treatment to the payer, and the new treatment is immediately approved at initial submission, the company's profit from the treatment's approval at price p_0 at initial submission is given by $\Pi_0(\mathrm{A}_0, p_0)$ in (7).

If the company submits the new treatment to the payer, and 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 not submitted after the post-marketing trial ends. We let $\Pi_1^*(t)$ denote the company profit across the two sets of outcomes at the end of the post-marketing trial of an OIR scheme – acceptance at price $p_1^{Seq,*}$ or no submission. Combining the two sets of outcomes at the end of the post-marketing trial, which are outlined in Prop. EC.3, and using the pre-posterior distribution of μ_1 to evaluate the expectation, $\mathbb{E}_{M_1}\left[\Pi_1^*(t) \,|\, \mu_0, n_0\right]$, we have

$$\begin{aligned}
\Pi_0(\mathrm{CA}^{\mathrm{I}}, p_i, n, t) &\triangleq n(p_i - v_{\mathcal{N}}) - f_{DC} - n v_{DC} + \mathbb{E}_{M_1}\left[\Pi_1^*(t) \,|\, \mu_0, n_0\right] \\
&= n(p_i - v_{\mathcal{N}}) - f_{DC} - n v_{DC} + \mathbb{E}_{M_1}\left[(1-t)N(M_1 + p_{\mathcal{S}} - v_{\mathcal{N}})^+ \,|\, \mu_0, n_0\right] \\
&= n(p_i - v_{\mathcal{N}}) - f_{DC} - n v_{DC} + (1-t)N\sigma_{M_1}\psi\left(\frac{v_{\mathcal{N}} - p_{\mathcal{S}} - \mu_0}{\sigma_{M_1}}\right), \qquad \text{(EC.13)}
\end{aligned}$$

Figure EC.1 The payer's best response given the company's submission of an immediate approval price, p_0, an interim price p_i, sample size n and duration t, in a Stackelberg model. We break ties by selecting in the order of immediate approval, conditional approval, and rejection.



which also follows from (9).

We analyze the company's optimal submission and pricing decision in three steps. We first find the parameter values that maximize the company's profit from an OIR scheme, $\Pi_0(\mathrm{CA}^{\mathrm{I}}, p_i, n, t)$. Second, we find those that maximize the profit from immediate approval, $\Pi_0(\mathrm{A}_0, p_0)$. And finally, we characterize the company's optimal action at initial submission.

Expected Profit from an OIR Scheme. The company obtains the highest possible profit from an OIR scheme by choosing the values for (p_i, n, t) that maximize (EC.13) given that the payer would accept the OIR scheme. Figure EC.1 shows that the value of p_0 impacts whether or not the payer accepts the OIR scheme, and (EC.13) shows that p_0 does not affect the expected profit from the OIR scheme.

For any given (n, t), the company maximizes (EC.13) by setting $p_i = \mu_0 + p_{\mathcal{S}}$ and ensures the payer accepts the interim price by setting $p_0 > \mu_0 + p_{\mathcal{S}}$. We plug $p_i = \mu_0 + p_{\mathcal{S}}$ into (EC.13) and define the optimal values for the sample size and duration of the post-marketing trial as

$$\begin{aligned}(n^*, t^*) = \arg\max_{n,t}\ & n(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}}) - f_{DC} - n v_{DC} + (1-t) N \sigma_{M_1} \psi\left(\frac{v_{\mathcal{N}} - p_{\mathcal{S}} - \mu_0}{\sigma_{M_1}}\right) \\ \text{s.t. } & 0 \le 2n \le N r_{max} t. \end{aligned} \tag{EC.14}$$

We let $\sigma^*_{M_1} \triangleq \sqrt{\Sigma_X n^*/(n_0(n^* + n_0))}$ and write the maximum expected profit from an OIR scheme as

$$\Pi_0(\mathrm{CA}^{\mathrm{I}}, \mu_0 + p_{\mathcal{S}}, n^*, t^*) = n^*(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}}) - f_{DC} - n^* v_{DC} + (1-t^*) N \sigma^*_{M_1} \psi\left(\frac{v_{\mathcal{N}} - p_{\mathcal{S}} - \mu_0}{\sigma^*_{M_1}}\right). \tag{EC.15}$$

Remark EC.2. The maximization problem in (EC.14) is identical to one in (16). Therefore, the optimal values for the sample size and duration of the post-marketing trial as are the same for the Nash bargaining solution and the solution of the Stackelberg model. Furthermore, we have $\Pi_0(\mathrm{CA}^{\mathrm{I}}, \mu_0 + p_{\mathcal{S}}, n^*, t^*) = S_0(\mathrm{CA}^{\mathrm{I}})$, where $S_0(\mathrm{CA}^{\mathrm{I}})$ is defined in Prop. 3.

Expected Profit from Immediate Approval. The company obtains the highest possible profit from immediate approval by choosing the highest possible immediate approval price, which would maximize (7), given that the payer would immediately approve the new treatment. Figure EC.1 shows that the value of t does not impact the payer's decision, the values of p_i and n impact whether or not the payer would immediately approve the new treatment, and (7) shows that p_i and n do not affect the expected profit from immediate approval.

The company's profit from immediate approval, (7), is maximized by setting $p_0 = \mu_0 + p_{\mathcal{S}}$, and immediate approval is preferred by the payer if $p_i \ge \mu_0 + p_{\mathcal{S}}$, for any n and t.

Then, the company's maximum expected profit from immediate approval is

$$\Pi_0(\mathrm{A}_0, \mu_0 + p_{\mathcal{S}}) \ = \ N(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}}). \tag{EC.16}$$

Remark EC.3. We have $\Pi_0(\mathrm{A}_0, \mu_0 + p_{\mathcal{S}}) = S_0(\mathrm{A}_0)$, where $S_0(\mathrm{A}_0)$ is defined in Prop. 2.

Company's Optimal Decision. We now outline the optimal offer that would be submitted by the company at the initial submission:

- If $\Pi_0(\mathrm{A}_0, \mu_0 + p_{\mathcal{S}}) > \Pi_0(\mathrm{CA}^{\mathrm{I}}, \mu_0 + p_{\mathcal{S}}, n^*, t^*)$ and $\Pi_0(\mathrm{A}_0, \mu_0 + p_{\mathcal{S}}) \ge 0$, the company's optimal action is to submit $p_0^{Seq,*} = \mu_0 + p_{\mathcal{S}}$, $p_i^{Seq,*} \ge \mu_0 + p_{\mathcal{S}}$, n^* and t^*. Then, the treatment is immediately approved by the payer at the immediate approval price $p_0^{Seq,*} = \mu_0 + p_{\mathcal{S}}$.

- If instead $\Pi_0(\mathrm{CA}^{\mathrm{I}}, \mu_0+p_{\mathcal{S}}, n^*, t^*) > \Pi_0(\mathrm{A}_0, \mu_0+p_{\mathcal{S}})$ and $\Pi_0(\mathrm{CA}^{\mathrm{I}}, \mu_0+p_{\mathcal{S}}, n^*, t^*) \geq 0$, then the company's optimal action is to submit $p_i^{Seq,*} = \mu_0+p_{\mathcal{S}}$, $p_0^{Seq,*} > \mu_0+p_{\mathcal{S}}$, n^* and t^*. Then, the treatment is conditionally approved with an OIR scheme by the payer at the interim price $p_i^{Seq,*} = \mu_0+p_{\mathcal{S}}$ and with a post-marketing trial whose sample size is n^* and duration is t^*.
- If both $\Pi_0(\mathrm{A}_0, \mu_0+p_{\mathcal{S}}) < 0$ and $\Pi_0(\mathrm{CA}^{\mathrm{I}}, \mu_0+p_{\mathcal{S}}, n^*, t^*) < 0$, then the company would not submit the treatment to the payer, and both the payer and the company receive payoffs of zero.

For completeness, we note that, in the event that the expected profits from the two outcomes are non-negative and equal, we assume that the outcome chosen is immediate approval at price $p_0^{Seq,*} = \mu_0+p_{\mathcal{S}}$.

REMARK EC.4. Given the equivalences outlined in Remarks EC.2 and EC.3, the conditions under which the treatment is immediately approved, conditionally approved, or rejected are identical under the Stackelberg model and the Nash bargaining model. (See §3.3.) Furthermore, the Nash bargaining price at immediate approval for $\beta = 1$ is $p_0^* = p_0^{Seq,*}$, and the Nash bargaining interim price for $\beta = 1$ is $p_i^* = p_i^{Seq,*}$.

B.4.3. Comparison of the OIR and OWR Conditional Approval Schemes under the Stackelberg Model. This section parallels §4 and analyzes the Stackelberg model for the case in which both OIR and OWR conditional approval schemes are under consideration.

Payer's Reimbursement Decision at Reappraisal. Suppose that the company submits a reappraisal price p_1 at the conclusion of the post-marketing trial of an OWR scheme. In this case, the payer's payoff from rejection at reappraisal is $-f_r$, i.e. $V_1(\mathrm{R}_1) \triangleq -f_r$ for an OWR scheme.

The payer approves the new treatment at price p_1 if $V_1(\mathrm{A}_1, p_1, t) \geq V_1(\mathrm{R}_1)$, which implies $\mu_1+p_{\mathcal{S}}+f_r/((1-t)N) \geq p_1$. The payer rejects the new treatment, otherwise.

Company's Submission and Pricing Decisions at Reappraisal. The company's payoffs are the same under OIR and OWR schemes since the company does not face a reversal cost.

Because $\Pi_1(\mathrm{A}_1, p_1, t)$ increases with p_1, and because the payer would reject the treatment if $p_1 > \mu_1 + p_{\mathcal{S}} + f_r/((1-t)N)$ following an OWR scheme's post-marketing trial, $p_1 = \mu_1+p_{\mathcal{S}}+f_r/((1-t)N)$ maximizes the company's profit from continuing with the submission. Alternatively, withdrawing the submission at reappraisal results in a profit of zero, in which case the payer would still be responsible for the reversal cost (i.e. $V_1(\mathrm{NS}_1) \triangleq -f_r$).

Therefore, the company submits the new treatment at reappraisal with price $p_1^{Seq,W,*} = \mu_1+p_{\mathcal{S}}+f_r/((1-t)N)$ if $\Pi_1(\mathrm{A}_1, p_1^{Seq,W,*}, t) \geq 0$, which implies $\mu_1 + p_{\mathcal{S}} + f_r/((1-t)N) - v_{\mathcal{N}} \geq 0$. Otherwise, the company abandons the submission. (We break the ties by choosing to have the company submit the treatment.) Then, we have the following result:

PROP. EC.4. *Consider the reappraisal stage of an OWR scheme in the Stackelberg model outlined in §B.4.1. If $\mu_1+p_{\mathcal{S}}+f_r/((1-t)N)-v_{\mathcal{N}} \geq 0$ at the conclusion of the post-marketing trial, the company submits the reappraisal price $p_1^{Seq,W,*} = \mu_1 + p_{\mathcal{S}} + f_r/((1-t)N)$, and the payer approves the new treatment. The players' payoffs are then*

$$\Pi_1(A_1, p_1^{Seq,W,*}, t) = (1-t)N(\mu_1+p_{\mathcal{S}}+f_r/((1-t)N)-v_{\mathcal{N}}) \text{ and } V_1(A_1, p_1^{Seq,*}, t) = -f_r. \tag{EC.17}$$

Otherwise, the company withdraws the submission at the conclusion of the post-marketing trial, with $\Pi_1(NS_1) = 0$ and $V_1(NS_1) = -f_r$.

REMARK EC.5. Prop. EC.4 is equivalent to Prop. EC.1 when $\beta = 1$.

Payer's Reimbursement Decision at The Initial Submission Stage. The payer's payoffs from immediate approval, an OIR scheme and rejection are the same as those in §B.4.2. We now calculate the payer's expected payoff from an OWR scheme.

The payer's total expected INMB from an OWR conditional approval scheme depends on whether the new treatment is ultimately approved or rejected after the post-marketing trial ends. Combining the two sets of outcomes at the end of the post-marketing trial, which are outlined in Prop. EC.4, we denote the payer's total expected INMB after a post-marketing trial with duration t as $V_1^{*,\mathrm{W}}(t) = -f_r$. We then can define the payer's total expected INMB from an OWR scheme with sample size n^W and duration t^W, as of the time of initial submission, as $V_0(\mathrm{CA}^{\mathrm{W}}, p_i^W, n^W, t^W) = (Nt^W - n^W)(\mu_0 - p_i^W + p_{\mathcal{S}}) - f_r$, which follows from (EC.2).

The payer selects the outcome that would maximize its INMB, $\max\{V_0(\mathrm{A}_0, p_0), V_0(\mathrm{CA}^{\mathrm{I}}, p_i, n, t), V_0(\mathrm{CA}^{\mathrm{W}}, p_i^W, n^W, t^W), V_0(\mathrm{R}_0)\}$, and we break ties by selecting the outcome in the order of immediate approval, the OIR scheme, the OWR scheme, and rejection. Then, the payer immediately approves the new treatment at initial submission, i.e. $V_0(\mathrm{A}_0) = \max\{V_0(\mathrm{A}_0, p_0), V_0(\mathrm{CA}^{\mathrm{I}}, p_i, n, t), V_0(\mathrm{CA}^{\mathrm{W}}, p_i^W, n, t), V_0(\mathrm{R}_0)\}$, if

$$\mu_0 + p_{\mathcal{S}} \geq p_0, \quad (N-n)(\mu_0 + p_{\mathcal{S}}) \geq Np_0 - np_i \\ \text{and } (N(1-t^W) + n^W)(\mu_0 + p_{\mathcal{S}}) + f_r \geq Np_0 - (Nt^W - n^W)p_i^W. \tag{EC.18}$$

The payer conditionally approves the new treatment with an OIR scheme at initial submission, i.e. $V_0(\mathrm{CA}^{\mathrm{I}}, p_i, n, t) = \max\{V_0(\mathrm{CA}^{\mathrm{I}}, p_i, n, t), V_0(\mathrm{CA}^{\mathrm{W}}, p_i^W, n^W, t^W), V_0(\mathrm{R}_0)\} > V_0(\mathrm{A}_0, p_0)$, if

$$\mu_0 + p_{\mathcal{S}} \geq p_i, \quad (N-n)(\mu_0 + p_{\mathcal{S}}) < Np_0 - np_i, \\ \text{and } (n + n^W - Nt^W)(\mu_0 + p_{\mathcal{S}}) + f_r \geq np_i - (Nt^W - n^W)p_i^W. \tag{EC.19}$$

The payer conditionally approves the new treatment with an OWR scheme at initial submission, i.e. $V_0(\mathrm{CA}^{\mathrm{W}}, p_i^W, n^W, t^W) = \max\{V_0(\mathrm{CA}^{\mathrm{W}}, p_i^W, n^W, t^W), V_0(\mathrm{R}_0)\} > \max\{V_0(\mathrm{A}_0, p_0), V_0(\mathrm{CA}^{\mathrm{I}}, p_i, n, t)\}$, if

$$\mu_0 + p_{\mathcal{S}} - f_r/(Nt^W - n^W) \geq p_i^W, \quad (N(1-t^W) + n^W)(\mu_0 + p_{\mathcal{S}}) + f_r < Np_0 - (Nt^W - n^W)p_i^W, \\ \text{and } (n + n^W - Nt^W)(\mu_0 + p_{\mathcal{S}}) + f_r < np_i - (Nt^W - n^W)p_i^W. \tag{EC.20}$$

Finally the payer rejects the new treatment at initial submission, i.e. $V_0(\mathrm{R}_0) > \max\{V_0(\mathrm{A}_0, p_0), V_0(\mathrm{CA}^{\mathrm{I}}, p_i, n, t), V_0(\mathrm{CA}^{\mathrm{W}}, p_i^W, n^W, t^W)\}$, if

$$\mu_0 + p_{\mathcal{S}} < p_0, \qquad \mu_0 + p_{\mathcal{S}} < p_i, \qquad \text{and } \mu_0 + p_{\mathcal{S}} - f_r/(Nt^W - n^W) < p_i^W. \tag{EC.21}$$

Company's Submission and Pricing Decisions at Initial Submission. We first characterize the parameter values that maximize company's expected profit from an OWR scheme. We then identify the company's optimal action at initial submission when an OWR scheme is an option.

Expected Profit from an OWR Scheme. We let $\Pi_1^{*,\mathrm{W}}(t)$ denote the company's profit from the two sets of outcomes at the end of the OWR scheme's post-marketing trial. Recall from Prop. EC.4 that, if $\mu_1+p_{\mathcal{S}}+f_r/((1-t)N)-v_{\mathcal{N}}\geq 0$, the treatment is submitted and approved at price $p_1^{Seq,W,*}=\mu_1+p_{\mathcal{S}}+f_r/((1-t)N)$, and the company does not make a submission otherwise. Then we have

$$\begin{aligned}\mathbb{E}_{M_1}\left[\Pi_1^{*,\mathrm{W}}(t)\,|\,\mu_0,n_0\right] &= \mathbb{E}_{M_1}\left[(1-t)N(M_1+p_{\mathcal{S}}+f_r/((1-t)N)-v_{\mathcal{N}})^+\,|\,\mu_0,n_0\right]\\ &= (1-t)N\sigma_{M_1}\psi\left(\frac{v_{\mathcal{N}}-p_{\mathcal{S}}-f_r/((1-t)N)-\mu_0}{\sigma_{M_1}}\right).\end{aligned} \tag{EC.22}$$

In turn, the company's expected total profit from an OWR scheme at initial submission is

$$\Pi_0(\mathrm{CA}^{\mathrm{W}},p_i^W,n,t) \triangleq (Nt-n)(p_i^W-v_{\mathcal{N}})-f_{DC}-nv_{DC}+(1-t)N\sigma_{M_1}\psi\left(\frac{v_{\mathcal{N}}-p_{\mathcal{S}}-f_r/((1-t)N)-\mu_0}{\sigma_{M_1}}\right). \tag{EC.23}$$

The company obtains the highest possible profit from an OWR scheme by choosing values for p_i^W, n, and t that maximize (EC.23). For any given (n,t), the price that maximizes (EC.23) is the highest interim price at which the payer would accept an OWR scheme, $\mu_0+p_{\mathcal{S}}-f_r/(Nt-n)$. To make OWR the most attractive choice to the payer, the company sets other options' prices to satisfy $p_0>\mu_0+p_{\mathcal{S}}$ and $p_i>\mu_0+p_{\mathcal{S}}$.

Plugging $p_i^W=\mu_0+p_{\mathcal{S}}-f_r/(Nt-n)$ into (EC.23), we define the optimal sample size and duration as

$$\begin{aligned}(n^{*,W},t^{*,W}) = \arg\max_{n,t}\ & (Nt-n)(\mu_0+p_{\mathcal{S}}-v_{\mathcal{N}})-f_{DC}-nv_{DC}\\ & -f_r+(1-t)N\sigma_{M_1}\psi\left(\frac{v_{\mathcal{N}}-p_{\mathcal{S}}-f_r/((1-t)N)-\mu_0}{\sigma_{M_1}}\right)\\ \text{s.t. } & 0\leq 2n\leq Nr_{max}t.\end{aligned} \tag{EC.24}$$

We now let $\sigma_{M_1}^{*,\mathrm{W}}\triangleq\sqrt{\Sigma_X n^{*,\mathrm{W}}/(n_0(n^{*,\mathrm{W}}+n_0))}$ and write the maximum expected profit from an OWR scheme,

$$\begin{aligned}&\Pi_0(\mathrm{CA}^{\mathrm{W}},\mu_0+p_{\mathcal{S}}-f_r/(Nt^{*,\mathrm{W}}-n^{*,\mathrm{W}}),n^{*,\mathrm{W}},t^{*,\mathrm{W}})\\ &\quad=(Nt^{*,\mathrm{W}}-n^{*,\mathrm{W}})(\mu_0+p_{\mathcal{S}}-v_{\mathcal{N}})-f_{DC}-n^{*,\mathrm{W}}v_{DC}-f_r\\ &\qquad+(1-t^{*,\mathrm{W}})N\sigma_{M_1}^{*,\mathrm{W}}\psi\left(\frac{v_{\mathcal{N}}-p_{\mathcal{S}}-f_r/((1-t^{*,\mathrm{W}})N)-\mu_0}{\sigma_{M_1}^{*,\mathrm{W}}}\right).\end{aligned} \tag{EC.25}$$

Remark EC.6. The maximization problem in (EC.24) is identical to one in (EC.5). Therefore, the optimal values for the sample size and duration of the post-marketing trial as are the same for the Nash bargaining solution and the solution of the Stackelberg model. Furthermore, we have $\Pi_0(\mathrm{CA}^{\mathrm{W}},\mu_0+p_{\mathcal{S}}-f_r/(Nt^{*,\mathrm{W}}-n^{*,\mathrm{W}}),n^{*,\mathrm{W}},t^{*,\mathrm{W}})=S_0(\mathrm{CA}^{\mathrm{W}})$, where $S_0(\mathrm{CA}^{\mathrm{W}})$ is defined in (EC.6).

Company's Optimal Decision. The values of (p_0,p_i,n,t) that maximize the company's expected profit from immediate approval and from an OIR scheme are those identified in §B.4.2. Those values, together with the OWR trial parameters, $(n^{*,\mathrm{W}},t^{*,\mathrm{W}})$ and an OWR interim price satisfying $p_i^W>\mu_0+p_{\mathcal{S}}-f_r/(Nt^{*,\mathrm{W}}-n^{*,\mathrm{W}})$ ensure that the payer prefers the OIR scheme or immediate approval to the OWR scheme.

We now outline the optimal offer that would be submitted by the company at the initial submission when both OIR and OWR schemes are under consideration:

• If $\Pi_0(\mathrm{A}_0,\mu_0+p_{\mathcal{S}})=\max\{\Pi_0(\mathrm{A}_0,\mu_0+p_{\mathcal{S}}),\Pi_0(\mathrm{CA}^{\mathrm{W}},\mu_0+p_{\mathcal{S}}-f_r/(Nt^{*,\mathrm{W}}-n^{*,\mathrm{W}}),n^{*,\mathrm{W}},t^{*,\mathrm{W}}),\Pi_0(\mathrm{CA}^{\mathrm{I}},\mu_0+p_{\mathcal{S}},n^*,t^*),0\}$, the company's optimal action is to submit $p_0^{Seq,*}=\mu_0+p_{\mathcal{S}}$, and to set $p_i^{Seq,*}>\mu_0+p_{\mathcal{S}}$ and $p_i^{Seq,W,*}>\mu_0+p_{\mathcal{S}}-f_r/(Nt^{*,\mathrm{W}}-n^{*,\mathrm{W}})$, where the data collection (n,t) is determined by (n^*,t^*) for the OIR scheme and by $(n^{*,\mathrm{W}},t^{*,\mathrm{W}})$ for the OWR scheme. Then, the treatment is immediately approved by the payer at the immediate approval price $p_0^{Seq,*}$.

• If $\Pi_0(\mathrm{CA}^{\mathrm{I}},\mu_0+p_{\mathcal{S}},n^*,t^*)=\max\{\Pi_0(\mathrm{CA}^{\mathrm{W}},\mu_0+p_{\mathcal{S}}-f_r/(Nt^{*,\mathrm{W}}-n^{*,\mathrm{W}}),n^{*,\mathrm{W}},t^{*,\mathrm{W}}),\Pi_0(\mathrm{CA}^{\mathrm{I}},\mu_0+p_{\mathcal{S}},n^*,t^*),0\}>\Pi_0(\mathrm{A}_0,\mu_0+p_{\mathcal{S}})$, then the company's optimal action is to submit $p_i^{Seq,*}=\mu_0+p_{\mathcal{S}}$, and to set $p_0^{Seq,*}>\mu_0+p_{\mathcal{S}}$ and $p_i^{Seq,W,*}>\mu_0+p_{\mathcal{S}}-f_r/(Nt^{*,\mathrm{W}}-n^{*,\mathrm{W}})$, where the data collection (n,t) is determined by (n^*,t^*) for the OIR scheme and by $(n^{*,\mathrm{W}},t^{*,\mathrm{W}})$ for the OWR scheme. Then, the treatment is conditionally approved with an OIR scheme by the payer at the interim price $p_i^{Seq,*}$.

• If $\Pi_0(\mathrm{CA}^{\mathrm{W}},\mu_0+p_{\mathcal{S}}-f_r/(Nt^{*,\mathrm{W}}-n^{*,\mathrm{W}}),n^{*,\mathrm{W}},t^{*,\mathrm{W}})=\max\{\Pi_0(\mathrm{CA}^{\mathrm{W}},\mu_0+p_{\mathcal{S}}-f_r/(Nt^{*,\mathrm{W}}-n^{*,\mathrm{W}}),n^{*,\mathrm{W}},t^{*,\mathrm{W}}),0\}>\max\{\Pi_0(\mathrm{A}_0,\mu_0+p_{\mathcal{S}}),\Pi_0(\mathrm{CA}^{\mathrm{I}},\mu_0+p_{\mathcal{S}},n^*,t^*)\}$, then the company's optimal action is to submit $p_i^{Seq,W,*}=\mu_0+p_{\mathcal{S}}-f_r/(Nt^{*,\mathrm{W}}-n^{*,\mathrm{W}})$, and to set $p_i^{Seq,*}>\mu_0+p_{\mathcal{S}}$ and $p_0^{Seq,*}>\mu_0+p_{\mathcal{S}}$, where the data collection (n,t) is determined by (n^*,t^*) for the OIR scheme and by $(n^{*,\mathrm{W}},t^{*,\mathrm{W}})$ for the OWR scheme. Then, the treatment is conditionally approved with an OWR scheme by the payer at the interim price $p_i^{Seq,W,*}$.

• If $\max\{\Pi_0(\mathrm{A}_0,\mu_0+p_{\mathcal{S}}),\Pi_0(\mathrm{CA}^{\mathrm{W}},\mu_0+p_{\mathcal{S}}-f_r/(Nt^{*,\mathrm{W}}-n^{*,\mathrm{W}}),n^{*,\mathrm{W}},t^{*,\mathrm{W}}),\Pi_0(\mathrm{CA}^{\mathrm{I}},\mu_0+p_{\mathcal{S}},n^*,t^*)\}<0$, then the company would not submit the treatment to the payer.

As with the Nash bargaining model, we break ties by selecting immediate approval, an OIR scheme and an OWR scheme in this order.

REMARK EC.7. Given the equivalency outlined in Remark EC.6, the conditions under which the treatment is immediately approved, conditionally approved with an OIR or OWR scheme, or rejected are identical under the Stackelberg model and the Nash bargaining model. Furthermore, the Nash bargaining interim price for an OWR scheme for $\beta=1$ is $p_i^{*,\mathrm{W}}=p_i^{Seq,W,*}$.

B.5. Proofs of Mathematical Claims in §5

Prop. 5 shows when the payer would obtain a negative share of the gains at the reappraisal stage if our advance contracting mechanism is implemented for an OIR scheme, and we present the proof below.

Proof of Prop. 5. Case (i) directly follows from the fact that the Nash bargaining process is not disrupted when $\overline{p}_i\geq p_i^*$. Therefore there is no need for a readjustment to $(\beta,1-\beta)$ at the reappraisal stage.

If $\overline{p}_i<p_i^*$, the value of β_1^* is determined in a way to satisfy $\Pi_0(\mathrm{CA}^{\mathrm{I}},\overline{p}_i,n^*,t^*,\beta_1)=\beta S_0(\mathrm{CA}^{\mathrm{I}})$. By using (13) and (25) and solving

$$n^*(\overline{p}_i-v_{\mathcal{N}})-f_{DC}-n^*v_{DC}+\beta_1^*\,\mathbb{E}_{M_1}\left[S_1^*(t^*)\,|\,\mu_0,n_0\right]=\beta\left[n^*(\mu_0+p_{\mathcal{S}}-v_{\mathcal{N}})-f_{DC}-n^*v_{DC}+\mathbb{E}_{M_1}\left[S_1^*(t^*)\,|\,\mu_0,n_0\right]\right],$$

we find

$$\beta_1^*=\frac{\beta n^*(\mu_0+p_{\mathcal{S}})-n^*\overline{p}_i+(1-\beta)\left[f_{DC}+n^*v_{DC}+n^*v_{\mathcal{N}}\right]+\beta\,\mathbb{E}_{M_1}\left[S_1^*(t^*)\,|\,\mu_0,n_0\right]}{\mathbb{E}_{M_1}\left[S_1^*(t^*)\,|\,\mu_0,n_0\right]}. \tag{EC.26}$$

Because the denominator of the right hand side of (EC.26) is positive, for case (ii) we then have $\beta_1^* \leq 1$ if and only if

$$\begin{aligned}
\mathbb{E}_{M_1}\left[S_1^*(t^*) \mid \mu_0, n_0\right] &\geq \beta n^*(\mu_0 + p_{\mathcal{S}}) - n^*\overline{p}_i + (1-\beta)\left[f_{DC} + n^* v_{DC} + n^* v_{\mathcal{N}}\right] + \beta\,\mathbb{E}_{M_1}\left[S_1^*(t^*) \mid \mu_0, n_0\right], \\
(1-\beta)\,\mathbb{E}_{M_1}\left[S_1^*(t^*) \mid \mu_0, n_0\right] &\geq \beta n^*(\mu_0 + p_{\mathcal{S}}) - n^*\overline{p}_i + (1-\beta)\left[f_{DC} + n^* v_{DC} + n^* v_{\mathcal{N}}\right], \\
(1-\beta)\,\mathbb{E}_{M_1}\left[S_1^*(t^*) \mid \mu_0, n_0\right] &\geq n^*(p_i^* - \overline{p}_i) \\
\overline{p}_i &\geq p_i^* - (1-\beta)\,\mathbb{E}_{M_1}\left[S_1^*(t^*) \mid \mu_0, n_0\right]/n^*,
\end{aligned}$$

where the third line directly follows from the definition of p_i^* in Prop. 3.

For case (iii) we similarly have $\beta_1^* > 1$ if and only if

$$\begin{aligned}
\mathbb{E}_{M_1}\left[S_1^*(t^*) \mid \mu_0, n_0\right] &< \beta n^*(\mu_0 + p_{\mathcal{S}}) - n^*\overline{p}_i + (1-\beta)\left[f_{DC} + n^* v_{DC} + n^* v_{\mathcal{N}}\right] + \beta\,\mathbb{E}_{M_1}\left[S_1^*(t^*) \mid \mu_0, n_0\right], \\
(1-\beta)\,\mathbb{E}_{M_1}\left[S_1^*(t^*) \mid \mu_0, n_0\right] &< \beta n^*(\mu_0 + p_{\mathcal{S}}) - n^*\overline{p}_i + (1-\beta)\left[f_{DC} + n^* v_{DC} + n^* v_{\mathcal{N}}\right], \\
(1-\beta)\,\mathbb{E}_{M_1}\left[S_1^*(t^*) \mid \mu_0, n_0\right] &< n^*(p_i^* - \overline{p}_i) \\
\overline{p}_i &< \; p_i^* - (1-\beta)\,\mathbb{E}_{M_1}\left[S_1^*(t^*) \mid \mu_0, n_0\right]/n^*.
\end{aligned}$$

Moreover, $\beta_1^* > 1$ implies that $(1-\beta_1^*)\,\mathbb{E}_{M_1}\left[S_1^*(t^*) \mid \mu_0, n_0\right] < 0$, because the expectation in this expression is positive. □

Proof of Corollary 3. Now we show that $\overline{p}_i = \mu_0 + p_{\mathcal{S}}$ always satisfies Case (ii) of Prop. 5, which requires $\overline{p}_i \geq p_i^* - (1-\beta)\,\mathbb{E}_{M_1}\left[S_1^*(t^*) \mid \mu_0, n_0\right]/n^*$. We plug in the definition of p_i^* from Prop. 3 and $\overline{p}_i = \mu_0 + p_{\mathcal{S}}$:

$$\mu_0 + p_{\mathcal{S}} \geq v_{\mathcal{N}} + \beta(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}}) + (1-\beta)(v_{DC} + f_{DC}/n^*) - (1-\beta)\,\mathbb{E}_{M_1}\left[S_1^*(t^*) \mid \mu_0, n_0\right]/n^*,$$

and we rearrange terms to obtain

$$(1-\beta)(\mu_0 + p_{\mathcal{S}}) - (1-\beta)(v_{DC} + f_{DC}/n^* + v_{\mathcal{N}}) + (1-\beta)\,\mathbb{E}_{M_1}\left[S_1^*(t^*) \mid \mu_0, n_0\right]/n^* = (1-\beta)S_0(\mathrm{CA}^{\mathrm{I}})/n^* \geq 0.$$

The equality follows from the definition of $S_0(\mathrm{CA}^{\mathrm{I}})$. Thus, if $S_0(\mathrm{CA}^{\mathrm{I}}) \geq 0$, then $\overline{p}_i = \mu_0 + p_{\mathcal{S}}$ is sufficient for Case (ii) of Prop. 5 to hold. □

Price caps in OWR schemes. Next, we discuss the implications of putting a cap on the interim price under an OWR scheme. Suppose that the Nash bargaining outcome is an OWR scheme and Nash bargaining at initial submission obtains the interim price, $p_i^{*,\mathrm{W}}$. As in the discussion for OIR in §5, if $p_i^{*,\mathrm{W}} > \overline{p}_i$, then Nash bargaining solution violates the price cap, and either the cap or the details of the Nash bargaining must be modified.

When an OWR scheme is the Nash outcome, the details of Nash bargaining model can be relaxed in a manner similar to that of the risk-sharing mechanism discussed in §5. For alternative fractions $[\beta_1, (1-\beta_1)]$, we write the analogues to (24) and (25) for an OWR scheme:

$$V_0(\mathrm{CA}^{\mathrm{W}}, \overline{p}_i, n, t, \beta_1) \;=\; (Nt-n)(\mu_0 - \overline{p}_i + p_{\mathcal{S}}) + (1-\beta_1)\,\mathbb{E}_{M_1}\left[S_1^{*,\mathrm{W}}(t) \mid \mu_0, n_0\right], \quad \text{and} \tag{EC.27}$$

$$\Pi_0(\mathrm{CA}^{\mathrm{W}}, \overline{p}_i, n, t, \beta_1) \;=\; (Nt-n)(\overline{p}_i - v_{\mathcal{N}}) - f_{DC} - n v_{DC} + \beta_1\,\mathbb{E}_{M_1}\left[S_1^{*,\mathrm{W}}(t) \mid \mu_0, n_0\right]. \tag{EC.28}$$

Adding (EC.27) and (EC.28), we obtain $S_0(\text{CA}^{\text{W}}, n, t)$. The players aim to preserve the $[\beta, (1-\beta)]$ split of the joint surplus, $S_0(\text{CA}^{\text{W}})$, so that

$$V_0(\text{CA}^{\text{W}}, \overline{p}_i, n, t, \beta_1) = (1-\beta) S_0(\text{CA}^{\text{W}}) \qquad \text{and} \qquad \Pi_0(\text{CA}^{\text{W}}, \overline{p}_i, n, t, \beta_1) = \beta S_0(\text{CA}^{\text{W}}). \tag{EC.29}$$

The risk-sharing mechanism used when OWR is the Nash outcome implies that the players use (EC.27)-(EC.29) to identify and contract upon a $\beta_1^{*,\text{W}}$, which is the analogue of β_1^* for OIR. Because cooperative bargaining is conserved at initial submission, the players maintain the common objective of designing the post-marketing trial to maximize the expected joint surplus at reappraisal. Therefore they continue to agree to choose the same trial parameters $n^{*,\text{W}}$ and $t^{*,\text{W}} = 2n^{*,\text{W}}/(Nr_{max})$ identified in Appendix B.2.2.

Prop. 6 and Corollary 4 indicate when $\beta_1^{*,\text{W}}$ exceeds one and are analogous to Prop. 5 and Corollary 3.

Proof of Prop. 6. Case (i) directly follows from the fact that the Nash bargaining process is not disrupted when $\overline{p}_i \geq p_i^{*,\text{W}}$, therefore there is no need for a readjustment to $(\beta, 1-\beta)$ at the reappraisal stage.

If $\overline{p}_i < p_i^{*,\text{W}}$, the value of $\beta_1^{*,\text{W}}$ must satisfy $\Pi_0(\text{CA}^{\text{W}}, \overline{p}_i, n^{*,\text{W}}, t^{*,\text{W}}, \beta_1) = \beta S_0(\text{CA}^{\text{W}})$. Defining $\tilde{N} \triangleq Nt^{*,\text{W}} - n^{*,\text{W}}$ to simplify the expressions, we use (21) and (EC.28),

$$\begin{aligned}
&\tilde{N}(\overline{p}_i - v_{\mathcal{N}}) - f_{DC} - n^{*,\text{W}} v_{DC} + \beta_1^{*,\text{W}} \mathbb{E}_{M_1}\left[S_1^{*,\text{W}}(t^{*,\text{W}}) \,|\, \mu_0, n_0\right] \\
&\qquad = \beta\left[\tilde{N}(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}}) - f_{DC} - n^{*,\text{W}} v_{DC} + \mathbb{E}_{M_1}\left[S_1^{*,\text{W}}(t^{*,\text{W}}) \,|\, \mu_0, n_0\right]\right],
\end{aligned}$$

and solve the above equality for $\beta_1^{*,\text{W}}$:

$$\beta_1^{*,\text{W}} = \frac{\beta\tilde{N}(\mu_0 + p_{\mathcal{S}}) - \tilde{N}\overline{p}_i + (1-\beta)\left[f_{DC} + n^{*,\text{W}} v_{DC} + \tilde{N} v_{\mathcal{N}}\right] + \beta\,\mathbb{E}_{M_1}\left[S_1^{*,\text{W}}(t^{*,\text{W}}) \,|\, \mu_0, n_0\right]}{\mathbb{E}_{M_1}\left[S_1^{*,\text{W}}(t^{*,\text{W}}) \,|\, \mu_0, n_0\right]}. \tag{EC.30}$$

We now show that the denominator of the right-hand side of (EC.30) is positive when $S_0(\text{CA}^{\text{I}}) < S_0(\text{CA}^{\text{W}})$. Using the definition of $S_1^{*,\text{W}}(t^{*,\text{W}})$ in Prop. EC.1, substituting M_1 for μ_1, taking expectations, and applying the definition of $\psi(x)$, we have

$$\mathbb{E}_{M_1}\left[S_1^{*,\text{W}}(t^{*,\text{W}}) \,|\, \mu_0, n_0\right] = -f_r + (N - 2n^{*,\text{W}}/r_{max})\sigma_{M_1}^{*,\text{W}} \psi\left(\frac{v_{\mathcal{N}} - p_{\mathcal{S}} - f_r/((N - 2n^{*,\text{W}}/r_{max})) - \mu_0}{\sigma_{M_1}^{*,\text{W}}}\right).$$

Then, $\mathbb{E}_{M_1}\left[S_1^{*,\text{W}}(t^{*,\text{W}}) \,|\, \mu_0, n_0\right] > 0$ holds if and only if

$$\psi\left(\frac{v_{\mathcal{N}} - p_{\mathcal{S}} - f_r/((N - 2n^{*,\text{W}}/r_{max}))}{\sigma_{M_1}^{*,\text{W}}}\right) > \frac{f_r}{(N - 2n^{*,\text{W}}/r_{max})\sigma_{M_1}^{*,\text{W}}},$$

which follows from $r_{max} < 1$ and the definition of $\sigma_{M_1}^{*,\text{W}}$.

We recall from Prop. 4 that $S_0(\text{CA}^{\text{I}}) < S_0(\text{CA}^{\text{W}})$ holds only when $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} > 0$. Given $x \triangleq \mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} > 0$ and $y \triangleq f_r/((N - 2n^{*,\text{W}}/r_{max})\sigma_{M_1}^{*,\text{W}})$, we have $\psi(-x-y) > \psi(-y) > y$. Therefore, we have $\mathbb{E}_{M_1}\left[S_1^{*,\text{W}}(t^{*,\text{W}}) \,|\, \mu_0, n_0\right] > 0$ when $S_0(\text{CA}^{\text{I}}) < S_0(\text{CA}^{\text{W}})$.

Because the denominator of the right-hand side of (EC.30) is positive, for case (ii) we then have $\beta_1^{*,\text{W}} \leq 1$ if and only if we have $S_0(\text{CA}^{\text{I}}) < S_0(\text{CA}^{\text{W}})$ and:

$$\begin{aligned}
(1-\beta)\,\mathbb{E}_{M_1}\left[S_1^{*,\text{W}}(t^{*,\text{W}}) \,|\, \mu_0, n_0\right] &\geq \beta\tilde{N}(\mu_0 + p_{\mathcal{S}}) - \tilde{N}\overline{p}_i + (1-\beta)\left[f_{DC} + n^{*,\text{W}} v_{DC} + \tilde{N} v_{\mathcal{N}}\right], \\
(1-\beta)\,\mathbb{E}_{M_1}\left[S_1^{*,\text{W}}(t^{*,\text{W}}) \,|\, \mu_0, n_0\right] &\geq \tilde{N}(p_i^{*,\text{W}} - \overline{p}_i) + \beta f_r, \\
\overline{p}_i &\geq p_i^{*,\text{W}} + \beta f_r/\tilde{N} - (1-\beta)\,\mathbb{E}_{M_1}\left[S_1^{*,\text{W}}(t^{*,\text{W}}) \,|\, \mu_0, n_0\right]/\tilde{N},
\end{aligned}$$

where the second line directly follows from the definition of $p_i^{*,\mathrm{W}}$ in (22).

For case (iii) we similarly have $\beta_1^{*,\mathrm{W}} > 1$ if and only if

$$\begin{aligned}(1-\beta)\,\mathbb{E}_{M_1}\left[S_1^{*,\mathrm{W}}(t^{*,\mathrm{W}}) \mid \mu_0, n_0\right] &< \beta\tilde{N}(\mu_0 + p_{\mathcal{S}}) - \tilde{N}\overline{p}_i + (1-\beta)\left[f_{DC} + n^{*,\mathrm{W}} v_{DC} + \tilde{N} v_{\mathcal{N}}\right],\\ (1-\beta)\,\mathbb{E}_{M_1}\left[S_1^{*,\mathrm{W}}(t^{*,\mathrm{W}}) \mid \mu_0, n_0\right] &< \tilde{N}(p_i^{*,\mathrm{W}} - \overline{p}_i) + \beta f_r,\\ \overline{p}_i &< p_i^{*,\mathrm{W}} + \beta f_r/\tilde{N} - (1-\beta)\,\mathbb{E}_{M_1}\left[S_1^{*,\mathrm{W}}(t^{*,\mathrm{W}}) \mid \mu_0, n_0\right]/\tilde{N}.\end{aligned}$$

Moreover, $\beta_1^{*,\mathrm{W}} > 1$ also implies that $(1-\beta_1^{*,\mathrm{W}})\,\mathbb{E}_{M_1}\left[S_1^{*,\mathrm{W}}(t^{*,\mathrm{W}}) \mid \mu_0, n_0\right] < 0$, because the expectation in this expression is positive. □

Proof of Corollary 4. Now we show that $\overline{p}_i = \mu_0 + p_{\mathcal{S}}$ always satisfies Case (ii) of Prop. 6, which requires $\overline{p}_i \geq p_i^{*,\mathrm{W}} + \beta f_r/\tilde{N} - (1-\beta)\,\mathbb{E}_{M_1}\left[S_1^{*,\mathrm{W}}(t^{*,\mathrm{W}}) \mid \mu_0, n_0\right]/\tilde{N}$, where $\tilde{N} \triangleq Nt^{*,\mathrm{W}} - n^{*,\mathrm{W}}$. We plug in the definition of $p_i^{*,\mathrm{W}}$ from (22) and $\overline{p}_i = \mu_0 + p_{\mathcal{S}}$:

$$\begin{aligned}\mu_0 + p_{\mathcal{S}} \geq v_{\mathcal{N}} + \beta(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}}) + (1-\beta)(v_{DC} n^{*,\mathrm{W}} + f_{DC})/\tilde{N} - \beta f_r/\tilde{N}\\ + \beta f_r/\tilde{N} - (1-\beta)\,\mathbb{E}_{M_1}\left[S_1^{*,\mathrm{W}}(t^{*,\mathrm{W}}) \mid \mu_0, n_0\right]/\tilde{N},\end{aligned}$$

and we rearrange terms to obtain

$$\begin{aligned}(1-\beta)(\mu_0 + p_{\mathcal{S}}) - (1-\beta)((v_{DC} n^{*,\mathrm{W}} + f_{DC})/\tilde{N} + v_{\mathcal{N}}) + (1-\beta)\,\mathbb{E}_{M_1}\left[S_1^{*,\mathrm{W}}(t^{*,\mathrm{W}}) \mid \mu_0, n_0\right]/\tilde{N}\\ = (1-\beta) S_0(\mathrm{CA}^{\mathrm{W}})/\tilde{N} \geq 0.\end{aligned}$$

The equality follows from the definition of $S_0(\mathrm{CA}^{\mathrm{W}})$. Thus, if $S_0(\mathrm{CA}^{\mathrm{W}}) \geq 0$, then $\overline{p}_i = \mu_0 + p_{\mathcal{S}}$ is sufficient for Case (ii) of Prop. 6 to hold. □

Appendix C: Comparative Statics Results

We use comparative statics to explore the effect of key model parameters on the solution to the two-stage bargaining problem. Appendix C.1 discusses how model parameters influence joint surpluses, player payoffs, optimal sample size of the post-marketing trial and bargaining prices. Appendix C.2 discusses the sensitivity of Nash bargaining outcomes to model parameters. For parameters that cannot be unambiguously signed here, we offer numerical comparative statics results for the Votrient case study in Appendix E.

C.1. Sensitivity of Joint Surpluses, Player Payoffs and Prices to Key Model Parameters

Table EC.2 summarizes the derivatives of joint surpluses, $S_0(\mathrm{A}_0)$, $S_0(\mathrm{CA}^{\mathrm{I}})$, $S_0(\mathrm{CA}^{\mathrm{W}})$, the derivatives of optimal sample sizes, n^* and $n^{*,\mathrm{W}}$, and the derivatives of prices, p_0^*, p_i^* and $p_i^{*,\mathrm{W}}$, for the parameters (denoted by 'b') in the first column of the table. Appendix C.1.1, Appendix C.1.2 and Appendix C.1.3 present the algebra that leads to the results presented in Table EC.2. Appendix C.1.4 offers insights based on the comparative statics results for joint surpluses and prices.

C.1.1. Derivations of Comparative Statics Results for Joint Surpluses. Because $S_0(\mathrm{CA}^{\mathrm{I}})$ and $S_0(\mathrm{CA}^{\mathrm{W}})$ are obtained by solving their respective constrained optimization problems, we employ the envelope theorem for a constrained optimization problem to obtain the comparative statics for $S_0(\mathrm{CA}^{\mathrm{I}})$ and $S_0(\mathrm{CA}^{\mathrm{W}})$. We have shown in §3.2.3 and Appendix B.2 that it is optimal to set $t = 2n/(r_{max}N)$ and maximize over

the sample size for both problems. Then, we can rewrite each of these two optimization problems as an optimization over a single variable, n.

For ease of exposition, we focus on $S_0(\mathrm{CA^I})$, but the results continue to hold for $S_0(\mathrm{CA^W})$. We start by defining some additional notation. We let $\mathbf{b}$ to contain all problem parameters, and we let $f(n;\mathbf{b}) = S_0(\mathrm{CA^I}, n, 2n/(r_{max}N))$ represent the objective function of the optimization as a function of the decision variable, n, and problem parameters, $\mathbf{b}$. We define $g_1(n;\mathbf{b}) = n$ and $g_2(n;\mathbf{b}) = Nr_{max}/2 - n$. Therefore, our maximization problem has the following form:

$$S_0(\mathrm{CA^I}) = \max_n f(n;\mathbf{b})$$
$$\text{s.t. } g_i(n;\mathbf{b}) \geq 0 \text{ for } i = 1,2.$$

Let $\mathcal{L}$ be the Lagrangian expression of our problem:

$$\mathcal{L}(n;\mathbf{b}) = f(n;\mathbf{b}) + \lambda_1 g_1(n;\mathbf{b}) + \lambda_2 g_2(n;\mathbf{b})$$

where λ_1 and λ_2 are Lagrange multipliers associated with each constraint. Now we let $n^*(\mathbf{b})$ be the optimal solution that maximizes the objective function subject to constraints, and $\lambda_1^*(\mathbf{b})$ and $\lambda_2^*(\mathbf{b})$ be the Lagrange multipliers at the optimal solution. Then, the envelope theorem states that the derivative of the value function at the optimal solution with respect to a problem parameter $b \in \mathbf{b}$ satisfy the following

$$\frac{\partial S_0(\mathrm{CA^I})}{\partial b} = \frac{\partial f(n^*;\mathbf{b})}{\partial b} + \lambda_1^*(\mathbf{b})\frac{\partial g_1(n^*;\mathbf{b})}{\partial b} + \lambda_2^*(\mathbf{b})\frac{\partial g_2(n^*;\mathbf{b})}{\partial b}.$$

Furthermore, when both constraints are independent of the parameter of interest (i.e., $\partial g_i(n^*;\mathbf{b})/\partial b = 0$ for $i = 1,2$) or when neither constraint is binding (i.e., $\lambda_1^* = 0$ and $\lambda_2^* = 0$), the following condition holds:

$$\frac{\partial S_0(\mathrm{CA^I})}{\partial b} = \frac{\partial f(n^*;\mathbf{b})}{\partial b} = \frac{\partial S_0(\mathrm{CA^I}, n^*, 2n^*/(r_{max}N))}{\partial b}. \tag{EC.31}$$

For $S_0(\mathrm{CA^I})$ and $S_0(\mathrm{CA^W})$, neither constraint is a function of the following parameters: $\mu_0, n_0, p_{\mathcal{S}}, v_{\mathcal{N}}, f_{DC}, v_{DC}$ and β. Therefore, we can directly apply (EC.31) to examine the impact of each of these parameters. For the parameter N, we assume that the optimal value of the decision variable, n^*, lies in the interior of the problem domain.

Finally, we note the following derivative that will be used repeatedly: $\mathrm{d}\psi(x)/\mathrm{d}x = \Phi(x) - 1$.

Table EC.2 Comparative statics results for the joint surplus from immediate approval, $S_0(\mathbf{A}_0)$, the joint surplus from an OIR scheme, $S_0(\mathbf{CA^I})$, the joint surplus from an OWR scheme, $S_0(\mathbf{CA^W})$, the optimal sample size of an OIR scheme, n^*, the optimal sample size of an OWR scheme, $n^{*,\mathbf{W}}$, the immediate approval price, p_0^*, the interim price under an OIR scheme, p_i^*, and the interim price under an OWR scheme, $p_i^{*,\mathbf{W}}$.

Parameter(b)	$\partial S_0(\mathrm{A}_0)/\partial b$	$\partial S_0(\mathrm{CA^I})/\partial b$	$\partial S_0(\mathrm{CA^W})/\partial b$	$\partial n^*/\partial b$	$\partial n^{*,\mathrm{W}}/\partial b$	$\partial p_0^*/\partial b$	$\partial p_i^*/\partial b$	$\partial p_i^{*,\mathrm{W}}/\partial b$
μ_0	≥ 0	≥ 0	≥ 0	†	†	≥ 0	†	†
n_0	$= 0$	≤ 0	≤ 0	†	†	$= 0$	†	†
Σ_X	$= 0$	≥ 0	≥ 0	†	†	$= 0$	†	†
$p_{\mathcal{S}}$	≥ 0	≥ 0	≥ 0	†	†	≥ 0	†	†
$v_{\mathcal{N}}$	≤ 0	≤ 0	≤ 0	†	†	≥ 0	†	†
f_{DC}	$= 0$	≤ 0	≤ 0	$= 0$	$= 0$	$= 0$	≥ 0	≥ 0
v_{DC}	$= 0$	≤ 0	≤ 0	≤ 0	≤ 0	$= 0$	†	†
N	≥ 0	≥ 0	†	≥ 0	†	$= 0$	≤ 0	†
β	$= 0$	$= 0$	$= 0$	$= 0$	$= 0$	≥ 0	†	†

†It is not possible to unambiguously sign analytical expressions. Their closed forms are presented in Appendix C.1.1, Appendix C.1.2 and Appendix C.1.3, and their effects are numerically analyzed in Appendix E.

Prior Mean about the INMB-p. First, we observe that $S_0(\mathrm{A}_0)$ is linearly increasing in μ_0:

$$\frac{\partial S_0(\mathrm{A}_0)}{\partial \mu_0} = N.$$

Second, we show that $S_0(\mathrm{CA}^{\mathrm{I}})$ is increasing in μ_0:

$$\frac{\partial S_0(\mathrm{CA}^{\mathrm{I}},n,t)}{\partial \mu_0} = n + (1-t)N\left[1-\Phi\left(\frac{v_{\mathcal{N}}-p_{\mathcal{S}}-\mu_0}{\sigma_{M_1}}\right)\right],$$

which implies $\partial S_0(\mathrm{CA}^{\mathrm{I}})/\partial\mu_0 > 0$ by the envelope theorem.

Third, we show that $S_0(\mathrm{CA}^{\mathrm{W}})$ is increasing in μ_0:

$$\frac{\partial S_0(\mathrm{CA}^{\mathrm{W}},n,t)}{\partial \mu_0} = tN - n + (1-t)N\left[1-\Phi\left(\frac{v_{\mathcal{N}}-p_{\mathcal{S}}-f_r/((1-t)N)-\mu_0}{\sigma_{M_1}}\right)\right].$$

By definition $n \le tN$. Then, $\partial S_0(\mathrm{CA}^{\mathrm{W}})/\partial\mu_0 > 0$ by the envelope theorem.

Effective Sample Size of the Prior Distribution about the INMB-p. First, the fact that $S_0(\mathrm{A}_0)$ is independent of n_0 follows from its definition in (12).

Second, we show that $S_0(\mathrm{CA}^{\mathrm{I}})$ is decreasing in n_0. We recall from (3) that σ_{M_1} is a function of n_0.

$$\begin{aligned}
\frac{\partial S_0(\mathrm{CA}^{\mathrm{I}},n,t)}{\partial n_0} &= (1-t)N\left[\frac{\partial \sigma_{M_1}}{\partial n_0}\psi\left(\frac{v_{\mathcal{N}}-p_{\mathcal{S}}-\mu_0}{\sigma_{M_1}}\right) + \sigma_{M_1}\frac{\partial \psi\left(\frac{v_{\mathcal{N}}-p_{\mathcal{S}}-\mu_0}{\sigma_{M_1}}\right)}{\partial n_0}\right] \\
&= (1-t)N\left[\frac{\partial \sigma_{M_1}}{\partial n_0}\psi\left(\frac{v_{\mathcal{N}}-p_{\mathcal{S}}-\mu_0}{\sigma_{M_1}}\right) + \sigma_{M_1}\frac{\partial \psi\left(\frac{v_{\mathcal{N}}-p_{\mathcal{S}}-\mu_0}{\sigma_{M_1}}\right)}{\partial\left(\frac{v_{\mathcal{N}}-p_{\mathcal{S}}-\mu_0}{\sigma_{M_1}}\right)}\frac{\partial\left(\frac{v_{\mathcal{N}}-p_{\mathcal{S}}-\mu_0}{\sigma_{M_1}}\right)}{\partial \sigma_{M_1}}\frac{\partial \sigma_{M_1}}{\partial n_0}\right] \\
&= (1-t)N\frac{\partial \sigma_{M_1}}{\partial n_0}\left[\psi\left(\frac{v_{\mathcal{N}}-p_{\mathcal{S}}-\mu_0}{\sigma_{M_1}}\right) + \sigma_{M_1}\left(\Phi\left(\frac{v_{\mathcal{N}}-p_{\mathcal{S}}-\mu_0}{\sigma_{M_1}}\right)-1\right)\left(-\frac{v_{\mathcal{N}}-p_{\mathcal{S}}-\mu_0}{\sigma_{M_1}^2}\right)\right] \\
&= (1-t)N\frac{\partial \sigma_{M_1}}{\partial n_0}\left[\psi\left(\frac{v_{\mathcal{N}}-p_{\mathcal{S}}-\mu_0}{\sigma_{M_1}}\right) + \frac{v_{\mathcal{N}}-p_{\mathcal{S}}-\mu_0}{\sigma_{M_1}}\left(1-\Phi\left(\frac{v_{\mathcal{N}}-p_{\mathcal{S}}-\mu_0}{\sigma_{M_1}}\right)\right)\right] \\
&= (1-t)N\frac{\partial \sigma_{M_1}}{\partial n_0}\phi\left(\frac{v_{\mathcal{N}}-p_{\mathcal{S}}-\mu_0}{\sigma_{M_1}}\right),
\end{aligned}$$

where the last line follows from the definition of $\psi(x) = \phi(x) - x(1-\Phi(x))$.

Now we show that $\partial\sigma_{M_1}/\partial n_0 < 0$ and therefore $\partial S_0(\mathrm{CA}^{\mathrm{W}})/\partial n_0 < 0$ by the envelope theorem.

$$\frac{\partial \sigma_{M_1}}{\partial n_0} = \frac{\partial\sqrt{\Sigma_X n/(n_0(n+n_0))}}{\partial n_0} = -\sqrt{\Sigma_X n}\frac{1}{2}\left(\frac{1}{n_0(n+n_0)}\right)^{3/2}(n+2n_0) = -\frac{\sigma_{M_1}^3(n+2n_0)}{2n\Sigma_X} < 0.$$

Third, we show $S_0(\mathrm{CA}^{\mathrm{W}})$ is decreasing in n_0 following the same steps as we did for $S_0(\mathrm{CA}^{\mathrm{I}})$:

$$\frac{\partial S_0(\mathrm{CA}^{\mathrm{W}},n,t)}{\partial n_0} = (1-t)N\frac{\partial \sigma_{M_1}}{\partial n_0}\phi\left(\frac{v_{\mathcal{N}}-p_{\mathcal{S}}-f_r/((1-t)N)-\mu_0}{\sigma_{M_1}}\right).$$

Because $\partial\sigma_{M_1}/\partial n_0 < 0$, $\partial S_0(\mathrm{CA}^{\mathrm{W}})/\partial n_0 < 0$ by the envelope theorem.

Variance of Outcomes. First, $S_0(\mathrm{A}_0)$ is independent of Σ_X from its definition in (12).

Second, we show that $S_0(\mathrm{CA}^{\mathrm{I}})$ is increasing in Σ_X. We recall from (3) that σ_{M_1} is a function of Σ_X.

$$\frac{\partial S_0(\mathrm{CA}^{\mathrm{I}},n,t)}{\partial \Sigma_X} = (1-t)N\frac{\partial \sigma_{M_1}}{\partial \Sigma_X}\phi\left(\frac{v_{\mathcal{N}}-p_{\mathcal{S}}-\mu_0}{\sigma_{M_1}}\right),$$

where the derivation follows that for n_0.

Now we show that $\partial\sigma_{M_1}/\partial\Sigma_X > 0$, and therefore $\partial S_0(\mathrm{CA^I})/\partial\Sigma_X > 0$ by the envelope theorem.

$$\begin{aligned}\frac{\partial\sigma_{M_1}}{\partial\Sigma_X} &= \frac{\partial\sqrt{\Sigma_X n/(n_0(n+n_0))}}{\partial\Sigma_X}\\ &= \frac{\sqrt{\Sigma_X n/(n_0(n+n_0))}}{2\Sigma_X} > 0\end{aligned}$$

Third, we show $S_0(\mathrm{CA^W})$ is increasing in Σ_X following the same steps as we did for $S_0(\mathrm{CA^I})$:

$$\frac{\partial S_0(\mathrm{CA^W},n,t)}{\partial n_0} = (1-t)N\frac{\partial\sigma_{M_1}}{\partial\Sigma_X}\phi\left(\frac{v_{\mathcal{N}}-p_{\mathcal{S}}-f_r/((1-t)N)-\mu_0}{\sigma_{M_1}}\right).$$

In turn, $\partial\sigma_{M_1}/\partial\Sigma_X > 0$ implies $\partial S_0(\mathrm{CA^W})/\partial\Sigma_X > 0$ by the envelope theorem.

Price of the Standard of Care. We note that the price of the standard care, $p_{\mathcal{S}}$, always show up together with the prior mean about INMB-p, μ_0, in the equations for joint surpluses, and the two parameters have the same sign. Therefore, the direction of their effects on $S_0(\mathrm{A_0})$, $S_0(\mathrm{CA^I})$ and $S_0(\mathrm{CA^W})$ are the same.

Production Cost. We note that the price of the variable production cost, $v_{\mathcal{N}}$, always show up together with the prior mean about INMB-p, μ_0, in the equations for joint surpluses, and the two parameters have opposite signs. Therefore, the direction of their effects on $S_0(\mathrm{A_0})$, $S_0(\mathrm{CA^I})$ and $S_0(\mathrm{CA^W})$ are the opposite.

Fixed Cost of Post-marketing Data Collection. It directly follows from their definitions that $S_0(\mathrm{A_0})$ is independent of f_{DC}, and $S_0(\mathrm{CA^I})$ and $S_0(\mathrm{CA^W})$ are linearly decreasing in f_{DC}.

Variable Cost of Post-marketing Data Collection. First, it directly follows from its definition in (12) that $S_0(\mathrm{A_0})$ is independent of v_{DC}.

Second, we note that $S_0(\mathrm{CA^I})$ and $S_0(\mathrm{CA^W})$ are decreasing v_{DC}:

$$\frac{\partial S_0(\mathrm{CA^I},n,t)}{\partial v_{DC}} = -n \text{ and } \frac{\partial S_0(\mathrm{CA^W},n,t)}{\partial v_{DC}} = -n.$$

From envelope theorem, $\partial S_0(\mathrm{CA^I})/\partial v_{DC} < 0$ and $\partial S_0(\mathrm{CA^W})/\partial v_{DC} < 0$.

Population Size. First, we analyze $S_0(\mathrm{A_0})$:

$$\frac{\partial S_0(\mathrm{A_0})}{\partial N} = \mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}}.$$

Because immediate approval can be Nash bargaining outcome only if $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} \geq 0$, we say $S_0(\mathrm{A_0})$ is non-decreasing with N.

Second, we show that $S_0(\mathrm{CA^I})$ is increasing in N:

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

which implies $\partial S_0(\mathrm{CA^I})/\partial N > 0$ by the envelope theorem.

Third, we derive the derivative of $S_0(\mathrm{CA^W})$ with respect to N:

$$\begin{aligned}\frac{\partial S_0(\mathrm{CA^W},n,t)}{\partial N} &= t(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}}) + (1-t)\sigma_{M_1}\psi\left(\frac{v_{\mathcal{N}}-p_{\mathcal{S}}-f_r/((1-t)N)-\mu_0}{\sigma_{M_1}}\right)\\ &\quad - (1-t)N\sigma_{M_1}\left[1-\Phi\left(\frac{v_{\mathcal{N}}-p_{\mathcal{S}}-f_r/((1-t)N)-\mu_0}{\sigma_{M_1}}\right)\right]\left[\frac{f_r}{(1-t)N^2\sigma_{M_1}}\right]\end{aligned}$$

Therefore, the sign of $\partial S_0(\mathrm{CA^W})/\partial N$ is indeterminate.

Bargaining Power. By definition, $S_0(\mathrm{A_0})$, $S_0(\mathrm{CA^I})$ and $S_0(\mathrm{CA^W})$ are all independent of β.

C.1.2. Derivations of Comparative Statics Results for The Optimal Sample Size. We now explore how the optimal sample size changes with the problem parameters. We start with the OIR scheme. The optimal sample size n^* is determined as the n that sets $\partial S_0(\mathrm{CA}^{\mathrm{I}}, n, 2n/(Nr_{max}))/\partial n = 0$. Using the implicit function theorem, we have

$$\frac{\partial n}{\partial b} = -\frac{\partial^2 S_0(\mathrm{CA}^{\mathrm{I}}, n, 2n/(Nr_{max}))}{\partial n \partial b} \Bigg/ \frac{\partial^2 S_0(\mathrm{CA}^{\mathrm{I}}, n, 2n/(Nr_{max}))}{\partial n^2}$$

We know that, if the OIR scheme is the Nash bargaining outcome, $S_0(\mathrm{CA}^{\mathrm{I}}, n, 2n/(Nr_{max}))$ is concave at the optimal solution. (See Appendix B.3.) Then, the sign of $\partial n^*/\partial b$ is the same as the sign of $\partial^2 S_0(\mathrm{CA}^{\mathrm{I}}, n, 2n/(Nr_{max}))/\partial n \partial b$. Following the same argument, the sign of $\partial n^{*,\mathrm{W}}/\partial b$ is the same as the sign of $\partial^2 S_0(\mathrm{CA}^{\mathrm{W}}, n, 2n/(Nr_{max}))/\partial n \partial b$.

It is not possible to unambiguously sign the effects of some model parameters because the signs of $\partial^2 S_0(\mathrm{CA}^{\mathrm{I}}, n, 2n/(Nr_{max}))/\partial n \partial b$ and $\partial^2 S_0(\mathrm{CA}^{\mathrm{W}}, n, 2n/(Nr_{max}))/\partial n \partial b$ depend on other parameter values. Here we present the comparative statics results for f_{DC}, v_{DC} and β, whose effects can be unambiguously signed for the optimal sample sizes of the OIR and OWR schemes, and for N, whose effect can be unambiguously signed for the optimal sample size of the OIR scheme. We numerically analyze the effect of μ_0, $p_{\mathcal{S}}$, $v_{\mathcal{N}}$, n_0, Σ_X and N on n^* and $n^{*,\mathrm{W}}$ in Appendix E.

Fixed Cost of Post-marketing Data Collection. For an OIR scheme, $\partial S_0(\mathrm{CA}^{\mathrm{I}}, n, 2n/(Nr_{max}))/\partial n$ is given in (EC.7), and we see that the optimal sample size is independent of f_{DC}. And for an OWR scheme, we see from (EC.9) that the optimal sample size is independent of f_{DC}.

Variable Cost of Post-marketing Data Collection. We have

$$\frac{\partial^2 S_0(\mathrm{CA}^{\mathrm{I}}, n, 2n/(Nr_{max}))}{\partial n \partial v_{DC}} = -1, \ \frac{\partial^2 S_0(\mathrm{CA}^{\mathrm{W}}, n, 2n/(Nr_{max}))}{\partial n \partial v_{DC}} = -1$$

Then, the optimal sample sizes of an OIR scheme and an OWR scheme both decrease with the variable cost of data collection, v_{DC}.

Population Size. For an OIR scheme, we have

$$\frac{\partial^2 S_0(\mathrm{CA}^{\mathrm{I}}, n, 2n/(Nr_{max}))}{\partial n \partial N} = \frac{\partial \sigma_{M_1}}{\partial n} \phi\left(\frac{y}{\sigma_{M_1}}\right).$$

From (EC.8), we know $\partial \sigma_{M_1}/\partial n > 0$. Then, the optimal sample size of an OIR scheme increases with the population size, N.

Bargaining Power. We see from (EC.7) and (EC.9) that the optimal sample size is independent of β for both OIR and OWR schemes.

C.1.3. Derivations of Comparative Statics Results for Prices.

Immediate Approval Price. The immediate approval price, $p_0^* = v_{\mathcal{N}} + \beta(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}})$, is straightforward to analyze. The partial derivative of p_0^* with respect to μ_0, $p_{\mathcal{S}}$, $v_{\mathcal{N}}$ and β are

$$\frac{\partial p_0^*}{\partial \mu_0} = \beta \ , \ \frac{\partial p_0^*}{\partial p_{\mathcal{S}}} = \beta \ , \ \frac{\partial p_0^*}{\partial v_{\mathcal{N}}} = 1 - \beta \text{ and } \frac{\partial p_0^*}{\partial \beta} = \mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}}.$$

We note that the immediate approval can be the Nash bargaining outcome only if $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} \geq 0$, and $\beta \geq 0$ by definition. Then, p_0^* increases with μ_0, $p_{\mathcal{S}}$, $v_{\mathcal{N}}$ and β, and p_0^* is independent of all other parameters.

Interim Price of an OIR Scheme. From the definition in Prop. 3, we observe that p_i^* reduces to p_0^* for the special case of $\beta = 1$. Therefore, the comparative statics results outlined for p_0^* above holds also for p_i^* when $\beta = 1$. When $0 < \beta < 1$, p_i^* depends on the optimal sample size of the post-marketing trial, n^*. Therefore, it is not possible to unambiguously sign analytical expressions for the comparative statics of p_i^* if it is not possible to do so for the optimal n^*.

For the effect of the total number of patients in the population, N, on p_i^*, we have

$$\frac{\partial p_i^*}{\partial N} = -(1-\beta)\frac{f_{DC}}{(n^*)^2}\frac{\partial n^*}{\partial N}.$$

We showed $\partial n^*/\partial N > 0$ in Appendix C.1.2. Therefore, the OIR interim price, p_i^*, decreases with N if $\beta < 1$.

Because n^* is independent of f_{DC} and β (see Appendix C.1.2), we have

$$\frac{\partial p_i^*}{\partial f_{DC}} = \frac{1-\beta}{n^*} \quad \text{and} \quad \frac{\partial p_i^*}{\partial \beta} = \mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} - v_{DC} - f_{DC}/n^*.$$

Given that $n^* \geq 0$ by definition, p_i^* is non-decreasing with f_{DC}, and p_i^* increases with β if $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} - v_{DC} - f_{DC}/n^* > 0$.

For the rest of the parameters, μ_0, $p_{\mathcal{S}}$, $v_{\mathcal{N}}$, v_{DC}, n_0 and Σ_X, we have the following expressions for the partial derivatives of p_i^*:

$$\begin{aligned}
&\frac{\partial p_i^*}{\partial \mu_0} = -(1-\beta)\frac{f_{DC}}{(n^*)^2}\frac{\partial n^*}{\partial \mu_0} + \beta \ , \ \frac{\partial p_i^*}{\partial p_{\mathcal{S}}} = -(1-\beta)\frac{f_{DC}}{(n^*)^2}\frac{\partial n^*}{\partial p_{\mathcal{S}}} + \beta, \\
&\frac{\partial p_i^*}{\partial v_{\mathcal{N}}} = -(1-\beta)\frac{f_{DC}}{(n^*)^2}\frac{\partial n^*}{\partial v_{\mathcal{N}}} + 1 - \beta \ , \ \frac{\partial p_i^*}{\partial v_{DC}} = -(1-\beta)\frac{f_{DC}}{(n^*)^2}\frac{\partial n^*}{\partial v_{DC}} + 1 - \beta, \\
&\frac{\partial p_i^*}{\partial n_0} = -(1-\beta)\frac{f_{DC}}{(n^*)^2}\frac{\partial n^*}{\partial n_0} \ , \ \frac{\partial p_i^*}{\partial \Sigma_X} = -(1-\beta)\frac{f_{DC}}{(n^*)^2}\frac{\partial n^*}{\partial \Sigma_X}.
\end{aligned}$$

We observe that the effect of these parameters on the OIR interim price, p_i^*, depends both on their effect on the optimal sample size, n^*, the optimal sample size itself, the fixed data collection cost, f_{DC}, and the bargaining power, β. By varying these values these partial derivatives can be made positive or negative. Therefore, the effects of μ_0, $p_{\mathcal{S}}$, $v_{\mathcal{N}}$, v_{DC}, n_0 and Σ_X on p_i^* are indeterminate and we numerically analyze these effects on p_i^* in Appendix E using parameters from the Votrient case study.

Although the effects are indeterminate, we make one structural observation concerning the partial derivative of p_i^* with respect to n_0 and Σ_X: the effect of n_0 (or Σ_X) on the optimal sample size, n^*, and on the OIR interim price, p_i^*, are directional opposites if $\beta < 1$. In other words, if the optimal sample size increases with n_0 (or Σ_X), the OIR interim price decreases with n_0 (or Σ_X).

Interim Price of an OWR Scheme. From the definition in Prop. EC.2, $p_i^{*,\mathrm{W}}$ reduces to $p_0^* - f_r/(2n^{*,\mathrm{W}}/r_{max} - n^{*,\mathrm{W}})$ for the special case of $\beta = 1$. When $\beta = 1$ and there is no reversal cost, $f_r = 0$, the comparative statics results outlined for p_0^* above holds also for $p_i^{*,\mathrm{W}}$. When $0 < \beta < 1$ or $f_r > 0$, $p_i^{*,\mathrm{W}}$ depends on the optimal sample size of the post-marketing trial, $n^{*,\mathrm{W}}$. Thus, it is not possible to unambiguously sign analytical expressions for the comparative statics of $p_i^{*,\mathrm{W}}$ if it is not possible to do so for $n^{*,\mathrm{W}}$.

Because β and f_{DC} do not impact the value of $n^{*,\mathrm{W}}$ (see Appendix C.1.2), we have

$$\frac{\partial p_i^{*,\mathrm{W}}}{\partial f_{DC}} = \frac{1-\beta}{n^{*,\mathrm{W}}(2/r_{max} - 1)} \quad \text{and} \quad \frac{\partial p_i^{*,\mathrm{W}}}{\partial \beta} = \mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} - \frac{n^{*,\mathrm{W}} v_{DC} + f_{DC} + f_r}{n^{*,\mathrm{W}}(2/r_{max} - 1)}.$$

Given that $r_{max} < 1$ by definition, $p_i^{*,\mathrm{W}}$ always increases with f_{DC}. And $p_i^{*,\mathrm{W}}$ increases with β when $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} - (n^{*,\mathrm{W}} v_{DC} + f_{DC} + f_r)/(n^{*,\mathrm{W}}(2/r_{max} - 1)) > 0$.

For the rest of the parameters, μ_0, $p_{\mathcal{S}}$, $v_{\mathcal{N}}$, v_{DC}, n_0, Σ_X and N, we have the following expressions for the partial derivative of $p_i^{*,\mathrm{W}}$:

$$\frac{\partial p_i^{*,\mathrm{W}}}{\partial \mu_0} = -\frac{(1-\beta)f_{DC} - \beta f_r}{(n^{*,\mathrm{W}})^2(2/r_{max}-1)}\frac{\partial n^{*,\mathrm{W}}}{\partial \mu_0} + \beta \ , \quad \frac{\partial p_i^{*,\mathrm{W}}}{\partial p_{\mathcal{S}}} = -\frac{(1-\beta)f_{DC} - \beta f_r}{(n^{*,\mathrm{W}})^2(2/r_{max}-1)}\frac{\partial n^{*,\mathrm{W}}}{\partial p_{\mathcal{S}}} + \beta,$$
$$\frac{\partial p_i^{*,\mathrm{W}}}{\partial v_{\mathcal{N}}} = -\frac{(1-\beta)f_{DC} - \beta f_r}{(n^{*,\mathrm{W}})^2(2/r_{max}-1)}\frac{\partial n^{*,\mathrm{W}}}{\partial v_{\mathcal{N}}} + 1 - \beta \ , \quad \frac{\partial p_i^{*,\mathrm{W}}}{\partial v_{DC}} = -\frac{(1-\beta)f_{DC} - \beta f_r}{(n^{*,\mathrm{W}})^2(2/r_{max}-1)}\frac{\partial n^{*,\mathrm{W}}}{\partial v_{DC}} + 1 - \beta \ ,$$
$$\frac{\partial p_i^{*,\mathrm{W}}}{\partial n_0} = -\frac{(1-\beta)f_{DC} - \beta f_r}{(n^{*,\mathrm{W}})^2(2/r_{max}-1)}\frac{\partial n^{*,\mathrm{W}}}{\partial n_0} \ , \quad \frac{\partial p_i^{*,\mathrm{W}}}{\partial \Sigma_X} = -\frac{(1-\beta)f_{DC} - \beta f_r}{(n^{*,\mathrm{W}})^2(2/r_{max}-1)}\frac{\partial n^{*,\mathrm{W}}}{\partial \Sigma_X},$$
$$\frac{\partial p_i^{*,\mathrm{W}}}{\partial N} = -\frac{(1-\beta)f_{DC} - \beta f_r}{(n^{*,\mathrm{W}})^2(2/r_{max}-1)}\frac{\partial n^{*,\mathrm{W}}}{\partial N}.$$

The effects of these parameters on the OWR interim price are indeterminate, and we numerically analyze the effect of μ_0, $p_{\mathcal{S}}$, $v_{\mathcal{N}}$, n_0, Σ_X, v_{DC} and N on $p_i^{*,\mathrm{W}}$ in Appendix E.

Although the effects are indeterminate, we make one structural observation concerning the partial derivative of $p_i^{*,\mathrm{W}}$ with respect to n_0 and Σ_X: the effect of n_0 on the optimal sample size, $n^{*,\mathrm{W}}$ and on the OWR interim price, $p_i^{*,\mathrm{W}}$, are directional opposites only if $(1-\beta)f_{DC} > \beta f_r$. If $(1-\beta)f_{DC} < \beta f_r$, the directional effect of n_0 on $n^{*,\mathrm{W}}$ and on $p_i^{*,\mathrm{W}}$ are the same. And if $(1-\beta)f_{DC} = \beta f_r$, a change in the value of n_0 does not impact $p_i^{*,\mathrm{W}}$. The same insight also applies to Σ_X and N. Whereas for μ_0, $p_{\mathcal{S}}$, $v_{\mathcal{N}}$ and v_{DC}, it is possible for both $n^{*,\mathrm{W}}$ and $p_i^{*,\mathrm{W}}$ to increase with the parameter.

C.1.4. Insights Based on the Comparative Statics Results. We now interpret the comparative statics results presented in Table EC.2. We start by discussing how the joint surplus and player payoffs change with model parameters and continue with how the prices are impacted by various model parameters.

Sensitivity of Player Payoffs to Model Parameters. Because the bargaining framework implies that the joint surplus is shared between the payer and the company, the signs for $\partial S_0(\mathrm{A}_0)/\partial b$, $\partial S_0(\mathrm{CA}^{\mathrm{I}})/\partial b$ and $\partial S_0(\mathrm{CA}^{\mathrm{W}})/\partial b$ presented in Table EC.2 hold also for the payer's net benefit and the company's profit, with the exception of the bargaining power, β. A higher bargaining power of the company, β, implies that the company receives a higher share of the surplus, therefore the company's profit always increases with β and the payer's net benefit decreases with β.

The impact of most parameters are straightforward to interpret, so we focus on highlighting two interesting observations. The first is that, under conditions that lead to conditional approval outcome (OIR or OWR), the company's profit is the highest when the effective sample size is as low as possible. And the second one is that the profit from immediate approval is not impacted by the effective sample size. Together, these two facts imply that once enough data is collected in Phase III to ensure immediate approval, the company has no incentive to collect further samples.

Sensitivity of Prices to Model Parameters. The immediate approval price, $p_0^* = v_{\mathcal{N}} + \beta(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}})$, is higher when the prior mean and the price of the standard of care are higher and lower when the production cost is lower. Recalling Prop. 2, immediate approval can be optimal only when $S_0(\mathrm{A}_0) = N(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}}) \geq 0$. Thus, for new technologies that are immediately approved, the price, p_0^* (weakly) increases with β.

We now turn our attention to interim prices. The fixed cost of the trial, f_{DC}, leads to an increase in both OIR and OWR interim prices because the interim price acts as a cost-sharing mechanism. The OIR interim price decreases as the total number of patients in the population, N, increases, because the optimal sample size of an OIR scheme increases with N and the fixed data collection cost can be divided across a larger patient pool. The effect of N on the OWR interim price is more complicated due to the reversal cost.

The OIR interim price, p_i^*, may increase or decrease with the bargaining power of the company. To see this, recall from Prop. 3 that the interim price is $p_i^* = p_0^* + (1-\beta)(v_{DC} + f_{DC}/n^*)$. If $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} > 0$, 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 trial is small, then the first term will dominate, so that the interim price increases with β. If the treatment is marginally favorable and cost of the trial is low, then the second term will dominate, meaning that the interim price decreases with β. When $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} < 0$, 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.

To analyze the sensitivity of $p_i^{*,\mathrm{W}}$ to β, we recall from Prop. EC.2 that the OWR interim price is

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

If $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} > 0$, then p_0^* increases and $-\beta(n^{*,\mathrm{W}} v_{DC} + f_{DC} + f_r)/(n^{*,\mathrm{W}}(2/r_{max} - 1))$ decreases with β, and the direction of change depends on their balance. And if $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} < 0$, so immediate approval is not attractive, both decrease with β, and $p_i^{*,\mathrm{W}}$ unambiguously decreases. We note that the term $(n^{*,\mathrm{W}} v_{DC} + f_{DC} + f_r)/(n^{*,\mathrm{W}}(2/r_{max} - 1))$ is the total data collection cost plus potential reversal cost of an OWR trial divided across all patients treated with the new treatment during the post-marketing data collection period.

Unambiguously characterizing the effect of the rest of the parameters on the interim prices, p_i^* and $p_i^{*,\mathrm{W}}$, is not possible because their impact on depends on their impact on the optimal sample size. We numerically explore the comparative statics for μ_0, $p_{\mathcal{S}}$, $v_{\mathcal{N}}$, n_0, Σ_X, v_{DC} and N on the optimal sample sizes (n^*, $n^{*,\mathrm{W}}$) and Nash bargaining interim prices (p_i^*, $p_i^{*,\mathrm{W}}$) for the Votrient case study in Appendix E.

C.2. Sensitivity of the Nash Bargaining Outcomes to Key Model Parameters.

In §6.2, we numerically explore the sensitivity of Nash outcomes when an OWR scheme is also feasible. In this appendix, we analyze the impact of model parameters on the Nash bargaining outcome. We focus on the case of an OWR scheme being infeasible due to a high cost of reversal.

We recall from §3.3 that the Nash bargaining outcome depends on which joint surplus is the highest among $S_0(\mathrm{A}_0)$ and $S_0(\mathrm{CA}^{\mathrm{I}})$. Therefore, in Appendix C.2.1, we start by analyzing the impact of key model parameters on the difference $S_0(\mathrm{A}_0) - S_0(\mathrm{CA}^{\mathrm{I}})$ to understand how parameters impact the choice between immediate approval and an OIR scheme. Then, in Appendix C.2.2, we present the insights about the sensitivity of the Nash bargaining outcomes to model parameters.

C.2.1. Sensitivity of the Difference between Joint Surpluses to Selected Model Parameters.

Table EC.3 summarizes the derivatives of the difference between the joint surpluses from immediate approval and an OIR scheme, $S_0(\mathrm{A}_0) - S_0(\mathrm{CA}^{\mathrm{I}})$, for selected parameters which are denoted by 'b' and shown in the first column of the table. As in Appendix C.1.1, we use the envelope theorem to obtain the values for $\partial(S_0(\mathrm{A}_0) - S_0(\mathrm{CA}^{\mathrm{I}}))/\partial b$.

Table EC.3 Derivatives of the difference between the joint surpluses from immediate approval and an OIR scheme, $S_0(\mathbf{A}_0) - S_0(\mathbf{CA}^{\mathrm{I}})$, with respect to model parameters.

Parameter(b)	$\partial(S_0(\mathrm{A}_0) - S_0(\mathrm{CA}^{\mathrm{I}}))/\partial b$
μ_0	≥ 0
n_0	≥ 0
Σ_X	≤ 0
$p_{\mathcal{S}}$	≥ 0
$v_{\mathcal{N}}$	≤ 0
f_{DC}	≥ 0
v_{DC}	≥ 0
N	‡
β	$= 0$

‡It is not possible to unambiguously sign analytical expressions, but their closed forms are presented in text.

Prior Mean of the INMB-p. We show that $S_0(\mathrm{A}_0) - S_0(\mathrm{CA}^{\mathrm{I}})$ is increasing in μ_0:

$$\begin{aligned}\frac{\partial(S_0(\mathrm{A}_0) - S_0(\mathrm{CA}^{\mathrm{I}}, n, t))}{\partial \mu_0} &= (N-n) - (1-t)N\left[1 - \Phi\left(\frac{v_{\mathcal{N}} - p_{\mathcal{S}} - \mu_0}{\sigma_{M_1}}\right)\right] \\ &= (N-n) - (1-t)N + (1-t)N\Phi\left(\frac{v_{\mathcal{N}} - p_{\mathcal{S}} - \mu_0}{\sigma_{M_1}}\right) \\ &= -n + tN + (1-t)N\Phi\left(\frac{v_{\mathcal{N}} - p_{\mathcal{S}} - \mu_0}{\sigma_{M_1}}\right).\end{aligned}$$

By definition, $n \leq tN$. Then, we write $\partial(S_0(\mathrm{A}_0) - S_0(\mathrm{CA}^{\mathrm{I}}))/\partial \mu_0 > 0$ by the envelope theorem.

Effective Sample Size of the Prior Distribution of the INMB-p. We show that $S_0(\mathrm{A}_0) - S_0(\mathrm{CA}^{\mathrm{I}})$ is increasing in n_0, which follows directly from $\partial S_0(\mathrm{CA}^{\mathrm{I}})/\partial n_0$ because $S_0(\mathrm{A}_0)$ is independent of n_0:

$$\frac{\partial(S_0(\mathrm{A}_0) - S_0(\mathrm{CA}^{\mathrm{I}}, n, t))}{\partial n_0} = -(1-t)N\frac{\partial \sigma_{M_1}}{\partial n_0}\phi\left(\frac{v_{\mathcal{N}} - p_{\mathcal{S}} - \mu_0}{\sigma_{M_1}}\right)$$

where $\partial \sigma_{M_1}/\partial n_0 < 0$. Then, $\partial(S_0(\mathrm{A}_0) - S_0(\mathrm{CA}^{\mathrm{I}}))/\partial n_0 > 0$ by the envelope theorem.

Variance of Outcomes. We show that $S_0(\mathrm{A}_0) - S_0(\mathrm{CA}^{\mathrm{I}})$ is decreasing in Σ_X, which follows directly from $\partial S_0(\mathrm{CA}^{\mathrm{I}})/\partial \Sigma_X$ because $S_0(\mathrm{A}_0)$ is independent of Σ_X:

$$\frac{\partial(S_0(\mathrm{A}_0) - S_0(\mathrm{CA}^{\mathrm{I}}, n, t))}{\partial \Sigma_X} = -(1-t)N\frac{\partial \sigma_{M_1}}{\partial \Sigma_X}\phi\left(\frac{v_{\mathcal{N}} - p_{\mathcal{S}} - \mu_0}{\sigma_{M_1}}\right)$$

where $\partial \sigma_{M_1}/\partial \Sigma_X > 0$. Then, $\partial(S_0(\mathrm{A}_0) - S_0(\mathrm{CA}^{\mathrm{I}}))/\partial \Sigma_X < 0$ by the envelope theorem.

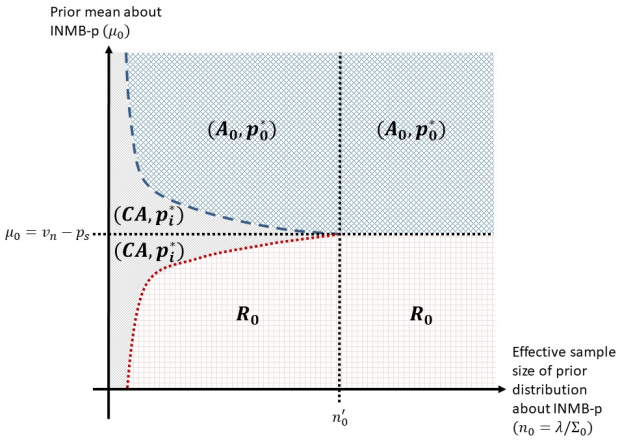
Price of the Standard of Care. We note that the price of the standard care, $p_{\mathcal{S}}$, always show up together with the prior mean about INMB-p, μ_0, in the equations for joint surpluses, and the two parameters have the same sign. Therefore, the direction of their effects on the surpluses are the same.

Production Cost. We note that the price of the variable production cost, $v_{\mathcal{N}}$, always show up together with the prior mean about INMB-p, μ_0, in the equations for joint surpluses, and the two parameters have opposite signs. Therefore, the direction of their effects are the opposite.

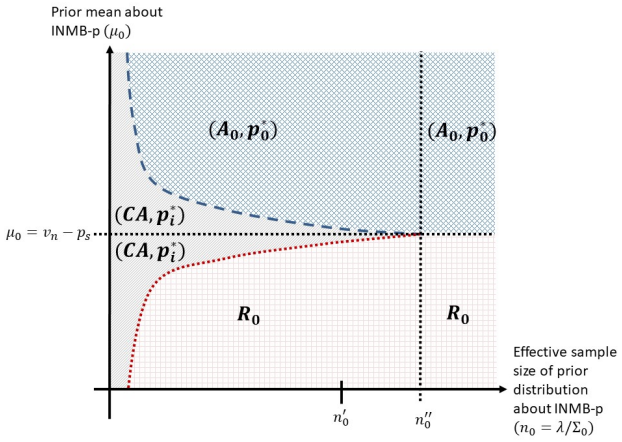
Fixed Cost of Post-Marketing Data Collection. It directly follows from its definition that $S_0(\mathrm{A}_0) - S_0(\mathrm{CA}^{\mathrm{I}})$ is linearly increasing in f_{DC}.

Figure EC.2 Nash bargaining outcomes at the initial submission stage for different value of μ_0 and n_0 for different fixed data collection costs. The value of n_0' satisfies $(f_{DC}+n^*v_{DC})/((1-t^*)N\psi(0))=\sqrt{(\Sigma_X n^*)/(n^*n_0'+n_0'n_0')}$ and the value of n_0'' satisfies $(f''_{DC}+n^*v_{DC})/((1-t^*)N\psi(0))=\sqrt{(\Sigma_X n^*)/(n^*n_0''+n_0''n_0'')}$ for $f''_{DC}<f_{DC}$.

(a) Higher fixed data collection cost.



(b) Lower fixed data collection cost.



Variable Cost of Post-Marketing Data Collection. We show that $S_0(\mathrm{A}_0)-S_0(\mathrm{CA}^{\mathrm{I}})$ is increasing in v_{DC}, which follows directly from $\partial S_0(\mathrm{CA}^{\mathrm{I}})/\partial v_{DC}$ because $S_0(\mathrm{A}_0)$ is independent of v_{DC}:

$$\frac{\partial(S_0(\mathrm{A}_0)-S_0(\mathrm{CA}^{\mathrm{I}},n,t))}{\partial v_{DC}}=n.$$

Population Size. We analyze how $S_0(\mathrm{A}_0)-S_0(\mathrm{CA}^{\mathrm{I}})$ changes with N:

$$\frac{\partial(S_0(\mathrm{A}_0)-S_0(\mathrm{CA}^{\mathrm{I}},n,t))}{\partial N}=\mu_0+p_{\mathcal{S}}-v_{\mathcal{N}}-(1-t)\sigma_{M_1}\psi\left(\frac{v_{\mathcal{N}}-p_{\mathcal{S}}-\mu_0}{\sigma_{M_1}}\right).$$

Because $\psi(x)\geq 0$ for all x, we conclude that, when $\mu_0+p_{\mathcal{S}}-v_{\mathcal{N}}\leq 0$, $\partial(S_0(\mathrm{A}_0)-S_0(\mathrm{CA}^{\mathrm{I}}))/\partial N\leq 0$. When $\mu_0+p_{\mathcal{S}}-v_{\mathcal{N}}>0$, the sign of $\partial(S_0(\mathrm{A}_0)-S_0(\mathrm{CA}^{\mathrm{I}}))/\partial N$ depends on other parameter values.

Bargaining Power. By definition, $S_0(\mathrm{A}_0)-S_0(\mathrm{CA}^{\mathrm{I}})$ is independent of β.

C.2.2. Sensitivity of the Nash Bargaining Outcomes to Key Model Parameters. Figure EC.2 presents two figures, each depicting the Nash bargaining outcomes at the initial submission stage for different values of μ_0 and n_0 and divided into six regions. The fixed data collection cost, f_{DC}, used in Figure EC.2a is higher than the one used in Figure EC.2b.

We use the results presented in Table EC.2 and Table EC.3 to show the existence and general structure of the regions shown in Figure EC.2. We start by deriving n_0' used in Figure EC.2a. If $\mu_0=v_{\mathcal{N}}-p_{\mathcal{S}}$, then:

$$\begin{aligned}S_0(\mathrm{A}_0)&=0,\\ S_0(\mathrm{CA}^{\mathrm{I}})&=-f_{DC}-n^*v_{DC}+(1-t)N\sigma^*_{M_1}\psi(0),\\ S_0(\mathrm{A}_0)-S_0(\mathrm{CA}^{\mathrm{I}})&=f_{DC}+n^*v_{DC}-(1-t^*)N\sigma^*_{M_1}\psi(0).\end{aligned}$$

We note that $\sigma^*_{M_1}$ is a function of n_0, and we define n_0' as the point that satisfies $\frac{f_{DC}+n^*v_{DC}}{(1-t^*)N\psi(0)}=\sigma^*_{M_1}$. Then, at the coordinate $\mu_0=v_{\mathcal{N}}-p_{\mathcal{S}}$ and $n_0=n_0'$, we can show that $S_0(\mathrm{A}_0)$, $S_0(\mathrm{CA}^{\mathrm{I}})$ and $S_0(\mathrm{A}_0)-S_0(\mathrm{CA}^{\mathrm{I}})$ are all

zero. As we note in §3.3, we assume that, in this case, the Nash bargaining outcome is immediate approval of the new treatment.

Now we show that n_0' in Figure EC.2a is always smaller than n_0'' in Figure EC.2b. We observe that $\sigma^*_{M_1}$ that satisfies the equation $\frac{f_{DC}+n^* v_{DC}}{(1-t^*)N\psi(0)} = \sigma^*_{M_1}$ increases as f_{DC} increases. Using the fact that n^* is independent of f_{DC} and that $\partial\sigma_{M_1}/\partial n_0 < 0$, the n_0 that satisfies this equality decreases as f_{DC} increases. Therefore, $n_0' < n_0''$ if $f''_{DC} < f_{DC}$.

We then analyze the four regions separated by $\mu_0 = v_{\mathcal{N}} - p_{\mathcal{S}}$ and $n_0 = n_0'$ in Figure EC.2a and Figure EC.2b, one by one. We will use the following facts: (1) $S_0(\mathrm{A}_0) - S_0(\mathrm{CA}^{\mathrm{I}})$ is increasing in both μ_0 and n_0, and (2) $S_0(\mathrm{CA}^{\mathrm{I}})$ is increasing in μ_0 and decreasing in n_0.

First, we focus on the region defined by $\mu_0 > v_{\mathcal{N}} - p_{\mathcal{S}}$ and $n_0 < n_0'$. Using the fact that $S_0(\mathrm{A}_0) - S_0(\mathrm{CA}^{\mathrm{I}})$ increases as μ_0 increases and decreases as n_0 decreases, we conclude that there is a strictly decreasing line (represented by the dashed line in Figure EC.2a and Figure EC.2b) on which $S_0(\mathrm{A}_0) - S_0(\mathrm{CA}^{\mathrm{I}}) = 0$, above which $S_0(\mathrm{A}_0) - S_0(\mathrm{CA}^{\mathrm{I}}) > 0$ and below which $S_0(\mathrm{A}_0) - S_0(\mathrm{CA}^{\mathrm{I}}) < 0$. Therefore, the Nash bargaining outcome in this region is immediate approval above the line and OIR below the line. The exact shape (convexity vs. concavity) of this line is obtained by numerical analysis based on the parameters estimated in §6.1.

Second, we analyze the region defined by $\mu_0 > v_{\mathcal{N}} - p_{\mathcal{S}}$ and $n_0 > n_0'$. In this region, we have $S_0(\mathrm{A}_0) > 0$ because $\mu_0 > v_{\mathcal{N}} - p_{\mathcal{S}}$, and we have $S_0(\mathrm{A}_0) - S_0(\mathrm{CA}^{\mathrm{I}}) > 0$ because $S_0(\mathrm{A}_0) - S_0(\mathrm{CA}^{\mathrm{I}})$ increases as μ_0 and n_0 increases. Therefore, the Nash bargaining outcome in this region is immediate approval.

Third, we study the region defined by $\mu_0 < v_{\mathcal{N}} - p_{\mathcal{S}}$ and $n_0 < n_0'$. In this region. we have $S_0(\mathrm{A}_0) < 0$ because $\mu_0 < v_{\mathcal{N}} - p_{\mathcal{S}}$. We conclude that immediate approval is not the Nash bargaining outcome in this region. Using the fact that $S_0(\mathrm{CA}^{\mathrm{I}})$ decreases as μ_0 decreases and increases n_0 decreases, we conclude that there is a strictly increasing line (represented by the dotted line in Figure EC.2a and Figure EC.2b) on which $S_0(\mathrm{CA}^{\mathrm{I}}) = 0$, above which $S_0(\mathrm{CA}^{\mathrm{I}}) > 0$ and below which $S_0(\mathrm{CA}^{\mathrm{I}}) < 0$. Therefore, the Nash bargaining outcome in this region is OIR above the line and rejection below the line. The exact shape of this line is obtained by numerical analysis using the parameters estimated in §6.1.

Finally, we focus on the region defined by $\mu_0 < v_{\mathcal{N}} - p_{\mathcal{S}}$ and $n_0 > n_0'$. In this region, we have $S_0(\mathrm{A}_0) < 0$ because $\mu_0 < v_{\mathcal{N}} - p_{\mathcal{S}}$, and we have $S_0(\mathrm{CA}^{\mathrm{I}}) < 0$ because $S_0(\mathrm{CA}^{\mathrm{I}})$ decreases as μ_0 decreases and n_0 increases. Therefore, the Nash bargaining outcome in this region is rejection of the new treatment.

We observe from Figure EC.2a and Figure EC.2b that treatments with high prior mean beliefs about INMB-p with a high effective sample size in the prior receive immediate approval, while treatments with low prior mean beliefs are immediately rejected. An OIR scheme is used either when 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 $\mathbb{E}_{M_1}[p_1^* \mid M_1 > v_{\mathcal{N}} - p_{\mathcal{S}}]$ is significantly larger than p_0^* and for which the VoI is high.

We next discuss the effect of the fixed and variable costs of the post-marketing trial. Figure EC.2b shows the change in Nash bargaining outcomes for a fixed cost of the post-marketing trial that is lower than that used in Figure EC.2a. We observe that regions in which OIR is the Nash outcome expand as the fixed cost of the post-marketing trial decreases. Table EC.2 shows that fixed and variable costs of data collection only impact the joint surplus from an OIR scheme not the one from immediate approval, and the direction of

their impact is the same. Therefore, the impact of a lower variable cost on the Nash bargaining outcome would be similar.

We continue with the impact of other parameters on the Nash bargaining outcome. Recalling that, by definition $n_0 = \Sigma_X/\Sigma_0$, it is straightforward to infer the impact of Σ_X from the observations regarding n_0. For low values of Σ_X, the VoI is not high enough, and the Nash bargaining outcome is approval when $\mu_0 > v_{\mathcal{N}} - p_{\mathcal{S}}$ and rejection otherwise. As Σ_X grows, the VoI increases and there is a region in which OIR is the Nash outcome.

Similarly, we can infer the impact of the price of the standard of care, $p_{\mathcal{S}}$ and the production cost, $v_{\mathcal{N}}$, from the fact that the joint surplus per patient from immediate approval of the new treatment is $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}}$. These three parameters always appear together in equations for joint surpluses. The direction of the effect on the joint surplus is the same for μ_0 and $p_{\mathcal{S}}$, and the direction of the effect is the opposite for μ_0 and $v_{\mathcal{N}}$.

Regarding the effect of the population size, we can show that $\partial(S_0(\mathrm{A}_0) - S_0(\mathrm{CA}^{\mathrm{I}}))/\partial N \leq 0$ when $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} \leq 0$. Then, for treatments with negative per-patient joint surplus from immediate approval of the new treatment, OIR is the Nash bargaining outcome for high values of N and rejection is the outcome for low values. When $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} > 0$, it is not possible to unambiguously determine the impact of the population size, N, on the Nash bargaining outcomes.

We finally discuss the effect of the bargaining power parameter, β. Because the bargaining power of the company, β, and the payer, $1-\beta$, do not impact the joint surplus from immediate or conditional approval, they do not affect either the optimal sample size, n^* or the optimal duration of the post-marketing trial, t^*, nor do they affect which treatments are immediately or conditionally approved. This follows from the fact that we model prior beliefs regarding the distribution of the health-economic benefit of treatments as being independent of bargaining power.

Appendix D: Additional Numerical Results for Votrient Case Study

Appendix D.1 provides details of how we fit parameter values used for the Votrient case study in §6.2 based on data from UK NICE and industry, and Appendix D.2 presents additional numerical results related to §6.2, with particular focus on the OWR scheme and interim pricing. Appendix E presents numerical comparative statics results for this case study.

D.1. Parameter Values of Votrient Case Study

To specify beliefs regarding the INMB-p of Votrient relative to Sutent, we use QALY and cost data presented in the NICE guidance for Votrient. NICE (2011) reports that the mean effectiveness of Votrient and Sutent are 1.966 and 1.898 QALYs, respectively. NICE (2011) also states that the per-patient cost of adverse effects and additional resources is £7,314 for Votrient and £7,323 for Sutent, so we set the mean belief about the per-patient cost of Votrient, $C_{\mathcal{N}}$, and Sutent, $C_{\mathcal{S}}$, as £7,314 and £7,323, respectively. Assuming a maximum willingness-to-pay CPQ threshold of $\lambda =$ £30,000/QALY (NICE 2014), the prior mean for the INMB-p of Votrient at the the initial submission stage is then $\mu_0 =$ £30,000 $(1.966 - 1.898) - (7{,}314 - 7{,}323) =$ £2,049.

Next, we estimate the variance of outcomes and the prior variance of the belief about INMB-p. The standard error of the mean in terms QALYs gained is reported to be 0.84 over 1,000 simulation runs (NICE

2011). We calculate the population variance of INMB-p as $\Sigma_X = £^2(30{,}000 \times 0.84\sqrt{1{,}000})^2$. We set the effective sample size at the initial submission stage to be $n_0 = 290$, which is the sample size of the clinical trial whose results were available at the time of initial submission. The implied prior variance of the belief about INMB-p is then $\Sigma_0 = \Sigma_X/290$.

To determine the total number of patients, N, we use a time horizon of 10 years, which is consistent with NICE (2011). NICE (2011) also states that 2,120 patients are eligible to receive treatment with Votrient per year in the UK. Therefore, $N = 21{,}200$.

We calculate the NHS's price for Sutent using NICE's guidance regarding Sutent (NICE 2009), as well as the study by Motzer et al. (2009). The median number of treatment cycles needed for a patient receiving Sutent is 7.4 (Motzer et al. 2009), where £3,139 is the cost of one Sutent treatment cycle (NICE 2009). Therefore, $p_S = (7.4-1) \times 3{,}139 = £20{,}089$, where we subtract one because the first treatment cycle of Sutent is free for the NHS (NICE 2009).

We estimate the maximum recruitment rate for the post-marketing trial based on the sample size and duration of COMPARZ. The trial was planned to last 2 years (NICE 2011), and given the time horizon of 10 years, we let $t = 2/10 = 0.2$ for COMPARZ. The planned sample size of COMPARZ was 876 patients (ClinicalTrials.gov 2010) and, we use the optimality of recruiting patients as quickly as possible, shown in §3, to determine the maximum recruitment rate. Assuming that COMPARZ was designed optimally, we set $r_{max} = 876/(21{,}200 \times 0.2) \approx 0.2$.

We follow the analysis in Hill et al. (2016) to estimate the variable production cost, $v_{\mathcal{N}}$, which we assume to equal the price charged by a contract manufacturer to produce Votrient. Votrient is sold as 200mg and 400mg tablets. We base our calculation on 400mg tablets. Export data for India[2] suggests that the price of the active pharmaceutical ingredient (API) for Votrient is US$2,850/kg, or US$1.14 per 400mg tablet. We add costs of US$0.38 per tablet for excipients and US$0.42 per tablet for coating and tableting (Hill et al. 2016), for a total of US$1.94 per 400mg tablet. The standard daily dose of Votrient is 800mg (NICE 2011), giving a monthly cost of US$116.40. We allow US$0.35/month for bottling, package insert, shipping and duties, and a 50% mark-up for the contract manufacturer (Hill et al. 2016). As a result, the monthly production cost is US$175. The median treatment duration for Votrient is 11.1 months (NICE 2011). Thus, the production cost of Votrient per patient is US$1,944. We set $v_{\mathcal{N}} = £1{,}205$ using the average exchange rate in 2011.

Finally, we estimate the costs associated with running a post-marketing trial. We use the average costs reported in Sertkaya et al. (2014) to determine the fixed cost and total per-patient cost of running a post-marketing trial to be $\$16 \times 10^6$ and $\$2.2 \times 10^6$, respectively. Therefore, we set $f_{DC} = £10 \times 10^6$ using the average exchange rate in 2011. Similarly, we set $v_{DC} = 2 \times (£1.4 \times 10^6)/446 = £6{,}226$ where 446 is the median sample size of a Phase III clinical trial (Moore et al. 2018).

[2] Export data for 2017 and 2018, retrieved from http://www.infodriveindia.com on 5/10/2019.

Table EC.4 Votrient Case Study: The interim price and the expected reappraisal price conditional on approval for different values of the cost of reversal. All values are in £.

	When $f_r = £9 \times 10^7$		When $f_r = £24 \times 10^7$		When $f_r = £30 \times 10^7$	
	$p_i^{*,\mathrm{W}}$	$\mathbb{E}_{M_1}[p_1^{*,\mathrm{W}} \mid \mathcal{A}_1^W]$	$p_i^{*,\mathrm{W}}$	$\mathbb{E}_{M_1}[p_1^{*,\mathrm{W}} \mid \mathcal{A}_1^W]$	$p_i^{*,\mathrm{W}}$	$\mathbb{E}_{M_1}[p_1^{*,\mathrm{W}} \mid \mathcal{A}_1^W]$
$\beta = 0.1$	3,921	5,273	−288	5,748	−2,155	5,948
$\beta = 0.3$	2,765	13,409	−10,269	14,834	−16,047	15,434
$\beta = 0.5$	1,609	21,545	−20,250	23,921	−29,939	24,920
$\beta = 0.7$	453	29,682	−30,231	33,007	−43,830	34,406
$\beta = 0.9$	−703	37,818	−40,212	42,093	−57,722	43,892
$\beta = 1.0$	−1,281	41,889	−45,202	46,546	−64,668	48,541

D.2. Additional Numerical Results

We present additional numerical results related to the case study in §6.2, particularly those related to Table 2, to characterize the effect of reversal costs on resulting interim prices. Table EC.4 displays the interim price, $p_i^{*,\mathrm{W}}$, and the expected reappraisal price conditional on eventual approval, $\mathbb{E}_{M_1}[p_1^{*,\mathrm{W}} \mid \text{Approval}]$, for three different values of the cost of reversal, f_r. Recall that OWR is the Nash bargaining outcome only when $f_r < £24 \times 10^7$ in our example.

Table EC.4 shows that the expected reappraisal price increases with f_r, but the reversal cost's impact is minimal. Table EC.4 also suggests that the expected reappraisal price after an OWR scheme is higher than the immediate approval price, and the expected reappraisal price after an OWR scheme increases as β increases for all values of $f_r > 0$, which matches the observations made in §6.2 for $f_r = 0$.

Table EC.4 shows that, for $f_r > 0$, the expected reappraisal price after an OWR scheme is always higher than the OWR interim price. For $f_r = 0$, we found in §6.2 that the relationship between the OWR interim price and the expected OWR reappraisal price depends on the value of β.

Table EC.4 provides insights regarding the effect of the reversal cost on the OWR scheme's interim price. As the reversal cost increases, the interim price decreases and may even become negative, acting as a per-patient fee with which the company compensates the payer to be a part of the OWR scheme. Note that if the new treatment is approved at reappraisal, after an OWR scheme, the reappraisal price is appropriately higher to compensate the company for this so-called fee.

A comparison of Table 2 and Table EC.4 shows that the interim price under the OIR scheme is higher than that under OWR for all values of the reversal cost, $f_r > 0$, which matches our observation in §6.2 for $f_r = 0$. Furthermore, the gap between the OIR and OWR interim prices increases with the reversal cost.

As opposed to the findings in §6.2 for $f_r = 0$, Table EC.4 displays the interim price of an OWR scheme decreasing with β when $f_r > 0$. This is expected from the comparative statics results in Appendix C.1.3, which shows that $p_i^{*,\mathrm{W}}$ decreases with β when $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} - (n^{*,\mathrm{W}} v_{DC} + f_{DC} + f_r)/(n^{*,\mathrm{W}}(2/r_{max} - 1)) < 0$. Again, as opposed to the findings in §6.2 for $f_r = 0$, the interim price of an OWR scheme is higher than the immediate approval price only for $\beta = 0.1$ and $f_r = £9 \times 10^7$ and is lower than the immediate approval price for all other parameter values.

Appendix E: Numerical Comparative Statics Results

Appendix C showed that some but not all comparative statics results can be signed unambiguously. We now explore the comparative statics for the Nash bargaining prices based on the case study in §6.2. For this

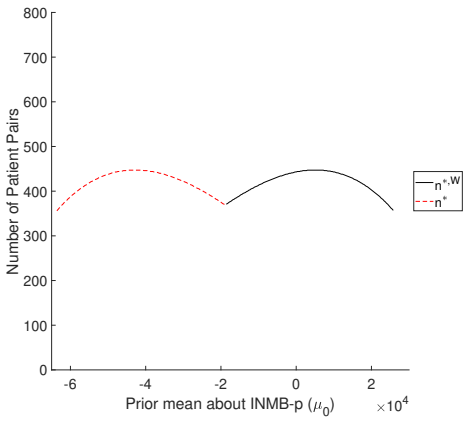
case study, we assess how the optimal sample size (n^*, $n^{*,\mathrm{W}}$) and Nash bargaining interim price (p_i^*, $p_i^{*,\mathrm{W}}$) for OIR and OWR schemes change as one parameter of the model is changed, while the other parameters remain fixed at the values in Table 1. We do so for low, medium and high values of the negotiating power parameter, $\beta \in \{0.1, 0.5, 0.9\}$. In this section, we assume $f_r = 0$.

Before presenting those results, we recall that we showed in §6.2 that the OWR scheme is the Nash bargaining outcome for Votrient case study when $f_r = 0$. Furthermore, Prop. 4 states that, for $f_r = 0$, the OWR scheme is preferred to the OIR scheme if $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} > 0$, and the OIR scheme is preferred if $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} < 0$. (We break ties by selecting the OIR scheme.) Therefore, as we vary the values of μ_0, $v_{\mathcal{N}}$ and $p_{\mathcal{S}}$, the Nash bargaining outcome for the case study might change to an OIR scheme. Indeed, for some values of μ_0 that are lower than that for the Votrient case study, and for some values of $v_{\mathcal{N}}$ that are higher than that for the Votrient case study, the Nash bargaining solution is an OIR scheme. For all values of $p_{\mathcal{S}}$ we explored, the OWR scheme is preferred to the OIR scheme. For the rest of the parameters, the OWR scheme is preferred to the OIR scheme. This is expected because Prop. 4 shows that the choice between OIR and OWR scheme is not impacted by other parameters when $f_r = 0$.

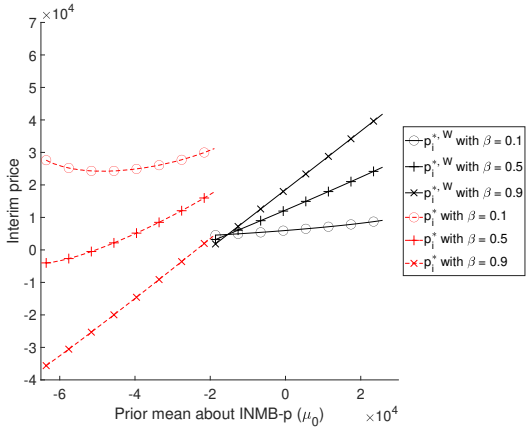
Prior mean, μ_0. Figure EC.3 displays the comparative statics results for the prior mean of INMB-p, μ_0. Figure EC.3a shows that, for both OWR and OIR schemes, the optimal sample size is first increasing and then decreasing with μ_0. The optimal sample sizes are largest for the case of OIR and OWR schemes are for values of μ_0 are most in the interior regions of the optimality zones for those schemes. This can be visualized by drawing a vertical line at the '+' for Votrient in Figure 3a of the main paper and then noting that each maximum occurs in the interior of the region that falls between the horizontal line that marks $\mu_0 = v_{\mathcal{N}} - p_{\mathcal{S}}$ and the boundary at which the respective conditional approval scheme is no longer optimal.

Figure EC.3 Optimal sample sizes and interim prices for different values of μ_0.

(a) Optimal number of patient pairs under OWR ($n^{*,\mathrm{W}}$) and OIR (n^*) schemes.



(b) Nash bargaining interim price under OWR ($p_i^{*,\mathrm{W}}$) and OIR (p_i^*) schemes.



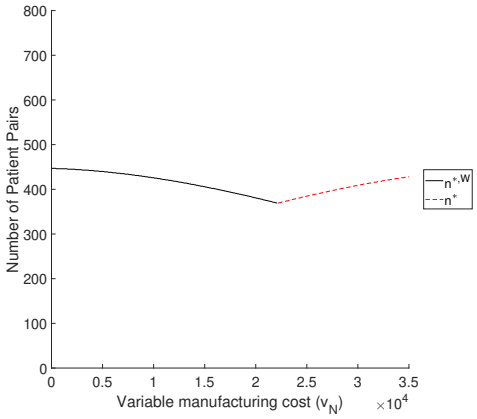
In Figure EC.3b, we observe that the interim price is increasing with μ_0 except for low values of μ_0 and β. For example, if $\beta = 0.1$, then the OIR interim price, which is the bargaining outcome for low values of μ_0,

is first decreasing and then increasing with μ_0. Interestingly, the optimal interim price with $\beta = 0.5$ and 0.9 is negative for the OIR scheme. In this case, the expected value of the information per-patient is high, and the company's compensation to the payer for patients who receive the new treatment in the trial is (more than) counterbalanced by the expected value of a potential approval upon reappraisal.

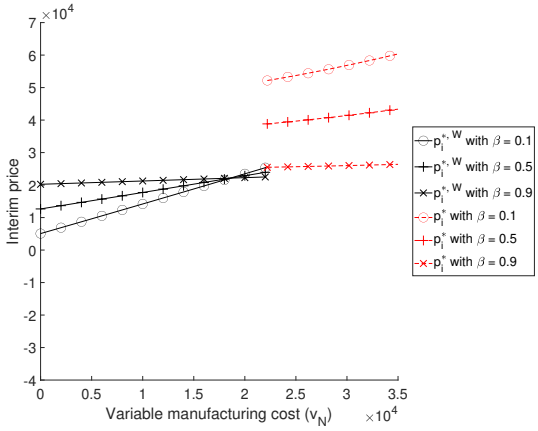
Variable manufacturing cost, $v_{\mathcal{N}}$. Figure EC.4 displays the comparative statics results for the variable manufacturing cost of the new treatment, $v_{\mathcal{N}}$. As opposed to the results for μ_0, the OWR scheme is the Nash outcome for lower values of $v_{\mathcal{N}}$, and the OIR scheme is the Nash outcome for higher values of $v_{\mathcal{N}}$. We see in Figure EC.4a that the optimal sample size of the OWR scheme is decreasing with $v_{\mathcal{N}}$, while the optimal sample size of the OIR scheme is increasing. Figure EC.4b shows that the interim prices increase with $v_{\mathcal{N}}$ for both OIR and OWR schemes and for all values of β. The interim prices for both OWR and OIR schemes decrease with β when $v_{\mathcal{N}} > \mu_0 + p_{\mathcal{S}}$ (which implies $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} < 0$) and the figure quantifies the magnitude of comparative statics results in §C.1.4.

Figure EC.4 Optimal sample sizes and interim prices for different values of $v_{\mathcal{N}}$.

(a) Optimal number of patient pairs under OWR ($n^{*,\mathrm{W}}$) and OIR (n^*) schemes.



(b) Nash bargaining interim price under OWR ($p_i^{*,\mathrm{W}}$) and OIR (p_i^*) schemes.



Price of the standard of care, $p_{\mathcal{S}}$. Figure EC.5 displays the comparative statics results for the price of the standard of care, $p_{\mathcal{S}}$. Figure EC.5a shows that the optimal sample size of an OWR scheme is first increasing and then decreasing with $p_{\mathcal{S}}$. And Figure EC.5b displays that the interim price of an OWR scheme is increasing with $p_{\mathcal{S}}$.

Effective sample size of prior distribution, n_0. Figure EC.6 displays the comparative statics results for the effective sample size of prior distribution about INMB-p, n_0. Figure EC.6a shows that the optimal sample size of an OWR scheme is increasing with n_0. Figure EC.6b displays that the interim price of an OWR scheme is decreasing with the n_0. As expected from Appendix C.1.3, the effect of n_0 on the optimal sample size and on the interim price are opposite.

Figure EC.5 Optimal sample sizes and interim prices for different values of p_S. The OWR scheme is the Nash bargaining outcome for all values tested.

(a) Optimal number of patient pairs under OWR ($n^{*,\mathrm{W}}$). (b) Nash bargaining interim price under OWR ($p_i^{*,\mathrm{W}}$).

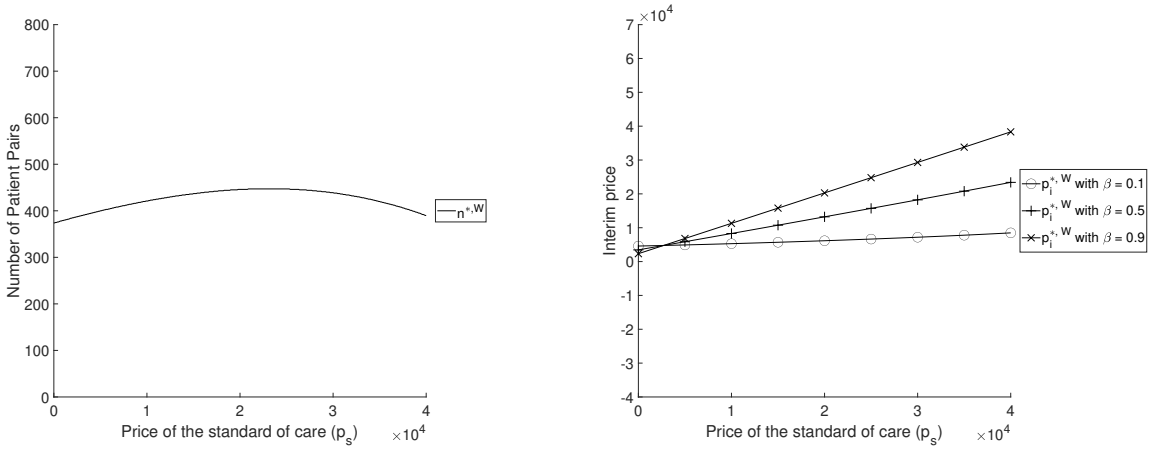
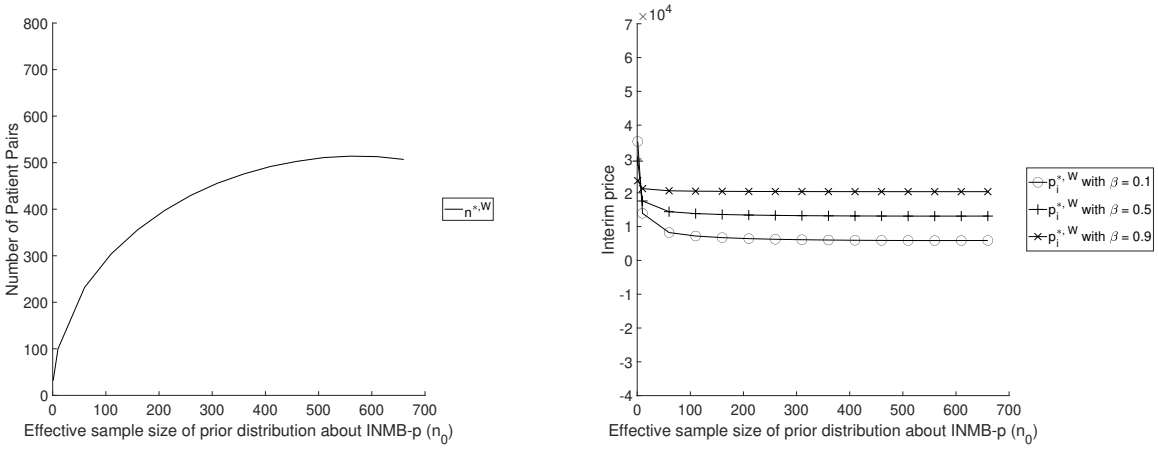


Figure EC.6 Optimal sample sizes and interim prices for different values of n_0. The OWR scheme is the Nash bargaining outcome for all values tested.

(a) Optimal number of patient pairs under OWR ($n^{*,\mathrm{W}}$). (b) Nash bargaining interim price under OWR ($p_i^{*,\mathrm{W}}$).



Variance of outcomes, Σ_X. Figure EC.7 displays the comparative statics results for the variance of outcomes, Σ_X. The effect of Σ_X is similar to that of n_0. The scale of the y-axis of Figure EC.7b was chosen to match that of other similar figures in this section for ease of comparison. What is not visible in Figure EC.7b (without zooming in) is a slight decrease in interim price as Σ_X increases from 0 to approximately 5.5×10^{11}, followed by an even slighter increase as Σ_X grows larger.

Variable cost per patient part in the post-marketing trial, v_{DC}. Figure EC.8 displays the comparative statics results for the variable cost per patient pair of the post-marketing trial, v_{DC}. Figure EC.8a shows that the optimal sample size of an OWR scheme is decreasing with v_{DC}. Figure EC.8b displays that the interim price of an OWR scheme is increasing with v_{DC}.

Figure EC.7 Optimal sample sizes and interim prices for different values of Σ_X. The OWR scheme is the Nash bargaining outcome for all values tested.

(a) Optimal number of patient pairs under OWR ($n^{*,\mathrm{W}}$). (b) Nash bargaining interim price under OWR ($p_i^{*,\mathrm{W}}$).

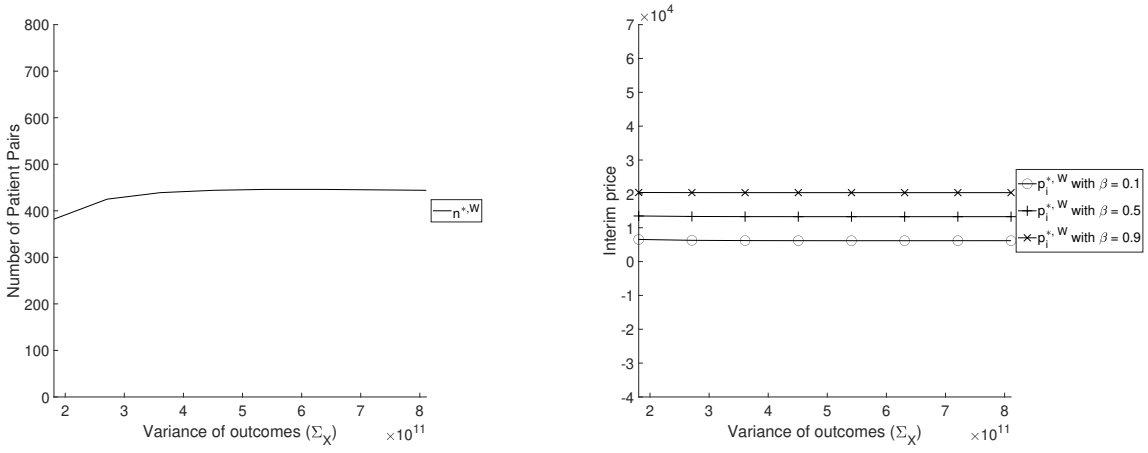
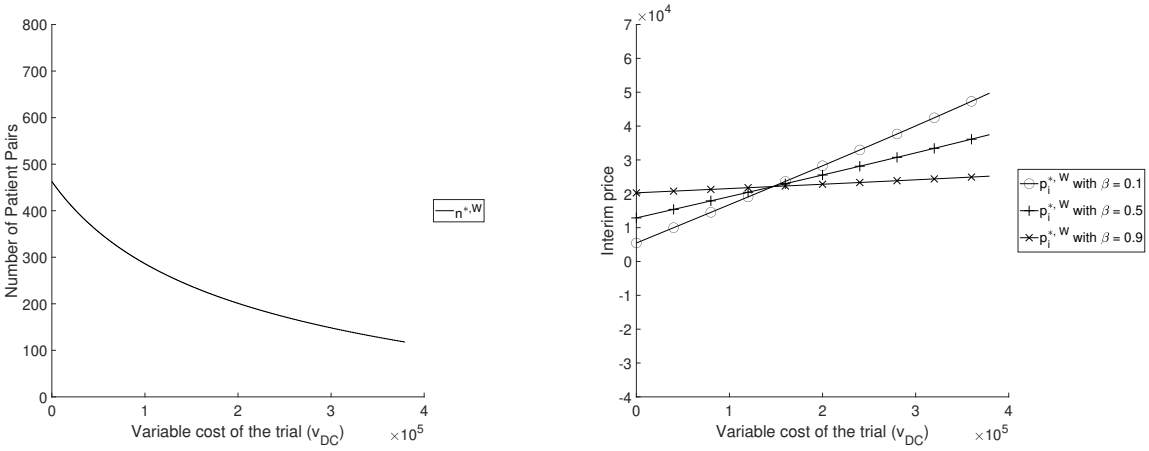


Figure EC.8 Optimal sample sizes and interim prices for different values of v_{DC}. The OWR scheme is the Nash bargaining outcome for all values tested.

(a) Optimal number of patient pairs under OWR ($n^{*,\mathrm{W}}$). (b) Nash bargaining interim price under OWR ($p_i^{*,\mathrm{W}}$).



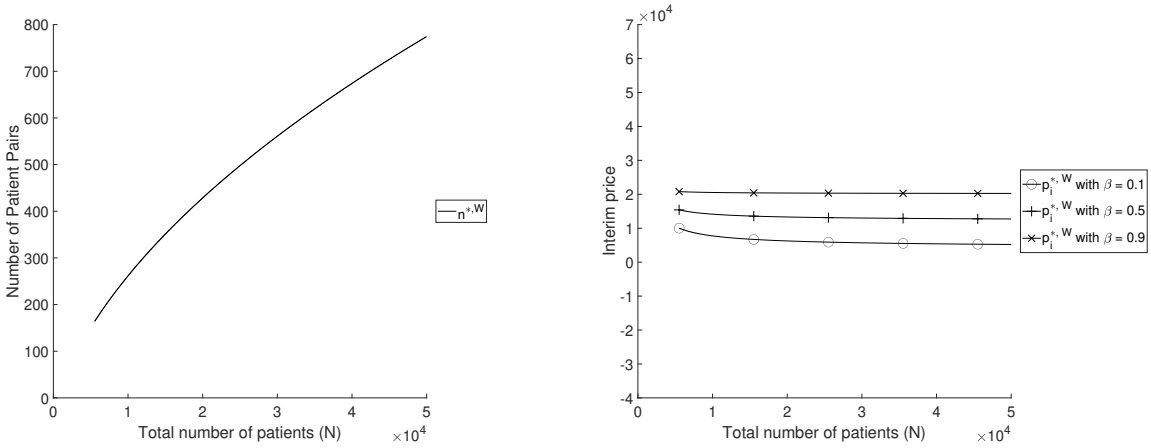
Total number of patients in the target population, N. Figure EC.9 displays comparative statics results for the total number of patients in the target population, N. Figure EC.9a shows that the optimal sample size of an OWR scheme is increasing with N. For much larger N (data not shown), we see that the optimal sample size appears to be proportional to $\sqrt{N}$, a result consistent with related analytical results (Alban et al. 2023, Prop. 5). Figure EC.9b displays that the interim price of an OWR scheme is decreasing with N.

Appendix F: Justification of Discussions Regarding Assumptions in §7

Our model and analysis assume that risk neutral players share the economic surplus induced by health gains, net of costs, and that there does not exist a distinct, incumbent manufacturer that would attempt to maintain its sales by lowering the price of the standard of care. In this appendix, we justify claims in §7

Figure EC.9 Optimal sample sizes and interim prices for different values of N. The OWR scheme is the Nash bargaining outcome for all values tested.

(a) Optimal number of patient pairs under OWR ($n^{*,\mathrm{W}}$). (b) Nash bargaining interim price under OWR ($p_i^{*,\mathrm{W}}$).



regarding the relaxation of both assumptions. First, in Appendix F.1, we characterize how the bargaining outcomes of our model influence the probability that the new health technology will be cost-effective, one measure of the payer's risk (e.g., Barton et al. 2008, Danzon et al. 2018). Second, in Appendix F.2, we address the probability that the entire conditional approval process itself is cost-effective. Third, in Appendix F.3, we delineate the influence that potential price reductions by an incumbent manufacturer may have on the outcome of negotiations between the payer and the company.

F.1. Probability that a New Treatment is Cost-Effective

The payer in our model is risk-neutral, an assumption that is consistent with the literature. That said, Barton et al. (2008) note that, even if it is not used to determine the optimal decision, the probability of cost-effectiveness can complement expected value of information calculations, describing risk or uncertainty surrounding the optimal choice. In this section, we consider the Nash bargaining solution's probability of cost-effectiveness. In each case, these probabilities are based on population averages - for example the probability the mean incremental net monetary benefit is positive, given information available at the time of the assessment of the probability. The uncertainty regards population-average health benefits that stem from the finite sample used to inform their means and does not reflect the probability that a health outcome is cost-effective for a given, randomly chosen patient from the population. See O'Hagan and Stevens (2002), for example, for further discussion.

A new treatment is considered cost-effective compared to the standard of care if its INMB, based on an expected population-wide benefit, exceeds zero. Note also that cost-effectiveness depends on the new treatment's price, as well as on data available regarding its INMB-p compared to the standard of care.

Table EC.5 presents the probability that the new treatment is cost-effective for various values for the bargaining power parameter, β, calculated using the information available at the time of initial submission. (We recall that corresponding prices for each β are found in Table 2.) At the immediate approval price

associated with a given β, p_0^*, the probability is defined as $\mathbb{P}(CE(p_0^*) \mid \mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} \geq 0) \triangleq \mathbb{P}(\theta - (p_0^* - p_{\mathcal{S}}) > 0 \mid \mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} \geq 0)$, where $\theta \sim \texttt{Normal}(\mu_0, \Sigma_0)$ and the condition $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} \geq 0$ ensures the immediate approval price can be negotiated. For OIR and OWR conditional approval schemes, the probability is calculated separately for interim and reappraisal prices. The probability of the new treatment being cost-effective at an interim price, p_i, is defined as $\mathbb{P}(CE(p_i)) \triangleq \mathbb{P}(\theta - (p_i - p_{\mathcal{S}}) > 0)$.

Note that the reappraisal price of a conditional approval scheme is defined only if the new treatment is approved at reappraisal. For an OIR scheme, the event that the treatment is approved upon reappraisal, denoted by $\mathcal{A}_1$, is associated with reappraisal price p_1^*, and we define the probability of the new treatment being cost-effective, conditional on approval, as

$$\mathbb{P}(CE(p_1^*) \mid \mathcal{A}_1) \triangleq \mathbb{P}\left(\theta - (p_1^* - p_{\mathcal{S}}) > 0 \mid M_1 + p_{\mathcal{S}} - v_{\mathcal{N}} \geq 0\right),$$

where p_1^* is a function of M_1, as defined in Prop. 1, M_1 depends on the data collected in the OIR post-marketing trial in (2), and the probability is calculated with respect to $\theta \sim \texttt{Normal}(\mu_0, \Sigma_0)$ and the OIR data's sample mean $\sum_{j=1}^{n^*} X^j/n^* \mid \theta \sim \texttt{Normal}(\theta, \Sigma_X/n^*)$. The OWR scheme's reappraisal price, $p_1^{*,\mathrm{W}}$, is similarly conditioned on the new treatment's approval at reappraisal, denoted by $\mathcal{A}_1^W$, and we define the marginal probability of the new treatment's cost-effectiveness, conditional on approval, as

$$\mathbb{P}(CE(p_1^{*,\mathrm{W}}) \mid \mathcal{A}_1^W) \triangleq \mathbb{P}\left(\theta - (p_1^{*,\mathrm{W}} - p_{\mathcal{S}}) > 0 \mid M_1 + p_{\mathcal{S}} + f_r/(N - 2n^{*,\mathrm{W}}/r_{max}) - v_{\mathcal{N}} \geq 0\right),$$

where $p_1^{*,\mathrm{W}}$ is a function of M_1 by its definition in (23), M_1 depends on the data collected in the OWR post-marketing trial in (2), and the probability is calculated with respect to θ and the OWR data's sample mean $\sum_{j=1}^{n^{*,\mathrm{W}}} X^j/n^{*,\mathrm{W}} \mid \theta \sim \texttt{Normal}(\theta, \Sigma_X/n^{*,\mathrm{W}})$.

The relationship between the probability of being cost-effective under immediate approval price, $\mathbb{P}(CE(p_0^*) \mid \mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} \geq 0)$, and the probability of being cost-effective at the interim prices, $\mathbb{P}(CE(p_i^*))$ and $\mathbb{P}(CE(p_i^{*,\mathrm{W}}))$, follows that among the prices p_0^*, p_i^* and $p_i^{*,\mathrm{W}}$. Not surprisingly, the results in each column of Table EC.5 are consistent with those in Table 2: $\mathbb{P}(CE)$ decreases as price increases.

In Table EC.5, we also see that the probability of being cost-effective at the immediate approval price, $\mathbb{P}(CE(p_0^*) \mid \mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} \geq 0)$, is consistently lower than that at the reappraisal price, conditioned on approval, $\mathbb{P}(CE(p_1^*) \mid \mathcal{A}_1)$ and $\mathbb{P}(CE(p_1^{*,\mathrm{W}}) \mid \mathcal{A}_1^W)$, assuming $\beta < 1$. The additional data obtained through conditional approval increases the probability that Votrient is cost-effective even though it also increases the expected reappraisal price.

Table EC.5 also reveals a connection between the probability the new technology is cost-effective (a measure of risk, Barton et al. 2008) and the company's Nash bargaining power, β. In the immediate approval column, the probability the new technology is cost-effective, conditional on the event the technology is immediately approved, decreases at the negotiated prices, given immediate approval, as the company's market power β increases. In the OIR and OWR columns, the probability of cost-effectiveness from an OIR or an OWR scheme, conditional on approval at the reappraisal, also decreases as β increases. And for the special case in which the company extracts all surplus value, $\beta = 1$, Table EC.5 shows that the probability of cost-effectiveness is 0.5 for Nash bargaining prices, a result which is consistent with Danzon et al. (2018). (The row in Table EC.5 for $\beta = 1$ has entries that are not statistically different from 0.5 with 95% confidence.)

Table EC.5 Votrient Case Study: Probability of Votrient being cost-effective at prices in Table 2. Standard errors in all estimates are between 4×10^{-5} and 6×10^{-5}, and the 95% CI for values in the bottom row all contain 0.5.

	Immediate Approval	OIR		OWR with $f_r=0$	
	$\mathbb{P}(CE(p_0^*)\mid \mu_0+p_{\mathcal{S}}-v_{\mathcal{N}}\geq 0)$	$\mathbb{P}(CE(p_i^*))$	$\mathbb{P}(CE(p_1^*)\mid \mathcal{A}_1)$	$\mathbb{P}(CE(p_i^{*,\mathrm{W}}))$	$\mathbb{P}(CE(p_1^{*,\mathrm{W}})\mid \mathcal{A}_1^W)$
$\beta=0.1$	0.65641	0.27582	0.77092	0.63362	0.81914
$\beta=0.3$	0.62293	0.32168	0.72827	0.60469	0.77827
$\beta=0.5$	0.58849	0.37044	0.67502	0.57519	0.72193
$\beta=0.7$	0.55337	0.42138	0.61084	0.54530	0.64598
$\beta=0.9$	0.51789	0.47368	0.53804	0.51517	0.55143
$\beta=1.0$	0.50005	0.50005	0.50001	0.50005	0.50008

In the following three propositions, we show that the effect of the company's bargaining power on the probability of cost-effectiveness at the immediate approval and reappraisal prices holds beyond this specific case-study. Prop. EC.5 is for the probability of cost-effectiveness, conditional on the event the technology is immediately approved; Prop. EC.6 is for the probability of cost-effectiveness from an OIR scheme, conditional on approval at the reappraisal; and Prop. EC.7 is for the probability of cost-effectiveness from an OWR scheme, conditional on approval at the reappraisal.

PROP. EC.5. *The probability of cost-effectiveness of the new technology conditional on immediate approval, $\mathbb{P}(CE(p_0^*)\mid \mu_0+p_{\mathcal{S}}-v_{\mathcal{N}}\geq 0)$, is 0.5 if $\mu_0+p_{\mathcal{S}}-v_{\mathcal{N}}=0$. And if $\mu_0+p_{\mathcal{S}}-v_{\mathcal{N}}>0$, $\mathbb{P}(CE(p_0^*)\mid \mu_0+p_{\mathcal{S}}-v_{\mathcal{N}}\geq 0)$ decreases with $0<\beta<1$ and is 0.5 when $\beta=1$.*

Proof. We recall the value of p_0^* from Prop. 2. Then, we have

$$\begin{aligned}\mathbb{P}(CE(p_0^*)\mid \mu_0\geq v_{\mathcal{N}}-p_{\mathcal{S}}) &= \mathbb{P}(\theta-(p_0^*-p_{\mathcal{S}})>0\mid \mu_0+p_{\mathcal{S}}-v_{\mathcal{N}}\geq 0)\\ &= \mathbb{P}(\theta-(v_{\mathcal{N}}+\beta(\mu_0+p_{\mathcal{S}}-v_{\mathcal{N}})-p_{\mathcal{S}})>0\mid \mu_0+p_{\mathcal{S}}-v_{\mathcal{N}}\geq 0)\\ &= \mathbb{P}(\theta>v_{\mathcal{N}}+\beta(\mu_0+p_{\mathcal{S}}-v_{\mathcal{N}})-p_{\mathcal{S}}\mid \mu_0+p_{\mathcal{S}}-v_{\mathcal{N}}\geq 0).\end{aligned}$$

We first analyze the case of $\mu_0+p_{\mathcal{S}}-v_{\mathcal{N}}=0$. We use $\mu_0=v_{\mathcal{N}}-p_{\mathcal{S}}$ to write $\mathbb{P}(CE(p_0^*)\mid \mu_0\geq v_{\mathcal{N}}-p_{\mathcal{S}})=\mathbb{P}(\theta>\mu_0\mid \mu_0\geq v_{\mathcal{N}}-p_{\mathcal{S}})$. Because $\theta\sim\texttt{Normal}(\mu_0,\Sigma_0)$, $\mathbb{P}(\theta>\mu_0\mid \mu_0\geq v_{\mathcal{N}}-p_{\mathcal{S}})=0.5$.

We next analyze the case of $\mu_0+p_{\mathcal{S}}-v_{\mathcal{N}}>0$. If $0<\beta<1$, we have $\mathbb{P}(CE(p_0^*)\mid \mu_0\geq v_{\mathcal{N}}-p_{\mathcal{S}})=\mathbb{P}(\theta>v_{\mathcal{N}}+\beta(\mu_0+p_{\mathcal{S}}-v_{\mathcal{N}})-p_{\mathcal{S}}\mid \mu_0+p_{\mathcal{S}}-v_{\mathcal{N}}\geq 0)=\mathbb{P}(\theta-\mu_0>-(1-\beta)(\mu_0+p_{\mathcal{S}}-v_{\mathcal{N}})\mid \mu_0+p_{\mathcal{S}}-v_{\mathcal{N}}\geq 0)$. The right-hand side of the inequality in the probability is negative given $\mu_0+p_{\mathcal{S}}-v_{\mathcal{N}}>0$, and we have $\theta-\mu_0\sim\texttt{Normal}(0,\Sigma_0)$. Therefore, $\mathbb{P}(\theta-\mu_0>-(1-\beta)(\mu_0+p_{\mathcal{S}}-v_{\mathcal{N}})\mid \mu_0+p_{\mathcal{S}}-v_{\mathcal{N}}\geq 0)>0.5$ if $0<\beta<1$. And as β increases, the right-hand side of the inequality in the probability decreases in the absolute value and therefore $\mathbb{P}(CE(p_0^*)\mid \mu_0\geq v_{\mathcal{N}}-p_{\mathcal{S}})$ decreases as β increases. Finally, when $\beta=1$, $\mathbb{P}(CE(p_0^*)\mid \mu_0\geq v_{\mathcal{N}}-p_{\mathcal{S}})=\mathbb{P}(\theta>\mu_0\mid \mu_0\geq v_{\mathcal{N}}-p_{\mathcal{S}})=0.5$ because $\theta\sim\texttt{Normal}(\mu_0,\Sigma_0)$. □

PROP. EC.6. *The probability of cost-effectiveness of the new technology at the OIR reappraisal price, conditional on the approval at the reappraisal, $\mathbb{P}(CE(p_1^*)\mid \mathcal{A}_1)$, decreases with $0<\beta<1$ and $\mathbb{P}(CE(p_1^*)\mid \mathcal{A}_1)=0.5$ if $\beta=1$.*

Proof. We recall the value of p_1^* from Prop. 1. Then, we have

$$\begin{aligned}
\mathbb{P}(CE(p_1^*) \mid \mathcal{A}_1) &= \mathbb{P}\left(\theta - (p_1^* - p_{\mathcal{S}}) > 0 \mid M_1 + p_{\mathcal{S}} - v_{\mathcal{N}} \geq 0\right) \\
&= \mathbb{P}\left(\theta - (v_{\mathcal{N}} + \beta(M_1 + p_{\mathcal{S}} - v_{\mathcal{N}}) - p_{\mathcal{S}}) > 0 \mid M_1 + p_{\mathcal{S}} - v_{\mathcal{N}} \geq 0\right) \\
&= \mathbb{P}\left(\theta > v_{\mathcal{N}} + \beta(M_1 + p_{\mathcal{S}} - v_{\mathcal{N}}) - p_{\mathcal{S}} \mid M_1 + p_{\mathcal{S}} - v_{\mathcal{N}} \geq 0\right) \\
&= \mathbb{E}[\mathbb{1}_{\{\theta > v_{\mathcal{N}} + \beta(M_1 + p_{\mathcal{S}} - v_{\mathcal{N}}) - p_{\mathcal{S}}\}} \mid M_1 + p_{\mathcal{S}} - v_{\mathcal{N}} \geq 0] \\
&= \mathbb{E}[\mathbb{E}[\mathbb{1}_{\{\theta > v_{\mathcal{N}} + \beta(\mu_1 + p_{\mathcal{S}} - v_{\mathcal{N}}) - p_{\mathcal{S}}\}} \mid M_1 = \mu_1] \mid M_1 + p_{\mathcal{S}} - v_{\mathcal{N}} \geq 0] \\
&= \mathbb{E}[\mathbb{P}(\theta > v_{\mathcal{N}} + \beta(\mu_1 + p_{\mathcal{S}} - v_{\mathcal{N}}) - p_{\mathcal{S}} \mid M_1 = \mu_1) \mid M_1 + p_{\mathcal{S}} - v_{\mathcal{N}} \geq 0],
\end{aligned}$$

where the fourth equality follows from the definition of probability, the fifth equality follows from the law of total expectation, and the final equality again follows from the definition of probability.

We first analyze the case of $\beta = 1$. We write $\mathbb{P}(CE(p_1^*) \mid \mathcal{A}_1) = \mathbb{E}[\mathbb{E}[\mathbb{1}_{\{\theta > \mu_1\}} \mid M_1 = \mu_1] \mid M_1 + p_{\mathcal{S}} - v_{\mathcal{N}} \geq 0]$. Because $\theta \mid \mu_1 \sim \texttt{Normal}(\mu_1, \Sigma_1)$, $\mathbb{E}[\mathbb{E}[\mathbb{1}_{\{\theta > \mu_1\}} \mid M_1 = \mu_1] \mid M_1 + p_{\mathcal{S}} - v_{\mathcal{N}} \geq 0] = \mathbb{E}[0.5 \mid M_1 + p_{\mathcal{S}} - v_{\mathcal{N}} \geq 0] = 0.5$.

We next show that $\mathbb{P}(CE(p_1^*) \mid \mathcal{A}_1)$ decreases in β for $\beta \in (0,1)$. We use $\theta \mid \mu_1 \sim \texttt{Normal}(\mu_1, \Sigma_1)$ to write $\mathbb{P}(\theta > v_{\mathcal{N}} + \beta(\mu_1 + p_{\mathcal{S}} - v_{\mathcal{N}}) - p_{\mathcal{S}} \mid M_1 = \mu_1) = \mathbb{E}[1 - \Phi\left((v_{\mathcal{N}} + \beta(\mu_1 + p_{\mathcal{S}} - v_{\mathcal{N}}) - p_{\mathcal{S}} - \mu_1)/\Sigma_1\right) \mid M_1 = \mu_1]$.

To simplify the notation, we define $f(\mu_1, \beta) \triangleq 1 - \Phi\left((v_{\mathcal{N}} + \beta(\mu_1 + p_{\mathcal{S}} - v_{\mathcal{N}}) - p_{\mathcal{S}} - \mu_1)/\Sigma_1\right)$. We have the following by definition: $f(\mu_1, \beta) : \mathcal{R} \times [0,1] \to \mathcal{R}$, $f(\mu_1, \beta)$ is integrable, $\partial f(\mu_1, \beta)/\partial\beta$ exists, and

$$\left|\partial f(\mu_1, \beta)/\partial\beta\right| = \left|-(\mu_1 + p_{\mathcal{S}} - v_{\mathcal{N}})\phi\left(\frac{v_{\mathcal{N}} + \beta(\mu_1 + p_{\mathcal{S}} - v_{\mathcal{N}}) - p_{\mathcal{S}} - \mu_1}{\Sigma_1}\right)\right| \leq \left|\mu_1 + p_{\mathcal{S}} - v_{\mathcal{N}}\right|,$$

where $|\mu_1 + p_{\mathcal{S}} - v_{\mathcal{N}}|$ is Lebesque integrable because $\mathbb{E}\left[|\mu_1 + p_{\mathcal{S}} - v_{\mathcal{N}}|\right] \leq \sigma_{M_1} - v_{\mathcal{N}} + p_{\mathcal{S}} < \infty$. Then,

$$\begin{aligned}
&\frac{\partial\, \mathbb{E}[\mathbb{E}[f(\mu_1, \beta) \mid M_1 = \mu_1] \mid M_1 + p_{\mathcal{S}} - v_{\mathcal{N}} \geq 0]}{\partial\beta} = \mathbb{E}\left[\mathbb{E}\left[\frac{\partial f(\mu_1, \beta)}{\partial\beta} \mid M_1 = \mu_1\right] \mid M_1 + p_{\mathcal{S}} - v_{\mathcal{N}} \geq 0\right] \\
&= \mathbb{E}\left[\mathbb{E}\left[-(\mu_1 + p_{\mathcal{S}} - v_{\mathcal{N}})\phi\left(\frac{v_{\mathcal{N}} + \beta(\mu_1 + p_{\mathcal{S}} - v_{\mathcal{N}}) - p_{\mathcal{S}} - \mu_1}{\Sigma_1}\right) \mid M_1 = \mu_1\right] \mid M_1 + p_{\mathcal{S}} - v_{\mathcal{N}} \geq 0\right] < 0.
\end{aligned}$$

This shows that $\mathbb{P}(CE(p_1^*) \mid \mathcal{A}_1)$ decreases with β. □

Prop. EC.7. *The probability of cost-effectiveness of the new technology at the OWR reappraisal price, conditional on the approval at the reappraisal, $\mathbb{P}(CE(p_1^{*,W}) \mid \mathcal{A}_1^W)$, decreases with $0 < \beta < 1$. And if $\beta = 1$, $\mathbb{P}(CE(p_1^{*,W}) \mid \mathcal{A}_1^W) = 0.5$ if $f_r = 0$ and $\mathbb{P}(CE(p_1^{*,W}) \mid \mathcal{A}_1^W) < 0.5$ if $f_r > 0$.*

Proof. We recall the value of $p_1^{*,\mathrm{W}}$ from (23). Then, we have

$$\begin{aligned}
\mathbb{P}(CE(p_1^{*,\mathrm{W}}) \mid \mathcal{A}_1^W)) &= \mathbb{P}\left(\theta - (p_1^* - p_{\mathcal{S}}) > 0 \mid \mathcal{A}_1^W\right) \\
&= \mathbb{P}\left(\theta - (v_{\mathcal{N}} + \beta(M_1 + p_{\mathcal{S}} - v_{\mathcal{N}}) + \beta\frac{f_r}{N - 2n^{*,\mathrm{W}}/r_{max}} - p_{\mathcal{S}}) > 0 \,\middle|\, \mathcal{A}_1^W\right) \\
&= \mathbb{P}\left(\theta > v_{\mathcal{N}} + \beta(M_1 + p_{\mathcal{S}} - v_{\mathcal{N}}) + \beta\frac{f_r}{N - 2n^{*,\mathrm{W}}/r_{max}} - p_{\mathcal{S}} \,\middle|\, \mathcal{A}_1^W\right) \\
&= \mathbb{E}[\mathbb{1}_{\{\theta > v_{\mathcal{N}} + \beta(M_1 + p_{\mathcal{S}} - v_{\mathcal{N}}) + \beta\frac{f_r}{N - 2n^{*,\mathrm{W}}/r_{max}} - p_{\mathcal{S}}\}} \mid \mathcal{A}_1^W] \\
&= \mathbb{E}[\mathbb{E}[\mathbb{1}_{\{\theta > v_{\mathcal{N}} + \beta(\mu_1 + p_{\mathcal{S}} - v_{\mathcal{N}}) + \beta\frac{f_r}{N - 2n^{*,\mathrm{W}}/r_{max}} - p_{\mathcal{S}}\}} \mid M_1 = \mu_1] \mid \mathcal{A}_1^W] \\
&= \mathbb{E}\left[\mathbb{P}\left(\theta > v_{\mathcal{N}} + \beta(\mu_1 + p_{\mathcal{S}} - v_{\mathcal{N}}) + \beta\frac{f_r}{N - 2n^{*,\mathrm{W}}/r_{max}} - p_{\mathcal{S}} \,\middle|\, M_1 = \mu_1\right) \,\middle|\, \mathcal{A}_1^W\right],
\end{aligned}$$

where $\mathcal{A}_1^W = \{M_1 + p_{\mathcal{S}} - v_{\mathcal{N}} - f_r/(N - 2n^{*,\mathrm{W}}/r_{max}) \geq 0\}$, the fourth equality follows from the definition of probability, the fifth equality follows from the law of total expectation, and the final equality again follows from the definition of probability.

We first analyze the case of $\beta = 1$. We write

$$\mathbb{P}(CE(p_1^{*,\mathrm{W}}) \mid \mathcal{A}_1^W)) = \mathbb{E}\left[\mathbb{P}\left(\theta > \mu_1 + \frac{f_r}{N - 2n^{*,\mathrm{W}}/r_{max}} \,\middle|\, M_1 = \mu_1\right) \,\middle|\, \mathcal{A}_1^W\right].$$

Because $\theta \mid \mu_1 \sim \texttt{Normal}(\mu_1, \Sigma_1)$, $\mathbb{P}(CE(p_1^{*,\mathrm{W}}) \mid \mathcal{A}_1^W)) = 0.5$ if $f_r = 0$ and $\mathbb{P}(CE(p_1^{*,\mathrm{W}}) \mid \mathcal{A}_1^W)) < 0.5$ if $f_r > 0$.

The proof that $\mathbb{P}(CE(p_1^{*,\mathrm{W}}) \mid \mathcal{A}_1^W))$ decreases in β for $\beta \in (0,1)$ follows the same steps found in the proof of Prop. EC.6. □

How β impacts the probability of cost-effectiveness at the interim prices, p_i^* and $p_i^{*,\mathrm{W}}$, depends on other parameters, however. The relationship between $\mathbb{P}(CE(p_i^*))$ and β depends on the values of $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}}$ and $v_{DC} + f_{DC}/n^*$, following a similar argument to that in §3.4 about the relationship between p_i^* and β. And the relationship between $\mathbb{P}(CE(p_i^{*,\mathrm{W}}))$ and β analogously depends on the values of $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}}$ and $(n^{*,\mathrm{W}} v_{DC} + f_{DC} + f_r)/(n^{*,\mathrm{W}}(2/r_{max} - 1))$, following an argument similar to that in Appendix C.1.4 regarding the relationship between $p_i^{*,\mathrm{W}}$ and β.

Remark EC.8. Price reduction schemes are a form of risk sharing that operate by lowering the sticker price of a drug to decrease the probability that a new health technology is cost ineffective if immediately approved (e.g., Claxton 2007). A sticker price can be somewhat arbitrary, however, and is not part of our model. Nevertheless, this type of risk-sharing model corresponds well to the discounting of a new health technology that is not cost effective at the sticker price, so that the discounted price makes it marginally cost effective at the mean INMB. This results in the INMB being positive or negative with equal probability, precisely what we find in the Immediate Approval column of Table EC.5 when $\beta = 1$.

F.2. Probability a Conditional Approval Scheme (CA) Itself is Cost-effective

Conditional approval (CA) schemes may provide additional information regarding the cost-effectiveness of a treatment, but CA schemes themselves are costly. A social planner may ask whether the CA scheme is worth it and may also wish to assess whether the total cost of the CA – data collection, technology adoption, and negotiated prices – is offset by the health benefits, net of treatment costs, that may accrue to all N patients who are involved in the CA scheme, whether or not they participate in the trial.

To model the cost-effectiveness of an OIR scheme for a new treatment under consideration, we define a random variable V_{OIR} that represents the payer's INMB from such a scheme:

$$V_{OIR} \triangleq \begin{cases} n^*(\theta - p_i^* + p_{\mathcal{S}}), & \text{if } \bar{\mathcal{A}}_1 \text{ occurs,} \\ n^*(\theta - p_i^* + p_{\mathcal{S}}) + (N - 2n^*/r_{max})(\theta - p_1^* + p_{\mathcal{S}}), & \text{if } \mathcal{A}_1 \text{ occurs,} \end{cases}$$

where the event $\mathcal{A}_1$ denotes approval at reappraisal and $\bar{\mathcal{A}}_1$ its complement. We similarly define a random variable V_{OWR} for the OWR scheme as:

$$V_{OWR} \triangleq \begin{cases} n^{*,\mathrm{W}}(2/r_{max} - 1)(\theta - p_i^{*,\mathrm{W}} + p_{\mathcal{S}}) - f_r, & \text{if } \bar{\mathcal{A}}_1^W \text{ occurs,} \\ n^{*,\mathrm{W}}(2/r_{max} - 1)(\theta - p_i^{*,\mathrm{W}} + p_{\mathcal{S}}) + (N - 2n^{*,\mathrm{W}}/r_{max})(\theta - p_1^{*,\mathrm{W}} + p_{\mathcal{S}}), & \text{if } \mathcal{A}_1^W \text{ occurs.} \end{cases}$$

Thus, unlike the quantities calculated within $\mathbb{P}(CE(p_1^*) \mid \mathcal{A}_1)$ and $\mathbb{P}(CE(p_1^{*,\mathrm{W}}) \mid \mathcal{A}_1^W)$, the terms defined in V_{OIR} and V_{OWR} include the costs of the trial and of reversal. As before, the random variable $V_A \triangleq N(\theta - p_0^* + p_S)$ models the payer's INMB from immediate approval.

The probability that an OIR scheme is cost-effective, as compared to immediate rejection, is then $\mathbb{P}(V_{OIR} \geq 0)$, with respect to the joint distribution of θ and sample mean of the OIR data. The probability that an OIR scheme is cost-effective, as compared to immediate approval, is $\mathbb{P}(V_{OIR} \geq V_A)$, and compared to the OWR scheme it is $\mathbb{P}(V_{OIR} \geq V_{OWR})$. Similarly, the probabilities of cost-effectiveness of an OWR scheme compared to other options are $\mathbb{P}(V_{OWR} \geq 0)$, $\mathbb{P}(V_{OWR} \geq V_A)$, and $\mathbb{P}(V_{OWR} \geq V_{OIR})$. Observe that, unlike $\mathbb{P}(CE(p_1^*) \mid \mathcal{A}_1)$ and $\mathbb{P}(CE(p_1^{*,\mathrm{W}}) \mid \mathcal{A}_1^W)$, these probabilities are *not* conditioned on approval. Rather, they include all outcomes, including those for which the end result of conditional approval is rejection.

In Figure EC.10, we plot the probability that the CA process is more cost-effective than each of the other options. These plots can also be interpreted as the probability that the Nash bargaining outcome is cost-effective, the probability taken over sample paths of the data collection process. We recall that the Nash bargaining outcome for Votrient is an OWR scheme if $f_r < £24 \times 10^7$ and is an OIR scheme otherwise. The probability that immediate approval is cost-effective compared to immediate rejection, $\mathbb{P}(V_A \geq 0) = \mathbb{P}(CE(p_0^*))$, is reported in Table EC.5.

In Figure EC.10a, the reversal cost is $f_r = 0$ and the OWR scheme is optimal for the Votrient case study. Here, Figure EC.10a shows that the probability that OWR is more cost-effective than OIR far exceeds 0.5, except when $\beta \to 1$, the case when the negotiation converges to that of a Stackelberg game. However, OWR is less likely than immediate approval to be cost-effective overall, even though OWR results in the highest expected joint surplus. (The probabilities in Figure EC.10a might not be precisely 0.5 when $\beta = 1$ because trial costs might not be zero and because of the opportunity cost of patient outcomes for those who received the sub-optimal treatment during the trial.)

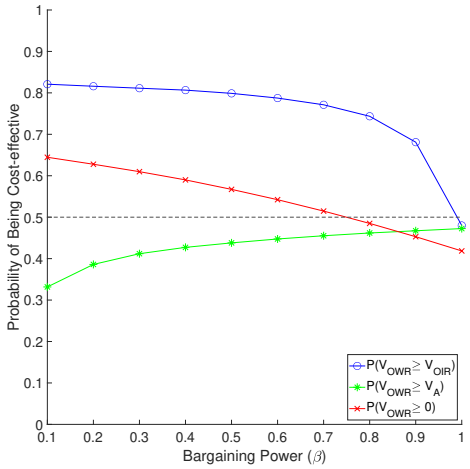
Remark EC.9. These observations add nuance to a high-level observation of Barton et al. (2008): In the context of collaborative bargaining, technology adoption based on a threshold for the probability of cost-effectiveness may or may not be consistent with the fact that a given conditional approval scheme gives positive expected net health-economic value to patients.

Figure EC.10b shows analogous graphs for $f_r = 30 \times 10^7$, a case in which an OIR scheme is optimal. The figure shows that the probability that an OIR scheme delivers positive value exceeds 50% if the company's bargaining power is not too high ($\beta < 0.6$). Even though OIR is the bargaining outcome, the probability that it is more cost-effective than OWR always falls below 0.5. Here, a small but nontrivial chance that V_{OWR} is highly suboptimal, due to high reversal costs, drags the expected value of OWR below that of OIR.

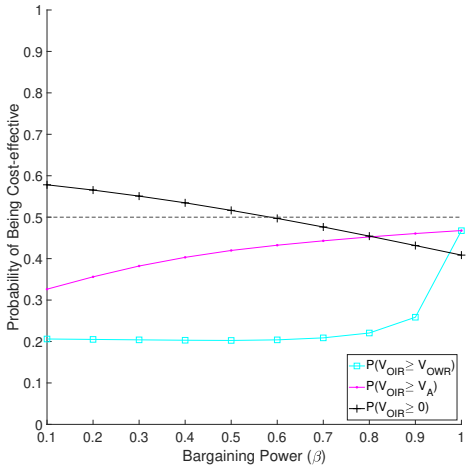
Remark EC.10. In both Figure EC.10a and Figure EC.10b, the optimal conditional approval scheme is cost effective with probability less than 50% when the company's bargaining power is high ($\beta \geq 0.8$ and $\beta \geq 0.6$, respectively). At the same time, the oft-assumed Stackelberg model corresponds to $\beta = 1 > 0.8 > 0.6$. This suggests that, if the company's bargaining power is high, then these CA schemes themselves have a risk of being cost-ineffective as compared to immediate adoption or rejection.

Figure EC.10 Votrient Case Study: The probability that OIR and OWR conditional approval schemes themselves are cost-effective, given different values of the bargaining power parameter β. Error bars are omitted because all standard errors from Monte Carlo simulation with 10^8 samples are less than 10^{-4}.

(a) $f_r = 0$, where OWR is optimal



(b) $f_r = 30 \times 10^7$, where OIR is optimal.



F.3. Competition from the Manufacturer of the Standard of Care

We now analyze how competition between the manufacturer of the standard of care, who we call *the incumbent*, and that of the new treatment would impact bargaining outcomes and prices. As a response to the submission of the new treatment made by the company, the incumbent might consider discounting the price of the standard of care, which would change the INMB of the new treatment and, in turn, could change the company's and payer's bargaining outcome for the new treatment. For simplicity we analyze the case in which only the OIR scheme is under consideration.

Payoffs with Competition from Incumbent. We now define the players' payoffs in the presence of a potential discount on the price of the standard of care. If the new treatment is rejected at the reappraisal stage, the remaining patients are treated with the standard of care, and the payer reimburses the incumbent at the discounted price $p_S - d_1$, where $d_1 \geq 0$ denotes the discount offered at reappraisal. In this case, the payer's payoff given rejection is $V_1(\mathrm{R}_1) \triangleq (1-t)Nd_1$, and the company's payoff is $\Pi_1(\mathrm{R}_1) \triangleq 0$. As in the base model, the payoffs and surplus from approval at the reappraisal are given in (5), (8), and (10). At the initial submission stage, if the new treatment is immediately rejected, all future patients continue using the standard of care, and the payer reimburses the incumbent at the discounted price $p_S - d_0$, where $d_0 \geq 0$ denotes the discount amount offered at the initial submission stage. Here, the payer's payoff is $V_0(\mathrm{R}_0) \triangleq Nd_0$ and the company's payoff is $\Pi_0(\mathrm{R}_0) \triangleq 0$. The payoffs from immediate approval are given in (4), (7), and the first equation of (12). The payoffs and surplus from conditional approval are derived below in this section and given in (EC.32)–(EC.34).

Recall that rejection of the new treatment at reappraisal or initial submission corresponds to the Nash bargaining solution's disagreement outcome. (See Appendix A.) For the case in which the incumbent offers a discount on the price of the standard of care, the disagreement outcome of the payer increases by the

discount, while that of the company remains zero. In comparison to the base model analyzed in 3, the new bargaining solution reflects the payer's ability to extract a higher proportion of the surplus, a difference that corresponds to the offered discount.

Analysis of the Reappraisal Stage. We first consider the reappraisal stage, discussing when and how the payer would negotiate a discount with the incumbent, as well as how a discount would impact bargaining between the payer and company. We denote the variable production cost of the standard of care by $v_{\mathcal{S}}$. We assume that the incumbent has a non-negative margin, $v_{\mathcal{S}} \leq p_{\mathcal{S}}$.

The first case occurs when the joint surplus from the new treatment is negative, $\mu_1 - v_{\mathcal{N}} + p_{\mathcal{S}} < 0$. Here, the new treatment is rejected regardless of the discount amount. Given that there is no incentive for the incumbent to agree to a discount, its value would be $d_1^* = 0$, the new treatment would be rejected at reappraisal, and the price of the standard of care would remain $p_{\mathcal{S}}$.

In the second case, the joint surplus from the new treatment is non-negative but lower than the margin on the standard of care, $p_{\mathcal{S}} - v_{\mathcal{S}} > \mu_1 - v_{\mathcal{N}} + p_{\mathcal{S}} \geq 0$. Here, the payer could ask the incumbent for a range of d_1's that would in theory be agreeable to both, so that $d_1 \in (\mu_1 - v_{\mathcal{N}} + p_{\mathcal{S}}, p_{\mathcal{S}} - v_{\mathcal{S}}]$. For all d_1 in this range, the new treatment would be rejected, the price of the standard of care would be updated to $p_{\mathcal{S}} - d_1$ for the remaining patients, and the payer and company would both receive their respective disagreement outcomes.

While a three-way bargaining model is beyond the scope of this paper, we note that the exact value of d_1 would depend on the relative bargaining power of the payer and incumbent. For simplicity, we assume here that d_1 is determined before negotiation between the payer and company begins, and we denote the discount amount that would arise from negotiation between the payer and incumbent by $d_1^* = p_{\mathcal{S}} - \underline{p_{\mathcal{S}}}$, where $\underline{p_{\mathcal{S}}} \geq v_{\mathcal{S}}$ is the value of the incumbent's outside option.

Finally, the third case occurs when the joint surplus from the new treatment is positive and higher than the margin on the standard of care, $\mu_1 - v_{\mathcal{N}} + p_{\mathcal{S}} \geq p_{\mathcal{S}} - v_{\mathcal{S}} \geq 0$. Here, the payer asks the incumbent for $d_1^* = p_{\mathcal{S}} - \underline{p_{\mathcal{S}}}$, the maximum amount of discount that satisfies the incumbent's participation constraint. Nash bargaining between the payer and company is successful if the joint surplus from approval exceeds the total disagreement payoff, $(1-t)N(\mu_1 + p_{\mathcal{S}} - v_{\mathcal{N}}) \geq (1-t)Nd_1^*$, so that $\mu_1 \geq v_{\mathcal{N}} - v_{\mathcal{S}} \geq v_{\mathcal{N}} - \underline{p_{\mathcal{S}}}$, with the reappraisal price $p_1^{*,d} \triangleq v_{\mathcal{N}} + \beta(\mu_1 + p_{\mathcal{S}} - d_1^* - v_{\mathcal{N}}) = v_{\mathcal{N}} + \beta(\mu_1 + \underline{p_{\mathcal{S}}} - v_{\mathcal{N}})$. We observe that the reduction in the price of the new treatment, due to competition, follows the payer's threat of continuing with the standard of care at a discounted price, $p_1^{*,d} \leq p_1^*$.

Analysis of the Initial Submission Stage. Recall that $S_0(\mathrm{A}_0)$ and $S_0(\mathrm{CA}^{\mathrm{I}})$ are the expected joint surpluses from immediate and conditional approval at initial submission, assuming that there is no competition. We denote the analogous joint surplus from conditional approval under competition by $S_0(\mathrm{CA}^{\mathrm{I}}, \underline{p_{\mathcal{S}}})$.

We first define the payer's and company's payoffs from conditional approval at the time of initial submission. We recall that M_1 is the random pre-posterior mean to be observed at the end of the post-marketing trial, with distribution given in (3), and we use the results for the reappraisal stage to define the payer's expected value of conditional approval:

$$V_0(\mathrm{CA}^{\mathrm{I}}, p_i, \underline{p_{\mathcal{S}}}, n, t) \triangleq n(\mu_0 - p_i + p_{\mathcal{S}})$$

$$+(1-t)N\,\mathbb{E}_{M_1}\left[\begin{cases} p_{\mathcal{S}}-\underline{p_{\mathcal{S}}}+(1-\beta)((M_1+p_{\mathcal{S}}-v_{\mathcal{N}})-(p_{\mathcal{S}}-\underline{p_{\mathcal{S}}})), & M_1\geq v_{\mathcal{N}}-v_{\mathcal{S}},\\ p_{\mathcal{S}}-\underline{p_{\mathcal{S}}}, & v_{\mathcal{N}}-v_{\mathcal{S}}>M_1\geq v_{\mathcal{N}}-p_{\mathcal{S}},\\ 0, & v_{\mathcal{N}}-p_{\mathcal{S}}>M_1. \end{cases}\middle|\,\mu_0,n_0\right]. \tag{EC.32}$$

The company's analogous expected value is

$$\begin{aligned}\Pi_0(\mathrm{CA}^{\mathrm{I}},p_i,\underline{p_{\mathcal{S}}},n,t)\triangleq\ & n(p_i-v_{\mathcal{N}})-f_{DC}-nv_{DC}\\ &+(1-t)N\,\mathbb{E}_{M_1}\left[\begin{cases}\beta((M_1+p_{\mathcal{S}}-v_{\mathcal{N}})-(p_{\mathcal{S}}-\underline{p_{\mathcal{S}}})), & M_1\geq v_{\mathcal{N}}-v_{\mathcal{S}},\\ 0, & v_{\mathcal{N}}-v_{\mathcal{S}}>M_1.\end{cases}\middle|\,\mu_0,n_0\right].\end{aligned} \tag{EC.33}$$

Then, we sum the players' payoffs, denote the total payoff by $S_0(\mathrm{CA}^{\mathrm{I}},\underline{p_{\mathcal{S}}},n,t)$, find the sample size and duration of the post-marketing trial that maximizes the total payoff and define $S_0(\mathrm{CA}^{\mathrm{I}},\underline{p_{\mathcal{S}}})$:

$$\begin{aligned}S_0(\mathrm{CA}^{\mathrm{I}},\underline{p_{\mathcal{S}}},n,t)\ \triangleq\ & n(\mu_0+p_{\mathcal{S}}-v_{\mathcal{N}})-f_{DC}-nv_{DC}\\ &+(1-t)N\,\mathbb{E}_{M_1}\left[\begin{cases}M_1+p_{\mathcal{S}}-v_{\mathcal{N}}, & M_1\geq v_{\mathcal{N}}-v_{\mathcal{S}},\\ p_{\mathcal{S}}-\underline{p_{\mathcal{S}}}, & v_{\mathcal{N}}-v_{\mathcal{S}}>M_1\geq v_{\mathcal{N}}-p_{\mathcal{S}},\\ 0, & v_{\mathcal{N}}-p_{\mathcal{S}}>M_1.\end{cases}\middle|\,\mu_0,n_0\right],\end{aligned} \tag{EC.34}$$

where

$$(n^{*,d},t^{*,d})\triangleq\underset{(n,t)}{\arg\max}\{S_0(\mathrm{CA}^{\mathrm{I}},\underline{p_{\mathcal{S}}},n,t)|0\leq 2n\leq Ntr_{max};0\leq t\leq 1\}. \tag{EC.35}$$

We define

$$S_0(\mathrm{CA}^{\mathrm{I}},\underline{p_{\mathcal{S}}})\triangleq S_0(\mathrm{CA}^{\mathrm{I}},\underline{p_{\mathcal{S}}},n^{*,d},t^{*,d}). \tag{EC.36}$$

By comparing $S_0(\mathrm{CA}^{\mathrm{I}},\underline{p_{\mathcal{S}}},n,t)$ in (EC.34) to $S_0(\mathrm{CA}^{\mathrm{I}},n,t)$ in (13), we observe that, for any given pair of n and t, we have $S_0(\mathrm{CA}^{\mathrm{I}},\underline{p_{\mathcal{S}}},n,t)\geq S_0(\mathrm{CA}^{\mathrm{I}},n,t)$. In particular, this is true for the optimal conditional approval trial for the case of no competition, where $n=n^*$, $t=t^*$. Thus,

$$S_0(\mathrm{CA}^{\mathrm{I}})=S_0(\mathrm{CA}^{\mathrm{I}},n^*,t^*)\leq S_0(\mathrm{CA}^{\mathrm{I}},\underline{p_{\mathcal{S}}},n^*,t^*)\leq S_0(\mathrm{CA}^{\mathrm{I}},\underline{p_{\mathcal{S}}}).$$

The last inequality follows directly from the definitions in (EC.35) and (EC.36).

In summary, in the OIR scheme, competition from the incumbent can lead to an increase in the payer's disagreement outcome. This shift leads to an increase in the bargaining surplus for conditional approval.

We now analyze different outcomes of the initial submission stage case by case. The first case occurs when $S_0(\mathrm{A}_0)<0$ and $S_0(\mathrm{CA}^{\mathrm{I}},\underline{p_{\mathcal{S}}})<0$. Then, the new treatment is immediately rejected, regardless of the discount, so that $d_0^*=0$ and and the price of the standard of care remains $p_{\mathcal{S}}$.

In the second case, $S_0(\mathrm{A}_0)\geq S_0(\mathrm{CA}^{\mathrm{I}},\underline{p_{\mathcal{S}}})$ and $p_{\mathcal{S}}-v_{\mathcal{S}}>S_0(\mathrm{A}_0)/N\geq 0$. Here, the new treatment would be immediately approved if the incumbent offered no discount at initial submission, but the joint surplus per patient from immediate approval is lower than the incumbent's margin on the standard of care. Therefore, the payer could ask the incumbent for a range of d_0's such that $d_0\in(S_0(\mathrm{A}_0)/N,p_{\mathcal{S}}-v_{\mathcal{S}}]$. For all d_0 in this range, the new treatment would be immediately rejected, and the price of the standard of care would be updated to $p_{\mathcal{S}}-d_0$ for the remaining patients. As with the reappraisal stage, the exact value of d_0 would depend on the relative bargaining powers of the payer and incumbent, and we denote the discount amount that would arise from the negotiation between the payer and incumbent by $d_0^*=p_{\mathcal{S}}-\underline{p_{\mathcal{S}}}$.

The third case occurs when $S_0(\mathrm{A}_0) \geq S_0(\mathrm{CA}^{\mathrm{I}}, \underline{p_{\mathcal{S}}})$ and $S_0(\mathrm{A}_0)/N \geq p_{\mathcal{S}} - v_{\mathcal{S}} \geq 0$. The payer can ask the incumbent for a discount $d_0^* = p_{\mathcal{S}} - \underline{p_{\mathcal{S}}}$, and the Nash bargaining outcome is immediate approval if the joint surplus from immediate approval exceeds the total disagreement payoff, $S_0(\mathrm{A}_0) = N(\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}}) \geq N d_0^*$ which holds if $\mu_0 \geq v_{\mathcal{N}} - \underline{p_{\mathcal{S}}}$. Because $S_0(\mathrm{A}_0)/N = \mu_0 - v_{\mathcal{N}} + p_{\mathcal{S}} \geq p_{\mathcal{S}} - v_{\mathcal{S}}$ implies $\mu_0 \geq v_{\mathcal{N}} - v_{\mathcal{S}} \geq v_{\mathcal{N}} - \underline{p_{\mathcal{S}}}$, the bargaining is successful, the new treatment would be immediately approved with the price $p_0^{*,d} = v_{\mathcal{N}} + \beta(\mu_0 + p_{\mathcal{S}} - d_0^* - v_{\mathcal{N}}) = v_{\mathcal{N}} + \beta(\mu_0 + \underline{p_{\mathcal{S}}} - v_{\mathcal{N}})$. As with the reappraisal price, we have $p_0^{*,d} \leq p_0^*$.

In the fourth case, $S_0(\mathrm{A}_0) < S_0(\mathrm{CA}^{\mathrm{I}}, \underline{p_{\mathcal{S}}})$ and $p_{\mathcal{S}} - v_{\mathcal{S}} > S_0(\mathrm{CA}^{\mathrm{I}}, \underline{p_{\mathcal{S}}})/N \geq 0$. Here, the treatment would be conditionally approved if the incumbent offered no discount, but the joint surplus from conditional approval is less than the margin on the standard of care. Again, the payer could ask the incumbent for a range of d_0's such that $d_0 \in (S_0(\mathrm{CA}^{\mathrm{I}}, \underline{p_{\mathcal{S}}})/N, p_{\mathcal{S}} - v_{\mathcal{S}}]$. For all d_0 in this range, the new treatment would be immediately rejected and the price of the standard of care would be updated to $p_{\mathcal{S}} - d_0$ for the remaining patients, with the exact value of d_0 depending on the relative bargaining power of the payer and incumbent. We denote the discount amount that would arise from the negotiation between the payer and incumbent by $d_0^* = p_{\mathcal{S}} - \underline{p_{\mathcal{S}}}$.

The fifth and final case occurs when $S_0(\mathrm{A}_0) < S_0(\mathrm{CA}^{\mathrm{I}}, \underline{p_{\mathcal{S}}})$ and $S_0(\mathrm{CA}^{\mathrm{I}}, \underline{p_{\mathcal{S}}})/N \geq p_{\mathcal{S}} - v_{\mathcal{S}} \geq 0$. Here, the payer asks the incumbent for a discount $d_0^* = p_{\mathcal{S}} - \underline{p_{\mathcal{S}}}$ and the Nash bargaining outcome is conditional approval, $S_0(\mathrm{CA}^{\mathrm{I}}, \underline{p_{\mathcal{S}}}) \geq N(p_{\mathcal{S}} - \underline{p_{\mathcal{S}}})$. In turn, $S_0(\mathrm{CA}^{\mathrm{I}}, \underline{p_{\mathcal{S}}})/N \geq p_{\mathcal{S}} - v_{\mathcal{S}} \geq p_{\mathcal{S}} - \underline{p_{\mathcal{S}}}$, and the Nash bargaining outcome is conditional approval. The interim price at the Nash bargaining outcome is calculated by using (EC.33) and $\Pi_0(\mathrm{CA}^{\mathrm{I}}, p_i, \underline{p_{\mathcal{S}}}, n^{*,d}, t^{*,d}) = \beta(S_0(\mathrm{CA}^{\mathrm{I}}, \underline{p_{\mathcal{S}}}) - N(p_{\mathcal{S}} - \underline{p_{\mathcal{S}}}))$, where $N(p_{\mathcal{S}} - \underline{p_{\mathcal{S}}})$ is the total disagreement outcome at the initial submission stage. Then,

$$\begin{aligned} p_i^{*,d} = {} & p_0^{*,d} + (1-\beta)(f_{DC}/n^{*,d} + v_{DC}) \\ & - \beta \frac{(N - n^{*,d})(p_{\mathcal{S}} - \underline{p_{\mathcal{S}}})}{n^{*,d}} + \beta \frac{(1 - t^{*,d})N(p_{\mathcal{S}} - \underline{p_{\mathcal{S}}})}{n^{*,d}} \left(1 - \Phi\left(\frac{v_{\mathcal{N}} - p_{\mathcal{S}} - \mu_0}{\sigma_{M_1}^{*,d}}\right)\right). \end{aligned} \tag{EC.37}$$

We observe that the $p_i^{*,d}$ that arises in the fifth case includes the immediate approval price plus the payer's share of data collection costs, an analogue to p_i^* in Prop. 3. The price $p_i^{*,d}$ differs from p_i^* in its additional, last two terms, however. The term $\beta(N - n^{*,d})(p_{\mathcal{S}} - \underline{p_{\mathcal{S}}})/n^{*,d}$ reflects the potential discount on the standard of care that the payer forgoes by conditionally approving the new treatment, and the final term in $p_i^{*,d}$ is a partial compensation for the company's potential profit loss at reappraisal. A comparison between $p_i^{*,d}$ and p_i^* depends on the values of $n^{*,d}$ and n^*. If $n^{*,d} \geq n^*$, we have $p_i^{*,d} \leq p_i^*$.

Summary of Outcomes. There are three types of outcomes in the presence of competition. The first outcome occurs when the incremental value from the new treatment is so low that it would be rejected even if there is no discount on the standard of care's price. Then, the new treatment is rejected and the price of the standard of care remains unchanged. The second outcome is when the incremental value from the new treatment is high enough to be approved if there were no competition but is lower than the incumbent's margin on the standard of care. Then, the incumbent offers to provide the standard of care at a discounted price, and the new treatment is rejected. The third and final type of outcome is when the incremental value from the new treatment is higher than the incumbent's margin. Then, the new treatment is approved at a price that is lower than the price under no-competition, because the payer uses the competition from the incumbent as a credible threat.

We now compare the bargaining outcomes under competition to the ones under no-competition. New treatments whose expected INMB satisfies $\mu_1 < v_{\mathcal{N}} - p_{\mathcal{S}}$ are rejected under both circumstances. Those whose expected INMB satisfies $v_{\mathcal{N}} - p_{\mathcal{S}} \leq \mu_1 < p_{\mathcal{S}} - v_{\mathcal{S}}$ are approved under no-competition but rejected under competition. Even though these new treatments are rejected when there is competition, their submission leads the incumbent to offer a price discount on the standard of care. Finally, new treatments whose expected INMB satisfies $p_{\mathcal{S}} - v_{\mathcal{S}} \leq \mu_1$ are approved under both circumstances, but the reappraisal price of the new treatment is weakly lower under competition.

At the initial submission stage, the bargaining outcome for the payer and company is the one that generates the highest joint surplus between the two players. The joint surplus from conditional approval under competition is weakly higher than the one under no-competition, i.e., $S_0(\mathrm{CA}^{\mathrm{I}}, \underline{p_{\mathcal{S}}}) \geq S_0(\mathrm{CA}^{\mathrm{I}})$. This is a result of the increase in the payer's expected payoff from the reappraisal stage due to the potential discount that the incumbent might offer at the conclusion of the post-marketing trial.

Furthermore, at initial submission, the new treatment is rejected if $\max\{S_0(\mathrm{A}_0), S_0(\mathrm{CA}^{\mathrm{I}}, \underline{p_{\mathcal{S}}})\} < p_{\mathcal{S}} - v_{\mathcal{N}}$ under competition, while the rejection condition is $\max\{S_0(\mathrm{A}_0), S_0(\mathrm{CA}^{\mathrm{I}})\} < 0$ under no-competition. Due to the increase in both the joint surplus from conditional approval and the rejection threshold, the region for immediate approval depicted in Figure 3c would be smaller under competition, while regions for conditional approval and rejection would be larger. The immediate approval price is weakly lower if there is competition. The effect of competition on the interim price is indeterminate because it depends on the details of the bargaining between the payer and the incumbent.

An analysis of competition with OWR conditional approval schemes is reserved for future work.

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