Online Companion: Appendices

Appendix EC.1 includes a table that summarizes the notation for our model. Appendix EC.2 recalls elements of the Nash bargaining problem that will be relevant to our model and its analysis. Appendix EC.3 provides the mathematical results that support the claims made in the main text. Appendix EC.4 presents comparative statics results to assess the effect of key parameters on the Nash bargaining outcome of our two-stage model and on the prices that arise from bargaining. Appendix EC.5 provides additional numerical results based on the case study presented in §6.

EC.1 Principle Notation

Table EC.1 summarizes the notation for our model.

Table EC.1 Principal Notation.

Symbol	*Definition*
N	Total number of patients who would switch to the new treatment if the new treatment 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 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 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 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 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 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 trial in a unit of time
f_{DC}	Fixed cost of running a post-marketing trial for further data collection ('DC')
v_{DC}	Variable cost per patient pair recruited during the post-marketing trial run
f_r	Reversal cost paid if new treatment is withdrawn at the end of an OWR scheme
$v_{\mathcal{N}}$	Variable, per-patient manufacturing cost of the new treatment
β	In Nash bargaining terminology, the company's '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

EC.2 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 the 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 is symmetric. We focus on the asymmetric case which involves two players with asymmetric bargaining powers. 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 and nonempty. 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 the 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 nonemptiness and boundedness conditions mean that some feasible payoffs 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.

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, other than the disagreement point that would not have been chosen, 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 $x_1 + x_2 \leq A$ 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. 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, therefore the bargaining fails and both payers receive the payoffs at the disagreement point.

EC.3 Proofs of Mathematical Claims

This appendix proves the mathematical claims made in the main text. Appendix EC.3.1 proves claims made in §3. Appendix EC.3.2 similarly supports the results in §4. Appendix EC.3.3 proves mathematical claims in §5.

EC.3.1 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 an asymmetric bargaining problem in which two players (called the payer and the company) negotiate to share the surplus from one of the two possible outcomes. Two surpluses are denoted by $S_0(\mathrm{A}_0)$ and $S_0(\mathrm{CA^I})$, and β and $1-\beta$ denote the bargaining power of the company and the payer, respectively.

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

Because $0 \le \alpha \le 1$, and because $S_0(\mathrm{A}_0)$ and $S_0(\mathrm{CA}^{\mathrm{I}})$ are constants, $\{(\alpha S_0(\mathrm{A}_0),(1-\alpha)S_0(\mathrm{A}_0))|0 \le \alpha \le 1\}$ 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 $\mathbb{R}^2$. We need to show that $\mathcal{F}_0$ is a convex and closed subset of $\mathbb{R}^2$. As is common in the Nash bargaining literature, we allow randomized actions to be taken over the set of feasible bargaining outcomes (Myerson 1997), $\mathcal{F}_0$, 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 EC.2). To show that $\mathcal{F}_0 \cap \{(x_1,x_2)|x_1 \ge 0 \text{ and } x_2 \ge 0\}$ is bounded, we note that the standard normal loss function is bounded.

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 $\mu_0 \ge v_{\mathcal{N}} - p_S$,

$$\begin{aligned}\mathbb{E}\left[p_1^* | M_1 \ge v_{\mathcal{N}} - p_S\right] &= \frac{\int_{v_{\mathcal{N}}-p_S}^{\infty} \left[v_{\mathcal{N}} + \beta(M_1 + p_S - v_{\mathcal{N}})\right] dF(M_1)}{\mathbb{P}(M_1 > v_{\mathcal{N}} - p_S)} \\ &> v_{\mathcal{N}} + \beta \int_{-\infty}^{\infty} (M_1 + p_S - v_{\mathcal{N}})\, dF(M_1) \;=\; v_{\mathcal{N}} + \beta(\mu_0 + p_S - v_{\mathcal{N}}) \;=\; p_0^*,\end{aligned}$$

where M_1, defined in (1), has cumulative distribution function $F(M_1)$. ■

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

EC.3.2 Proofs of Mathematical Claims in §4

EC.3.2.1 Analysis of The Reappraisal Stage when an OWR Scheme is Implemented.

With the inclusion of a positive cost of reversal, $f_r > 0$, 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 EC.2 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 (9). If there is a disagreement, the joint surplus would be $-f_r$. The Nash solution implies that an agreement is reached only if

$$S_1(\mathrm{A}_1, t) = (1-t)N(\mu_1 + p_S - v_{\mathcal{N}}) > -f_r \Rightarrow \mu_1 \geq v_{\mathcal{N}} - p_S - f_r/((1-t)N).$$

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

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

Using (4) and (7) 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.

PROPOSITION EC.1. *Consider an only with research scheme with the cost of reversal, $f_r \geq 0$. If $\mu_1 \geq v_{\mathcal{N}} - p_S - f_r/((1-t)N)$, the Nash bargaining outcome at the reappraisal stage is approval with the reappraisal price $p_1^{*,W} = v_{\mathcal{N}} + \beta(\mu_1 + p_S - v_{\mathcal{N}}) + \beta f_r/((1-t)N)$, and the joint surplus, the payer's INMB and the company's expected profit at the Nash bargaining outcome are*

$$\begin{aligned} S_1^{*,W}(t) &= \max\{(1-t)N(\mu_1 + p_S - v_{\mathcal{N}}), -f_r\}, \\ V_1^{*,W}(t) &= -f_r + (1-\beta)(S_1^{*,W}(t) + f_r)\;,\; \Pi_1^{*,W}(t) = \beta(S_1^{*,W}(t) + f_r). \end{aligned} \tag{EC.2}$$

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

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

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

where M_1, defined in (1), 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.

EC.3.2.2 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

$$V_0(\mathrm{CA}^{\mathrm{W}}, p_i, n, t) \triangleq (tN-n)(\mu_0 - p_i + p_S) + \mathbb{E}\left[V_1^{*,\mathrm{W}}(t)|\mu_0, n_0\right], \tag{EC.3}$$

where p_i, n, and t are determined by negotiation, and $V_1^{*,\mathrm{W}}(t)$ is defined in (EC.2). 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

$$\Pi_0(\mathrm{CA}^{\mathrm{W}}, p_i, n, t) \triangleq (tN-n)(p_i - v_{\mathcal{N}}) - f_{DC} - nv_{DC} + \mathbb{E}\left[\Pi_1^{*,\mathrm{W}}(t)|\mu_0, \Sigma_0\right], \tag{EC.4}$$

where $\Pi_1^{*,\mathrm{W}}(t)$ is defined in (EC.2).

As in §3.2.2, we obtain the joint surplus from an OWR scheme by adding (EC.3) and (EC.4).

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

where $S_1^{*,\mathrm{W}}(t)$ is defined in (EC.2). By substituting M_1 for μ_1, taking expectations, and applying the definition of $\psi(x)$ we have

$$\begin{aligned} S_0(\mathrm{CA}^{\mathrm{W}}, n, t) &= (tN-n)(\mu_0 + p_S - v_{\mathcal{N}}) - f_{DC} - nv_{DC} \\ &\quad - f_r + (1-t)N\sigma_{M_1}\psi\left(\frac{v_{\mathcal{N}} - p_S - f_r/((1-t)N) - \mu_0}{\sigma_{M_1}}\right). \end{aligned} \tag{EC.5}$$

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

$$\max_{n,t}\left\{S_0(\mathrm{CA}^{\mathrm{W}}, n, t) \;\middle|\; 0 \le 2n \le Nr_{max}t\right\}. \tag{EC.6}$$

From (EC.5), 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.5) with respect to t:

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

Because $\psi(x)+x\geq 0$, the first derivative is non-positive, and we conclude that the joint surplus from an OWR scheme decreases with t for a given n. Then (EC.6) 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

$$\begin{aligned}
S_0(\mathrm{CA^W}) &\triangleq S_0(\mathrm{CA^W},n^{*,\mathrm{W}},t^{*,\mathrm{W}})\\
&= n^{*,\mathrm{W}}(2/r_{max}-1)(\mu_0+p_{\mathcal{S}}-v_{\mathcal{N}})-f_{DC}-n^{*,\mathrm{W}}v_{DC}\\
&\quad-f_r+(N-2n^{*,\mathrm{W}}/r_{max})\sigma^{*,\mathrm{W}}_{M_1}\psi\left(\frac{v_{\mathcal{N}}-p_{\mathcal{S}}-f_r/((N-2n^{*,\mathrm{W}}/r_{max}))-\mu_0}{\sigma^{*,\mathrm{W}}_{M_1}}\right),
\end{aligned}\tag{EC.7}$$

where $\sigma^{*,\mathrm{W}}_{M_1}\triangleq\sqrt{\Sigma_X n^{*,\mathrm{W}}/(n_0(n^{*,\mathrm{W}}+n_0))}$.

Expected Payoffs from an OWR Scheme. By using (EC.3), (EC.4) and (EC.7), setting either $V_0(\mathrm{CA^W},p_i,n^{*,\mathrm{W}},t^{*,\mathrm{W}})=(1-\beta)S_0(\mathrm{CA^W})$ or $\Pi_0(\mathrm{CA^W},p_i,n^{*,\mathrm{W}},t^{*,\mathrm{W}})=\beta S_0(\mathrm{CA^W})$ and solving for p_i, we obtain the Nash bargaining outcome summarized in Proposition EC.2.

PROPOSITION 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*

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

where $S_0(CA^W)$ is defined in (EC.7). In turn, the interim price is $p_i^{*,W}=p_0^*+(1-\beta)\frac{n^{*,W}v_{DC}+f_{DC}}{n^{*,W}(2/r_{max}-1)}$.

We highlight that the cost of reversal, f_r, does not appear in $p_i^{*,\mathrm{W}}$. That is, while the cost of reversal directly affects the reappraisal price, $p_1^{*,\mathrm{W}}$, it affects the prices determined at the initial submission stage only through the optimal sample size, $n^{*,\mathrm{W}}$.

As with p_i^*, the interim price under an OWR scheme 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 a post-marketing trial. 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, and (ii) the optimal sample size for post-marketing trials are different.

Furthermore, we have the result that mirrors Corollary 2 follows from the definition of $p_i^{*,\mathrm{W}}$:

COROLLARY EC.2. *If p_0^* and $p_i^{*,W}$ exist, then $p_0^* < p_i^{*,W}$.*

EC.3.2.3 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, $S_0(\mathrm{A}_0)$, and 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. And 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 (15) and (EC.7), respectively.

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

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

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, and the equality from the definition of $S_0(\mathrm{CA}^{\mathrm{I}})$.

Second, we consider the case of $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} > 0$ and $f_r = 0$:

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

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 $S_0(\mathrm{CA}^{\mathrm{I}})$. ■

EC.3.3 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 gain-fractions 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 (12) and (22) and solving

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

we find

$$\beta_1^* = \frac{\beta n^*(\mu_0 + p_{\mathcal{S}}) - n^*\overline{p}_i + (1-\beta)\left[f_{DC} + n^* v_{DC} + n^* v_{\mathcal{N}}\right] + \beta\,\mathbb{E}\left[S_1^*(t^*)|\mu_0, n_0\right]}{\mathbb{E}\left[S_1^*(t^*)|\mu_0, n_0\right]}. \tag{EC.8}$$

Because the denominator in the right hand side of (EC.8) is positive, for case (ii) we then have $\beta_1^* \leq 1$ if and only if

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

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

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

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

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

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

and we rearrange terms to obtain

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

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

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, $p_i^{*,\mathrm{W}}$. Equivalent to 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.

The details of Nash bargaining model can be relaxed when an OWR scheme is the Nash outcome in a similar manner to the risk-sharing mechanism discussed in §5. For alternative fractions $[\beta_1,(1-\beta_1)]$, we write the analogues to (21) and (22) for an OWR scheme:

$$V_0(\mathrm{CA}^{\mathrm{W}},\overline{p}_i,n,t,\beta_1) \;=\; (Nt-n)(\mu_0-\overline{p}_i+p_S) + (1-\beta_1)\,\mathbb{E}\left[S_1^{*,\mathrm{W}}(t)|\mu_0,n_0\right], \text{ and} \tag{EC.9}$$

$$\Pi_0(\mathrm{CA}^{\mathrm{W}},\overline{p}_i,n,t,\beta_1) \;=\; (Nt-n)(\overline{p}_i-v_{\mathcal{N}}) - f_{DC} - nv_{DC} + \beta_1\,\mathbb{E}\left[S_1^{*,\mathrm{W}}(t)|\mu_0,n_0\right]. \tag{EC.10}$$

Adding (EC.9) and (EC.10), we obtain $S_0(\mathrm{CA}^{\mathrm{W}},n,t)$. The players aim to preserve the $[\beta,(1-\beta)]$ split of the joint surplus, $S_0(\mathrm{CA}^{\mathrm{W}})$, so that

$$V_0(\mathrm{CA}^{\mathrm{W}},\overline{p}_i,n,t,\beta_1) = (1-\beta)S_0(\mathrm{CA}^{\mathrm{W}}) \qquad \text{and} \qquad \Pi_0(\mathrm{CA}^{\mathrm{W}},\overline{p}_i,n,t,\beta_1) = \beta S_0(\mathrm{CA}^{\mathrm{W}}). \tag{EC.11}$$

The risk-sharing mechanism when OWR is the Nash outcome implies that the players use (EC.9)-(EC.11) to identify and contract upon a $\beta_1^{*,\mathrm{W}}$, 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 $n^{*,\mathrm{W}}$ and $t^{*,\mathrm{W}} = 2n^{*,\mathrm{W}}/(Nr_{max})$ identified in Appendix EC.3.2.2.

Prop. 6 and Corollary 4 indicate when $\beta_1^{*,\mathrm{W}}$ 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 $\overline{p}_i \geq p_i^{*,\mathrm{W}}$, therefore there is no need for a readjustment to gain-fractions at the reappraisal stage.

If $\overline{p}_i < p_i^{*,\mathrm{W}}$, the value of $\beta_1^{*,\mathrm{W}}$ is determined in a way to satisfy $\Pi_0(\mathrm{CA}^{\mathrm{W}}, \overline{p}_i, n^{*,\mathrm{W}}, t^{*,\mathrm{W}}, \beta_1) = \beta S_0(\mathrm{CA}^{\mathrm{W}})$. We define $\tilde{N} \triangleq Nt^{*,\mathrm{W}} - n^{*,\mathrm{W}}$ to simplify the expressions and use (19) and (EC.10):

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

And we solve the above equality for $\beta_1^{*,\mathrm{W}}$:

$$\beta_1^{*,\mathrm{W}} = \frac{\beta\tilde{N}(\mu_0 + p_{\mathcal{S}}) - \tilde{N}\overline{p}_i + (1-\beta)\left[f_{DC} + n^{*,\mathrm{W}} v_{DC} + \tilde{N} v_{\mathcal{N}}\right] + \beta\, \mathbb{E}\left[S_1^{*,\mathrm{W}}(t^{*,\mathrm{W}})|\mu_0, n_0\right]}{\mathbb{E}\left[S_1^{*,\mathrm{W}}(t^{*,\mathrm{W}})|\mu_0, n_0\right]}. \tag{EC.12}$$

Because the denominator in the right hand side of (EC.12) is positive, for case (ii) we then have $\beta_1^{*,\mathrm{W}} \leq 1$ if and only if:

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

where the second line directly follows from the definition of $p_i^{*,\mathrm{W}}$ in (20).

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

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

Moreover, $\beta_1^{*,\mathrm{W}} > 1$ also implies that $(1 - \beta_1^{*,\mathrm{W}})\, \mathbb{E}\left[S_1^{*,\mathrm{W}}(t^{*,\mathrm{W}})|\mu_0, n_0\right] < 0$, 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 $\overline{p}_i \geq p_i^{*,\mathrm{W}} - (1-\beta)\, \mathbb{E}\left[S_1^{*,\mathrm{W}}(t^{*,\mathrm{W}})|\mu_0, n_0\right]/\tilde{N}$, where $\tilde{N} \triangleq Nt^{*,\mathrm{W}} - n^{*,\mathrm{W}}$. We plug in the definition of $p_i^{*,\mathrm{W}}$ from (20) and $\overline{p}_i = \mu_0 + p_{\mathcal{S}}$:

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

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

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

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

and we rearrange terms to obtain

$$(1-\beta)(\mu_0+p_S)-(1-\beta)((v_{DC}n^{*,\mathrm{W}}+f_{DC})/\tilde{N}+v_{\mathcal{N}})+(1-\beta)\,\mathbb{E}\left[S_1^{*,\mathrm{W}}(t^{*,\mathrm{W}})|\mu_0,n_0\right]/\tilde{N}$$
$$=(1-\beta)S_0(\mathrm{CA}^{\mathrm{W}})/\tilde{N}\geq 0.$$

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

EC.4 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 EC.4.1 discusses how model parameters influence joint surpluses, player payoffs and prices. Appendix EC.4.2 discusses the sensitivity of Nash bargaining outcomes to model parameters.

EC.4.1 Sensitivity of Joint Surpluses, Player Payoffs and Prices to Key Model Parameters

Table EC.2 summarizes the derivatives of joint surpluses, $S_0(\mathrm{A}_0)$, $S_0(\mathrm{CA}^{\mathrm{I}})$, $S_0(\mathrm{CA}^{\mathrm{W}})$, 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 EC.4.1.1 and Appendix EC.4.1.2 present the algebra that leads to the results presented in Table EC.2, and Appendix EC.4.1.3 offers insights based on the comparative statics results for joint surpluses and prices.

EC.4.1.1 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 EC.3.2 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 $S_0(\text{CA}^\text{I})$, but the results continue to hold for $S_0(\text{CA}^\text{W})$. We start by defining some additional notation. We let $\mathbf{b}$ to contain all problem parameters, and we let $f(n;\mathbf{b}) = S_0(\text{CA}^\text{I}, n, 2n/(r_{max}N))$ 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 have the following form:

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

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

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

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:

$$\frac{\partial S_0(\text{CA}^\text{I})}{\partial b} = \frac{\partial f(n^*;\mathbf{b})}{\partial b} = \frac{\partial S_0(\text{CA}^\text{I}, n^*, 2n^*/(r_{max}N))}{\partial b}. \tag{EC.13}$$

For $S_0(\text{CA}^\text{I})$ and $S_0(\text{CA}^\text{W})$, 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.13) 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: $\mathrm{d}\psi(x)/\mathrm{d}x = \Phi(x) - 1$.

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

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

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

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

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 (11).

Second, we show that $S_0(\mathrm{CA}^{\mathrm{I}})$ is decreasing in n_0. We recall from (2) 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.

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

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 (11).

Second, we show that $S_0(\mathrm{CA}^{\mathrm{I}})$ is increasing in Σ_X. We recall from (2) 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 $\partial S_0(\mathrm{CA}^{\mathrm{I}}) / \partial \Sigma_X > 0$ 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 $S_0(\mathrm{CA}^{\mathrm{W}})$ is increasing in Σ_X following the same steps as we did for $S_0(\mathrm{CA}^{\mathrm{I}})$:

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

In turn, $\partial \sigma_{M_1} / \partial \Sigma_X > 0$ implies $\partial S_0(\mathrm{CA}^{\mathrm{W}}) / \partial \Sigma_X > 0$ 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 $S_0(\mathrm{A}_0)$, $S_0(\mathrm{CA}^{\mathrm{I}})$ and $S_0(\mathrm{CA}^{\mathrm{W}})$ 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 $S_0(\mathrm{A}_0)$, $S_0(\mathrm{CA}^{\mathrm{I}})$ and $S_0(\mathrm{CA}^{\mathrm{W}})$ 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 $S_0(\mathrm{CA}^{\mathrm{I}})$ and $S_0(\mathrm{CA}^{\mathrm{W}})$ are linearly decreasing in f_{DC}.

Variable Cost of Post-marketing Data Collection. First, it directly follows from its definition in (11) that $S_0(\mathrm{A}_0)$ is independent of v_{DC}.

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

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

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

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 $S_0(\mathrm{CA}^{\mathrm{I}})$ is increasing in N:

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

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

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

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

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

Bargaining Power. By definition, $S_0(\mathrm{A}_0)$, $S_0(\mathrm{CA}^{\mathrm{I}})$ and $S_0(\mathrm{CA}^{\mathrm{W}})$ are all independent of β.

EC.4.1.2 Derivations of Comparative Statics Results for Prices.

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.

Now we discuss the effect of problem parameters on the interim prices, p_i^* and $p_i^{*,\mathrm{W}}$. From their definitions in Prop. 3 and Prop. EC.2, we observe that both p_i^* and $p_i^{*,\mathrm{W}}$ depend on the optimal sample size of the post-marketing trial, n^* and $n^{*,\mathrm{W}}$. Therefore, it is not possible to unambiguously sign analytical expressions for the comparative statics of p_i^* and $p_i^{*,\mathrm{W}}$ if a parameter impacts the value of the optimal n.

We continue with parameters whose values does not impact the value of n^* of an OIR scheme. The objective function given in (13) is independent of β, therefore n^* does not depend on β. And f_{DC} does not show up in the first derivative of (13) with respect to n; therefore n^* also does not depend on f_{DC}. The partial derivative of p_i^* with respect to β and f_{DC} are

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

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 an OWR scheme, β and f_{DC} also do not impact the value of $n^{*,\mathrm{W}}$. The partial derivative of $p_i^{*,\mathrm{W}}$ with respect to β and f_{DC} are

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

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 $\mu_0 + p_{\mathcal{S}} - v_{\mathcal{N}} - \frac{n^{*,\mathrm{W}}v_{DC}+f_{DC}}{n^{*,\mathrm{W}}(2/r_{max}-1)} > 0$.

EC.4.1.3 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, $p_0^* = v_{\mathcal{N}} + \beta(\mu_0 + p_S - v_{\mathcal{N}})$, is higher when the prior mean and the price of the standard of care are higher and lower when the production cost is lower.

Unambiguously characterizing the effect of most 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. The fixed cost of the trial, f_{DC}, leads to an increase in the interim price because interim price acts as a cost-sharing mechanism.

The sensitivity of p_i^* to the bargaining power of the company, β, is discussed in §3.4 in detail. The sensitivity of $p_i^{*,\mathrm{W}}$ to β is analyzed in a similar manner, but the difference is that the balance is between p_0^* and $(1-\beta)(n^{*,\mathrm{W}} v_{DC} + f_{DC})/(n^{*,\mathrm{W}}(2/r_{max} - 1))$. We note that the second term is the total data collection cost of an OWR trial divided across all patients treated with the new treatment during the post-marketing data collection period, and the equivalent quantity under an OIR scheme would be $(1-\beta)(v_{DC} + f_{DC}/n^*)$.

EC.4.2 Sensitivity of the Nash Bargaining Outcomes to Key Model Parameters.

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. In §6.2, we numerically explore the sensitivity of Nash outcomes when an OWR scheme is also feasible.

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 EC.4.2.1, we start by analyzing the impact of key model

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

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 EC.4.2.2, we present the insights about the sensitivity of the Nash bargaining outcomes to model parameters.

EC.4.2.1 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 EC.4.1.1, we use the envelope theorem to obtain the values for $\partial(S_0(\mathrm{A}_0) - S_0(\mathrm{CA}^{\mathrm{I}}))/\partial b$.

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:

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

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:

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

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:

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

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}.

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.

EC.4.2.2 Sensitivity of the Nash Bargaining Outcomes to Key Model Parameters.

Figure EC.1 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.1a is higher than the one used in Figure EC.1b.

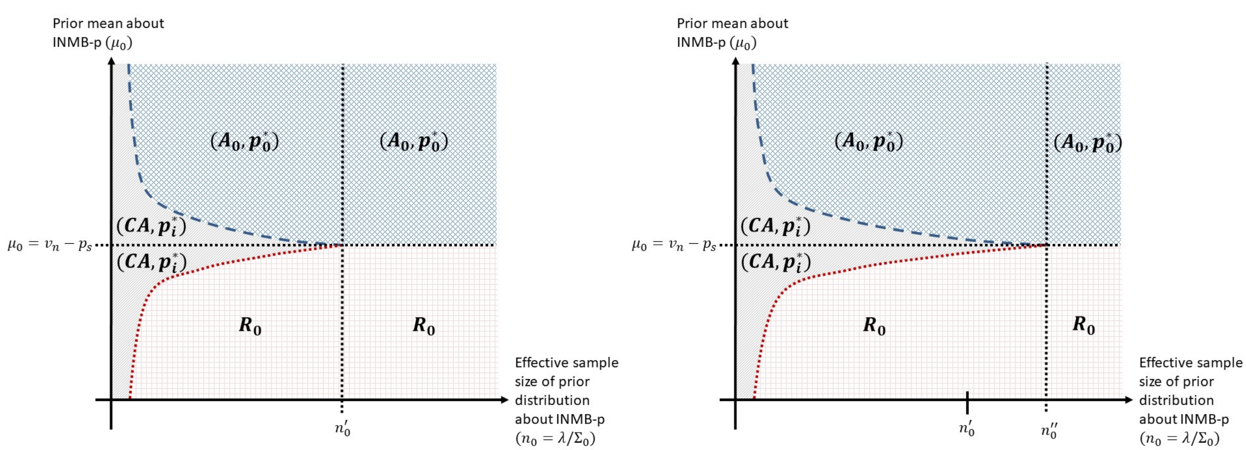
We use the results presented in Table EC.2 and Table EC.3 to show the existence and general structure of the regions shown in Figure EC.1. We start by deriving n_0' used in Figure EC.1a. If $\mu_0 = v_{\mathcal{N}} - p_{\mathcal{S}}$, then:

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

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.

Figure EC.1 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.



Now we show that n_0' in Figure EC.1a is always smaller than n_0'' in Figure EC.1b. 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 $\mu_0 = v_{\mathcal{N}} - p_S$ and $n_0 = n_0'$ in Figure EC.1a and Figure EC.1b, 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 $\mu_0 > v_{\mathcal{N}} - p_S$ 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.1a and Figure EC.1b) 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 $\mu_0 > v_{\mathcal{N}} - p_S$ and $n_0 > n_0'$. In this region, we have $S_0(\mathrm{A}_0) > 0$ because $\mu_0 > v_{\mathcal{N}} - p_S$, 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 $\mu_0 < v_{\mathcal{N}} - p_S$ and $n_0 < n_0'$. In this region. we have $S_0(\mathrm{A}_0) < 0$ because $\mu_0 < v_{\mathcal{N}} - p_S$. 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.1a and Figure EC.1b) on which

$S_0(\mathrm{CA^I}) = 0$, above which $S_0(\mathrm{CA^I}) > 0$ and below which $S_0(\mathrm{CA^I}) < 0$. 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 $S_0(\mathrm{CA^I}) < 0$ because $S_0(\mathrm{CA^I})$ 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.1a and Figure EC.1b 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 $\mathbb{E}[p_1^*|M_1 > v_{\mathcal{N}} - p_{\mathcal{S}}]$ 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.1b 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.1a. 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 $\partial(S_0(\mathrm{A_0}) - S_0(\mathrm{CA^I}))\big/\partial N \leq 0$ 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^*,

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 $f_r = £30 \times 10^7$	
	$p_i^{*,\mathrm{W}}$	$\mathbb{E}[p_1^{*,\mathrm{W}} \vert \text{Approval}]$	$p_i^{*,\mathrm{W}}$	$\mathbb{E}[p_1^{*,\mathrm{W}} \vert \text{Approval}]$	$p_i^{*,\mathrm{W}}$	$\mathbb{E}[p_1^{*,\mathrm{W}} \vert \text{Approval}]$
$\beta = 0.1$	6,263	4,990	6,446	4,946	6,525	4,928
$\beta = 0.3$	9,791	12,559	9,933	12,427	9,995	12,375
$\beta = 0.5$	13,318	20,128	13,420	19,908	13,464	19,822
$\beta = 0.7$	16,846	27,697	16,907	27,389	16,934	27,268
$\beta = 0.9$	20,374	35,266	20,394	34,870	20,403	34,715

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.

EC.5 Additional Numerical Results

We present additional numerical results related to the case study in §6.2, particularly to Table 1. Table EC.4 displays the interim price, $p_i^{*,\mathrm{W}}$, and the expected reappraisal price conditional on eventual approval, $\mathbb{E}[p_1^{*,\mathrm{W}} | \text{Approval}]$, for three different values of the cost of reversal, f_r. Recall that OWR is the Nash bargaining outcome only when $f_r < £24 \times 10^7$. Table EC.4 displays that the impact of f_r on the bargaining prices is minimal, and the observations made in §6.2 for $f_r = 0$ continues to hold for other values of f_r.

References

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