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Late-Stage Pharmaceutical R&D and Pricing Policies under Two-Stage Regulation

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Abstract

We present a model combining the two regulatory stages relevant to the approval of a new health technology: the authorisation of its commercialisation and the insurer's decision about whether to reimburse its cost. We show that the degree of uncertainty around the true value of the insurer's maximum willingness to pay for a unit increase in effectiveness has a non-monotonic impact on the price of the innovation, the firm's expected profit and the optimal sample size chosen for the clinical trial. A key result is that there exists a range of values of the uncertainty parameter over which a reduction in uncertainty benefits the firm, the insurer and patients. We consider how different policy parameters may be used as incentive mechanisms, and the incentives to invest in R&D for marginal projects such as those targeting rare diseases. The model is calibrated using data on a new treatment for cystic fibrosis.

JEL codes: L5, H51, I11, I18
Keywords: Rare Diseases; Pharmaceutical Pricing and Reimbursement; Optimal Sample Size

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1 Introduction

The fast pace of growth of health care expenditure relative to GDP growth that has been experienced by most developed countries, especially prior to the global economic crisis (OECD, 2013), has led regulators to look for innovative solutions to deal with the increasing demands on health care budgets. With a general consensus that technological innovation plays a central role in driving increased costs (Weisbrod, 1991), much effort has been targeted towards the process by which new technologies are adopted and priced. The aim has been to reduce two types of risk faced by regulators: paying for technologies that are not 'good value for money' and adopting technologies whose effectiveness, once deployed, is lower than the efficacy that was demonstrated in the clinical trials upon whose results the adoption decisions were made (Eichler et al., 2011).

Including an assessment of a new health technology's cost-effectiveness has been a common response to the first risk. However, the precise role played by cost-effectiveness results in determining adoption decisions is less than transparent. Even the National Institute for Health and Care Excellence (NICE) in the UK, probably one of the most open institutions in this respect, does not refer to a single value for the cost-effectiveness threshold, but to a range of between £20,000 and £30,000 per Quality Adjusted Life Year gained (NICE, 2008). Running a high quality, large, Phase III trial is instrumental in mitigating the second risk. However, in recent years, there has been a growing interest in risk-sharing agreements (Pita Barros, 2011; Towse and Garrison, 2010; Cook et al., 2008).

Somewhat surprisingly, as health care insurers have grown more concerned about technology-induced expenditure growth, suppliers of innovations have witnessed a substantial reduction in the number of new drugs approved per billion of US dollars spent on R&D (Scannell et al., 2012; Pammolli et al., 2011) and an increase in the average cost of development of a new drug (DiMasi et al., 2003). This has inspired investigation into the impact of specific regulatory decisions on the incentives to invest in R&D by the industry, including price regulation (Filson, 2012), cost-effectiveness thresholds (Jena and Philipson, 2008), value-based pricing (Danzon et al., 2015) and risk-sharing agreements (Levaggi et al., 2015). Empirical evidence suggests that tighter regulation presents weaker incentives for the industry to invest in R&D, and a delay in the adoption of innovations (Danzon and Epstein, 2008; Golec et al., 2010; Vernon, 2005; Danzon et al., 2005; Kyle, 2007).

The tension between the objective of curbing expenditure on health technologies that are already available in the market and the need to incentivise investment in R&D that will lead to future innovations is known as the trade-off between static and dynamic efficiency. However, equity concerns may also be relevant. For a regulatory framework which does not explicitly account for the size of the population to be treated, incentives to invest in R&D are weaker for technologies targeting comparatively rare diseases ('orphan diseases'). One reason why these are comparatively unattractive areas for R&D investment is that predicted sales revenue is proportional to the size of the population to treat, while R&D expenses are largely independent of it (Acemoglu and Linn, 2004; Dimitri, 2012). Moreover, for rare diseases, meeting the requirements set by authorities regulating market access may be more costly, and require a longer period for experimentation, due to the availability of a smaller population from which to obtain a sample.

Hence, disincentives for research into rare diseases may be found at both the commercialisation and the development, stage.

A new drug needs to pass two key regulatory stages if it is to be approved for use by a health care insurer. Firstly, it must be deemed to be safe and efficacious. If these conditions are met, the drug can be used, but it must be fully paid for by the patient. If, as is often the case, the majority of the cost is paid by an (often public) health insurer, that insurer must then decide whether the drug can be reimbursed at a particular price. This price is determined according to rules which vary considerably from country to country. The importance of the cost-effectiveness dimension has been growing in recent years. As a result, Phase III clinical trials, which previously aimed only to assess effectiveness, are often accompanied by an economic evaluation.

This paper presents a unified, Bayesian decision-theoretic framework for the analysis of these two regulatory stages, so as to investigate how late-stage R&D incentives for the pharmaceutical industry are determined by the interactions between key parameters and policy variables at each stage. We model a health technology provider operating within a defined jurisdiction (such as at the country level) and define its optimal sampling and pricing policies in a two period problem. In the first period, the provider decides whether to run a Phase III trial and, if it does so, the trial's sample size. In making its decision, the provider knows that, should the regulatory authority which reviews the trial evidence deem the treatment to be effective at a predefined level of statistical significance, the provider may apply for reimbursement by a health care insurer in the second period. This involves proposing a price for the new product which, when combined with the evidence on effectiveness provided by the trial, determines the incremental cost-effectiveness ratio upon which the health care insurer bases its reimbursement decision.

To the best of our knowledge, our model is the first to present a full analysis of how the 'double hurdle', in the form of the regulatory authority and the health care insurer, affects optimal pricing policies, expected profit and sample sizes. A key result is that the degree of uncertainty around the true value of the insurer's maximum willingness to pay for a unit increase in effectiveness has a non-monotonic impact on the optimal price of the innovation, the firm's expected profit and the optimal sample size chosen for the Phase III clinical trial investigating the technology's efficacy. This implies that there exists a range of values of the uncertainty parameter over which a reduction in uncertainty benefits the firm, the insurer and patients. Subsequent analysis considers how the regulatory framework may influence a health technology provider's incentive to invest in projects which are deemed by the provider to be 'marginal', that is, ones for which the expected profit is close to zero, by looking at the incentive to research treatments for rare diseases. In particular, we characterize the minimum size of a population to treat such that the firm is incentivised to invest in the development of a new drug. In an application using published data from trials of a new treatment for cystic fibrosis, we show how parameters and regulatory policies in both periods, such as the level of the Type I error that characterises the regulatory authority's decision and the level of the expected value of the incremental cost-effectiveness ratio (ICER) threshold that is set by the insurer, can affect the incentives to invest.

Section 2 presents a brief summary of the literature. Section 3 introduces the model, which is solved in Section 4. Section 5 presents the application. Section 6 discusses some of the main results, avenues for future research and concludes.

2 Background

The work builds on a number of statistical and economic approaches to Phase III trial design, drug approval decisions and research on rare diseases. Kikuchi and Gittins (2009) and Kikuchi et al. (2008) propose a 'Behavioural Bayes' (BeBay) model of sample size determination in a Phase III trial which accounts for the costs and benefits of the trial as well as the deployment of the new treatment. The model is 'behavioural' because, following the ideas of Gittins and Pezeshk (2000), although it maximises total expected net benefit from the perspective of the firm developing the drug, the behaviours of the regulator and users of the drug are not assumed to be optimal. The authors model the level of demand for the new treatment as an increasing function of the point estimate of effectiveness from the trial. Willan (2008) and Willan and Eckermann (2010) present Bayesian models of drug development in which the optimal sample size is chosen to maximise the expected value of sample information minus the costs of the trial.

Acemoglu and Linn (2004) consider the effect of the potential size of markets on pharmaceutical innovation and entry of new drugs. The authors derive an equilibrium condition for the levels of R&D effort and show that, the greater is the market size, the more profitable it is to supply the drug and so the greater will be the research effort required to gain market-leader position. Magazzini et al. (2013) consider the effects of R&D sunk cost and market size on a pharmaceutical company's decision to enter a clinical trial. They present a two-stage model with a number of firms which can enter one or more therapeutic submarkets and compete for customers. In line with Acemoglu and Linn, the authors predict that, the greater is the market size, the higher is the total R&D investment. With lower success rates and a higher cost per trial, fewer firms enter clinical testing. Further, an increase in sunk R&D expenditures lowers the number of trials and firms. Pennings and Sereno (2011) present a real options model of evaluating pharmaceutical R&D under what they term 'technical' and 'economic' uncertainty. They recognise the risk of failure (for example, due to safety issues) during drug development, but do not model clinical trial design or pricing for HTA approval. Dranove and Meltzer (1994) are concerned with the time for new medical entities to be approved in the US and conclude that, since the 1950s, more important drugs do indeed reach the market sooner than less important ones.

These models are important precursors to ours, but none of them explicitly combines the optimal choice of a trial's sample size with a price-setting rule, in the presence of uncertainty surrounding the health care insurer's maximum willingness to pay for a unit increase in effectiveness.

3 The model

We take the perspective of a Health Technology Provider (HTP) considering whether to commission a Phase III clinical trial to evaluate the efficacy of a new drug. If a trial is commissioned, upon its completion, a Regulatory Authority (RA) in charge of granting access to a market with k patients considers the evidence concerning the drug's efficacy, defined as the point estimate of incremental effectiveness, $\bar{x}$, together with its standard error. We call this stage – trial commissioning, conduct and RA assessment – 'Stage 0'. If RA approval is granted, the HTP tries

to have the new drug reimbursed by a Health Care Insurer (HCI) by proposing a price, $c > 0$, for the treatment of a single patient. This stage is called 'Stage 1'. The HTP's choice variables are therefore the following: 1. the Stage 0 decision of whether or not to commission a trial and, if a trial is commissioned, what its sample size, n, should be; 2. in the event that RA approval is granted, the Stage 1 decision of proposing a price to the HCI. The HTP's 'planning horizon', over which optimisation takes place, comprises both Stage 0 and Stage 1.

Let μ_X be the expected value of the incremental effectiveness (assumed unknown to all agents) of the new treatment versus standard in the population. We assume that the trial is placebo-controlled, an assumption which may be justified when there exists no approved treatment, or when the new treatment is given as an add-on to existing standard treatment.

It is assumed that the n responses observed in the trial are used to calculate the sample mean $\bar{X}$, an unbiased and consistent estimator of μ_X:

$$\bar{X} \mid \mu_X \sim \mathrm{N}\left(\mu_X, \frac{\sigma_X^2}{n}\right), \tag{1}$$

where σ_X is assumed known to all agents. We use the convention that upper case denotes a random variable (e.g., at the start of the planning horizon, $\bar{X}$ is a random variable) and lower case denotes its realisation (e.g., at the end of Stage 0, once the trial has concluded, $\bar{x}$ denotes the realisation of $\bar{X}$).

3.1 The Regulatory Authority

Conditional upon meeting a requirement for a minimum sample size, $n_{\min}$ for the trial, the RA's decision is based upon classical frequentist statistical criteria, so that the new treatment is required to show superiority to placebo at a given one-sided level of statistical significance, α, where α is conventionally taken to be 2.5% (Food and Drug Administration, 1998). Hence, approval for the new treatment will be granted if and only if

$$\bar{x} \geq h(n) \equiv \frac{z_\alpha \sigma_X}{\sqrt{n}} > 0 \text{ and } n \geq n_{\min}, \tag{2}$$

where z_α is the critical value for a standard normal random variable at α. If this condition is not satisfied, the treatment is rejected by the RA and is not taken forward to Stage 1. If the condition is satisfied, the HTP proceeds to Stage 1 and aims to have the cost reimbursed by the HCI.

3.2 The Health Care Insurer

The HCI aims to ensure that only innovations that are deemed to be 'good value for money' are reimbursed. It compares $\bar{x}$ with the price, c, proposed by the HTP, using the incremental cost effectiveness ratio (ICER). We ignore differences in costs which are not directly related to the cost of the drug, implying that the ICER considered by the HCI is $c \,/\, \bar{x}$. The drug is approved if the proposed ICER is less than, or equal to, the HCI's maximum willingness to pay (WTP) for an additional unit of effectiveness. The HTP does not know the value of the HCI's maximum

WTP. Instead, it considers the value to be a continuous random variable, Y, with cumulative probability distribution F_Y.

Let $\nu > 0$ and $\omega > 0$ be respectively the location and scale parameter of F_Y. Following the ideas in Van den Berg (2007) and Johnson and Myatt (2006), we introduce the following assumptions:

A1 (Ordering by increasing variance).
F_Y is assumed to have the form $F_Y(\, y;\, \nu,\, \omega\,) = F_T\left(\frac{y-\nu}{\omega}\right)$, where F_T is a twice continuously differentiable distribution of the random variable $T = \frac{Y-\nu}{\omega}$ whose expected value is equal to 0.

A2 (Increasing hazard rate).
The hazard rate of F_T, $r_T(t) = f_T(t)/(1 - F_T(t))$, satisfies $r'_T(t) > 0$.

A1 implies that F_Y belongs to the location-scale family defined by F_T. In the terminology of Johnson and Myatt (2006), it also implies that the family of distributions F_Y is ordered by increasing variance. This means that a change in the scale parameter ω rotates F_Y around the location parameter ν such that F_Y increases/decreases in ω according to whether Y is less than/greater than ν (see Figure 1). This property moves density from the centre of the distribution to the tails, whilst ensuring that the distribution functions cross only once. Formally, taking the partial derivative of F_Y with respect to ω,

$$y \gtreqless \nu \iff \frac{\partial F_Y}{\partial \omega} \lesseqgtr 0. \tag{3}$$

Note that the hazard rate for F_Y is given by $r_Y(y) = r_T\left(\frac{y-\nu}{\omega}\right)/\omega$[1]. **A2** may best be interpreted by referring to the concept of increasing duration dependence borrowed from the survival analysis literature: $r'_T(t) > 0$, giving $r'_Y(y) > 0$, implies that, in a 'guessing game' in which the HTP seeks to discover the HCI's maximum WTP by starting with a guess of 0 and then increasing that guess on Y's (continuous) support, the probability that the maximum WTP is affirmed to be just above y, given that it has not already been affirmed, is increasing in y.

A1 and **A2** are plausible assumptions, which are satisfied by very common distributions like, among others, the normal and the logistic.

3.3 The Health Technology Provider's Problem

At the beginning of Stage 0, the HTP must decide whether or not it should enter Phase III clinical testing and, if it does, the optimal sample size for the trial. The cost of performing the trial is assumed to be $I_0 + dn$, where $I_0 > 0$ is the fixed cost of setting up the trial and $d > 0$ is the cost of increasing the sample size by one unit.

The HTP encodes its uncertainty on μ_X using a normal prior density with mean μ_0 and standard deviation σ_0. The HTP uses the prior predictive distribution for $\bar{X}$ to compute the Stage 0 profit as the expected value of the optimal Stage 1 profit, minus the trial costs. Viewed from the

[1]Since $f_Y(y) = f_T\left(\frac{y-\nu}{\omega}\right)/\omega$, $r_Y(y) = \left(f_T\left(\frac{y-\nu}{\omega}\right)/\omega\right)/\left(1 - F_T\left(\frac{y-\nu}{\omega}\right)\right) = r_T\left(\frac{y-\nu}{\omega}\right)/\omega$.

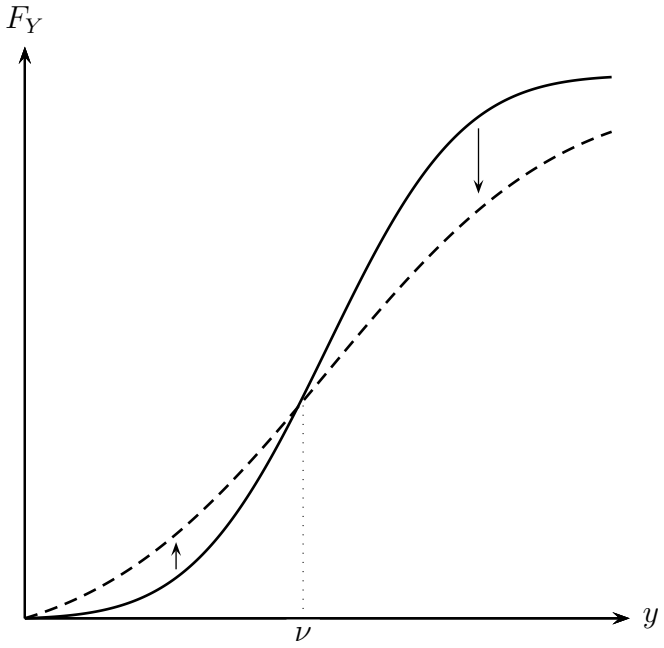


Figure 1: Rotation of F_Y around ν following an increase in ω

start of Stage 0, this prior predictive distribution is normal with mean μ_0 and standard deviation $\sqrt{\sigma_0^2 + \sigma_X^2/n}$ (Pratt et al., 1995).

Once the trial has taken place and $\bar{x}$ is known, if Eq. (2) is satisfied, so that RA approval is granted, the HTP's Stage 1 problem is to propose a price, c, to the HCI. We assume that the fixed cost of commercialising the drug, together with the marginal production cost, equal zero. This is plausible if production costs are negligible relative to R&D costs, which is true for most pharmaceuticals (Newhouse, 2004; JH and EJ, 2005). In Section 5 we relax this assumption and show that it does not affect the qualitative nature of our main findings.

The HCI will adopt the new drug with probability $1 - F_Y\,(\,c\,/\,\bar{x}\,;\nu,\,\omega\,)$. If the drug is not approved for reimbursement the HTP makes zero profits. Define $\boldsymbol{\beta} \equiv (\,k, \bar{x},\,\nu,\,\omega\,)$. If the HCI approves the drug for reimbursement, profits are $\Pi_1(\,c;\,\boldsymbol{\beta}\,) = k\,c$, implying that the Stage 1 expected profit function is:

$$\Gamma_1(\,c;\,\boldsymbol{\beta}\,) = \mathbb{E}\,[\,\Pi_1(\,c;\,\boldsymbol{\beta}\,)\,] = k\,c\,[\,1 - F_Y\,(\,c\,/\,\bar{x}\,;\nu,\,\omega\,)\,]\,. \tag{4}$$

4 Optimal Stage 0 and 1 policies

The HTP's problem is solved by backward induction. Firstly, it must establish an optimal Stage 1 pricing policy as a function of the realisation $\bar{x}$ that results from the trial. Then it must solve the Stage 0 problem, using the prior predictive distribution for $\bar{X}$ to establish the trial's optimal sample size, taking into account its optimal Stage 1 pricing policy. This will determine the

expected value of the whole project and therefore the decision about whether or not to invest.

4.1 Optimal Stage 1 pricing policy

Use * to denote an optimal value. Given RA approval, the HTP solves

$$\Gamma_1^*(\boldsymbol{\beta}) \equiv \max_{c>0} \Gamma_1(c; \boldsymbol{\beta}) = \max_{c>0} k\, c\, [1 - F_Y(c / \bar{x}; \nu, \omega)]. \tag{5}$$

Since k is constant, it will not affect the optimal price. Moreover, because $\bar{x}$ is known at the start of Stage 1, choosing c optimally implies choosing the optimal level of the ICER, defined as $\gamma = c / \bar{x}$. Hence, solving Eq. (5) is equivalent to solving

$$\max_{\gamma>0} \gamma\, [1 - F_Y(\gamma; \nu, \omega)].$$

The optimal price and profit may then be expressed in terms of $\gamma^*(\nu, \omega)$ as

$$c^*(\boldsymbol{\beta}) = \bar{x}\gamma^*(\nu, \omega), \tag{6}$$

$$\Gamma_1^*(\boldsymbol{\beta}) = \bar{x}\eta^*(k, \nu, \omega), \quad \text{where } \eta^*(k, \nu, \omega) \equiv k\gamma^*(\nu, \omega)\,[1 - F_Y(\gamma^*(\nu, \omega); \nu, \omega)]. \tag{7}$$

The first order condition for the optimal choice of γ may be written as

$$1 - F_Y(\gamma; \nu, \omega) - \gamma f_Y(\gamma; \nu, \omega) = 0, \tag{8}$$

or, equivalently,

$$\gamma r_Y(\gamma; \nu, \omega) = 1. \tag{9}$$

By Assumption **A1**, an optimal solution to the maximisation problem exists and satisfies Eq. (8) (Van den Berg, 2007). Assumption **A2** implies that $r_Y(\gamma; \nu, \omega)$ is strictly increasing in γ, so that the solution $\gamma^*(\nu, \omega)$ of Eq. (9) must be unique.

The Stage 1 problem may be thought of as a monopolist's pricing problem, in which marginal cost is equal to zero and there exists a true, fixed, maximum willingness to pay for the new drug which is not known for sure by the HTP but which is, instead, described by a probability distribution. The problem is also similar in nature to that of other models, such as a standard independent private value auction (Van den Berg, 2007). It is clear from Eq. (5) that $1 - F_Y(c / \bar{x}; \nu, \omega)$ can be interpreted as a demand function (decreasing in c and therefore in γ). Figure 2 plots the demand function (solid line), which is also the first part of Eq. (8), and the whole LHS of Eq. (8) (dashed line). γ^* corresponds to the point where the dashed line crosses the horizontal axis. Note that according to Assumption **A1**, an increase in ω rotates F_Y clockwise (Figure 1) and the demand function counter-clockwise, both around ν. The change in the slope of the demand function affects the value of γ^* through Eq. (8).

It is shown in Appendix A.1 that the following results hold for the comparative statics of the optimal expected Stage 1 profit Γ_1^*,

$$\text{(i)} \quad \frac{\partial \Gamma_1^*}{\partial k} > 0; \quad \text{(ii)} \quad \frac{\partial \Gamma_1^*}{\partial \bar{x}} > 0; \quad \text{(iii)} \quad \frac{\partial \Gamma_1^*}{\partial \nu} > 0, \tag{10}$$

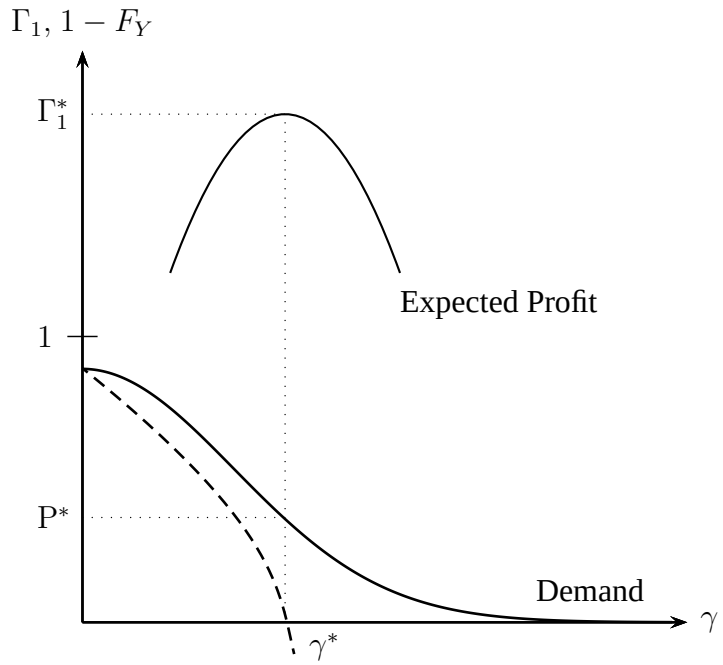


Figure 2: Optimal proposed ICER, probability of acceptance and expected profit for the HTP.

and the optimal price c^*,

$$\text{(i)} \quad \frac{\partial c^*}{\partial k} = 0; \quad \text{(ii)} \quad \frac{\partial c^*}{\partial \bar{x}} = \gamma^*(\nu, \omega) > 0, \quad \text{(iii)} \quad \frac{\partial c^*}{\partial \nu} > 0. \tag{11}$$

The result for the effect of an increase in the population size on the optimal profit and price is unsurprising (refer to Eq. (5)) since k affects the level of maximum profit, but not the profit-maximising price that the HTP proposes. By Eqs. (6) and (7) both the optimal price and profit are linear in $\bar{x}$, which is an important property when moving to the analysis of Stage 0.

We now consider the comparative statics with respect to the degree of uncertainty surrounding the true value of the HCI's WTP. The results are summarized in the following two propositions:

Proposition 1 (Impact of ω on Stage 1 optimal expected profit).
The optimal Stage 1 profit is a U-shaped function of ω, with a global minimum at $\hat{\omega} = \nu r_T(0)$. Moreover, $\nu \lesseqgtr \gamma^*(\nu, \omega) \iff \hat{\omega} \lesseqgtr \omega$.

Proof: See Section A.1 of the Appendix.

Note that Proposition 1 contains a result for the value of γ^* relative to ν according to the value of ω relative to $\hat{\omega}$. Concerning the response of γ^* to changes in ω, in Proposition 2 a sufficient condition is introduced that, by ensuring that $\partial\gamma^*/\partial\omega$ is an increasing function of ω, implies a U-shape also for c^* as a function of ω. The assumption involves Mill's ratio, defined as $m(t) = 1/r_T(t)$.

Proposition 2 (Impact of ω on Stage 1 optimal price).
If the Mill's ratio m satisfies $m'' > 0$, then the optimal price is a U-shaped function of ω, with a global minimum at some $\tilde{\omega} < \hat{\omega}$.

Proof: See Section A.1 of the Appendix.

It is worth mentioning that the additional sufficient condition on Mill's ratio holds for very common distributions such as the normal and the logistic.

The economic intuition for this result is as follows. When the uncertainty surrounding the true value of the maximum WTP is relatively small, the mass of the distribution of Y is concentrated around its expected value. Hence, if ω increases, a small reduction in the proposed price keeps the probability of adoption by the HCI comparatively high, while causing just a small reduction in the value of revenues conditional upon adoption. Hence c^* decreases with ω. On the other hand, if ω is very large small reductions of c affect the probability of adoption only marginally. Hence, if ω increases, it is then optimal to increase c^*.

The combination of Proposition 1 and 2 bears relevant policy implications, because it means that for ω sufficiently large ($\omega > \hat{\omega}$), by reducing the uncertainty around the true WTP for incremental effectiveness (i.e. by being more explicit about the decision process that leads to adoption/rejection decision) the HCI would induce HTPs to propose lower prices and accept lower expected profits. When there is small uncertainty ($\omega < \tilde{\omega}$) the same policy would lead to the opposite result, i.e. higher prices and higher expected profits. Interestingly, for intermediate values ($\tilde{\omega} < \omega < \hat{\omega}$), both parties would benefit from the greater transparency because optimal prices would be reduced and optimal expected profits increased. The reason is that with less uncertainty HTPs would decide to propose lower prices, but the increase in the probability of acceptance that this would imply is such that expected profits would be higher. Figure 4(a) of the application shows the three regions of ω for which these various effects may be observed.

4.2 The HTP's Stage 0 optimal policy

In Stage 0, the HTP first decides whether to invest in the R&D project, and then, if it does, the trial sample size. As usual, the model is solved backwards.

4.2.1 Optimal sample size determination

From the perspective of the start of Stage 0, define $\Gamma_0(n; k, \nu, \omega, I_0, d)$ as the expected reward of running a Phase III trial with a sample size n and pricing optimally during Stage 1 according to the policy defined in Section 4.1. From the perspective of Stage 0, the estimate of incremental effectiveness from the trial is a random variable, $\bar{X}$, which affects Γ_1^* via c^*. The Stage 0 optimal choice of n must therefore be computed using the prior predictive distribution for $\bar{X}$. Hence, by the linearity of Γ_1^* in $\bar{x}$ (see Eq. (7)), Γ_0 is given by

$$\Gamma_0(n; k, \nu, \omega, I_0, d) = \eta^*(k, \nu, \omega)\mathbb{E}\Big[\, \bar{X} \mid \bar{X} > h(n) \,\Big]\mathcal{P}(\, \bar{X} > h(n)\,) - (I_0 + dn). \tag{12}$$

$\mathcal{P}$ is the probability that the realisation of $\bar{x}$ from the trial exceeds the RA's lower acceptance threshold, $h(n)$:

$$\mathcal{P}(\,\bar{X} \,>\, h(n)\,) \,=\, 1 \,-\, \Phi(\,\sigma_p(n),\, h(n)\,), \tag{13}$$

where $\sigma_p(n) = \sqrt{\sigma_0^2 + \sigma_X^2/n}$ is the standard deviation of the predictive distribution for $\bar{X}$ and Φ is the CDF of the predictive distribution.

Recalling from Section 3.1 that n_{min} is the minimum sample size required by the RA, the Stage 0 problem to be solved by the HTP is the following:

$$\Gamma_0^*(k, \nu, \omega, I_0, d) \equiv \max_n \Gamma_0(n; k, \nu, \omega, I_0, d), \quad \text{subject to } n \geq n_{\text{min}}. \tag{14}$$

Eq. (13) shows that, when considering the optimal choice of the sample size of the trial at Stage 0, the HTP must account for two effects of a change in n, in addition to the cost of sampling: the impact on the standard deviation of the predictive distribution, σ_p, and the fact that raising the sample size lowers the acceptance threshold, h.

The solution to Eq. (14) is characterized by the following conditions:

$$\frac{\partial \Gamma_0(\cdot)}{\partial n}\Big|_{n^*} \leq 0,\;\; n^* - n_{\text{min}} \geq 0,\;\; (n^* - n_{\text{min}})\frac{\partial \Gamma_0(\cdot)}{\partial n}\Big|_{n^*} = 0. \tag{15}$$

For an interior solution, the optimality condition can be written as:

$$\eta^*(k, \nu, \omega)\frac{\mathbb{E}[\,\bar{X} \,|\, \bar{X} > h(n)\,]\mathcal{P}(\,\bar{X} \,>\, h(n)\,)}{n}\Big(e_{\mathbb{E}[\cdot],n} + e_{\mathcal{P}(\cdot),n}\Big) = d. \tag{16}$$

The marginal benefit is equal to the per-study-subject expected reward – the product of $\mathbb{E}[\,\bar{X} \,|\, \bar{X} \,>\, h(n)\,]$ and $\mathcal{P}(\,\bar{X} \,>\, h(n)\,)$ – valued in monetary terms using $\eta^*(k, \nu, \omega)$, multiplied by its elasticity (which, by a standard result for the elasticity of a product, is equal to the sum of the elasticities that is shown in Eq. (16)). The per-study-subject expected reward will be strictly positive because $h(n_{\text{min}})$ can never be less than zero. Hence the sign of the marginal benefit function is determined by the signs and sizes of the two elasticities. Since both $\mathbb{E}[\,\bar{X} \,|\, \bar{X} \,>\, h(n)\,] > 0$ and $\mathcal{P}(\bar{x} > h(n)) > 0$, the sign of each elasticity depends on the sign of the partial derivative that it contains.

In general, marginal benefit may be an increasing or decreasing function of n. There will exist a unique optimal value of $n^* > n_{\text{min}}$ if there is a single point where the first order condition is satisfied and the marginal benefit function is falling. This situation is illustrated in Figure 3. A full characterization of the Stage 0 optimality condition is hard to obtain, because a marginal increase in n produces several effects, which may operate in opposite directions. Here, we state some comparative statics results for Stage 0 for the case of a unique $n^* > n_{\text{min}}$.

Proposition 3 (Impact of ω on Stage 0 optimal expected profit and optimal sample size).
(a) If F_Y satisfies the assumptions of Section 3 and Γ_0^* is as defined in Eq. (14) then:

$$\frac{\partial \Gamma_0^*}{\partial \omega} \gtreqless 0 \iff \omega \gtreqless \hat{\omega}. \tag{17}$$

(b) Suppose F_Y satisfies the assumptions of Section 3 and that $n^*(k,\nu,\omega) > n_{min}$ solves Eq. (15) uniquely in some open set Ω. Suppose further that the conditions required for applying the Implicit Function Theorem in the computation of $\partial n^*/\partial\omega$ are fulfilled. Then, for $(k,\nu,\omega) \in \Omega$:

$$\frac{\partial n^*}{\partial \omega} \gtreqless 0 \iff \omega \gtreqless \hat{\omega}. \tag{18}$$

Proof: See Section A.2 of the Appendix.

Using the same methods of proof, it also follows that, under the assumptions leading to Eq. (17),

$$\text{(i)} \quad \frac{\partial \Gamma_0^*}{\partial k} > 0; \quad \text{(ii)} \quad \frac{\partial \Gamma_0^*}{\partial \nu} > 0, \tag{19}$$

and under the assumptions leading to Eq. (18),

$$\text{(i)} \quad \frac{\partial n^*}{\partial k} > 0; \quad \text{(ii)} \quad \frac{\partial n^*}{\partial \nu} > 0. \tag{20}$$

From the results above two policy implications which are relevant to our analysis follow. First, an increase in the expected value of the maximum WTP not only increases the expected profit of the project, but also the optimal sample size and hence the reliability of the trial, by increasing the marginal benefit of sampling. Second, since n^* decreases with a decreasing population size, $n_{\min}$ is more likely to be a binding constraint for rare diseases. The role of this regulatory parameter will be investigated in Section 5.

4.2.2 Investment decision

The dynamic efficiency implications of the regulatory framework, i.e., its ability to provide incentives for the HTP to invest in R&D can be assessed by considering the HTP's decision at the start of Stage 0. The project will be started if and only if $\Gamma_0^*(k,\nu,\omega,I_0,d) > 0$. Since $\Gamma_0^*(k=0) < 0$ and given Eq. (19(i)), this allows us to define the minimum size of a population to treat, such that the expected profit of investing in the development of a new treatment is positive:

$$k_{\min} = \min\left\{k \,\|\Gamma_0^*(k,\cdot) > 0\right\}. \tag{21}$$

This definition is required for some of the analysis of the incentives to invest in trials for rare diseases that is presented in Section 5.

5 Application

In this section we provide a calibrated application of the theoretical model, which we believe is important for a number of reasons. Firstly, it permits us to provide tentative estimates of the quantitative impact of changes in some key parameters on optimal values, using published data.

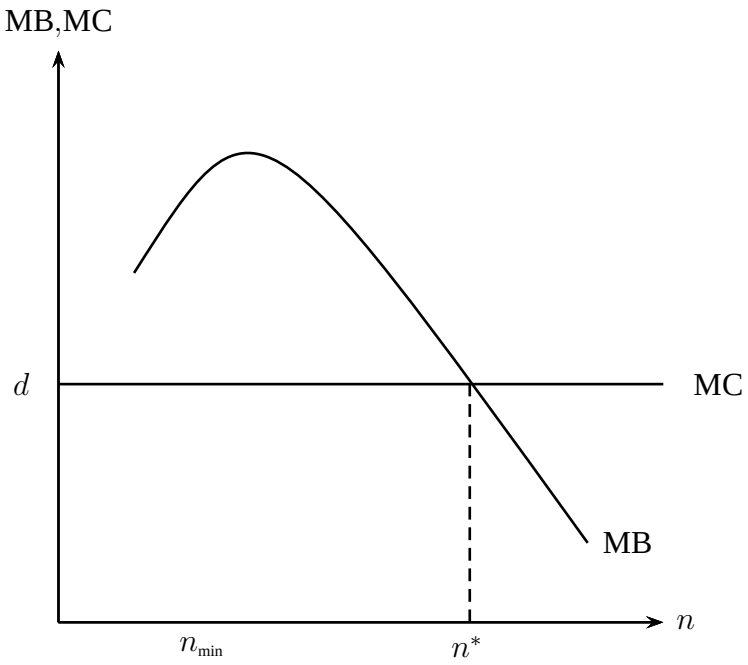


Figure 3: Determination of an interior solution for the optimal sample size (Eq. (16))

Secondly, the theory has highlighted the U-shaped nature of optimal pricing, profits and samples size and an application allows us to explore this in more details. Finally, we generalise the theory a little, which allows us to investigate the role of some additional policy parameters. Of course, the numerical results obtained in this section are valid for the specific setting under consideration and cannot be easily extended to different applications.

For the model to be operationalized, a specific functional form for F_Y must be specified. We use the logistic distribution, which satisfies all of the assumptions of Section 3.2 and the sufficient condition of Proposition 2. Moreover, it has been used for a recent empirical analysis of how estimates of cost-effectiveness and other variables affect NICE decisions (Dakin et al., 2014). The assumption of a logistic distribution for F_Y means that the probability that the HCI adopts the new technology in Stage 1 can be written as,

$$1 - F_Y\left(\, c \,/\, \bar{x} \,;\nu,\, \omega \,\right) = \left(1 + \exp\left(\frac{c/\bar{x} - \nu}{\omega}\right)\right)^{-1}. \tag{22}$$

Throughout Sections 3 and 4 we maintained the assumption of no cost to produce or commercialize the drug if it is approved for reimbursement by the HCI. This allowed us to simplify the proofs of some of the results, in particular concerning the choice of the optimal sample size in Stage 0. In order to enrich the contribution of our application, we relax this assumption by introducing the parameter $c_p(k) \equiv I_1/k + b > 0$, which is the production cost per patient treated. $I_1 > 0$ is a fixed investment cost and $b > 0$ is a constant marginal cost of production. Hence, the

Stage 1 expected profit function may be rewritten as

$$\Gamma_1(\, c;\, \boldsymbol{\beta}\,) = \mathbb{E}\,[\,\Pi_1(\, c;\, \boldsymbol{\beta}\,)\,] = k(c - c_p(k))\,[\,1 - F_Y\,(\, c\,/\,\bar{x}\,;\nu,\,\omega\,)\,]\,. \tag{23}$$

As anticipated, this does not alter the qualitative nature of our main results. In particular, it may be shown that the U-shaped nature of the optimal Stage 1 profit and optimal price functions (Propositions 1 and 2) remain unchanged provided that $\nu > c_p(k)/\bar{x}$. This is a reasonable condition, since it simply requires that the price that the HTP would set if it were known, with certainty, that the HCI's WTP is ν, would exceed $c_p(k)$. The main differences are that the optimal price is no longer independent of k, but decreasing in it, and the optimal ICER is no longer independent of $\bar{x}$. This in turn implies that the optimal Stage 1 profit is no longer linear in $\bar{x}$, which complicates the theoretical analysis of the optimal Stage 0 policy. Nevertheless, the U-shaped behaviour of Γ_0^* and n^* with respect to ω that was derived for the case $c_p(k) = 0$ can still be observed in our numerical example with $c_p(k) > 0$.

We study the recent NICE health technology appraisal of mannitol dry powder (Bronchitol) for inhalation for treating cystic fibrosis (NICE, 2012b), which is deemed to be a rare disease according to the Orphanet register of rare diseases, with a prevalence of approximately 12.6 per 100,000 in Europe (Orphanet, 2014).

The technology is chosen for a number of reasons. Firstly, high quality data on the clinical effectiveness, costs and QALYs upon which NICE made its recommendations are available in the NICE report itself and the publications reporting the results of the two key Phase III clinical trials (Bilton et al. 2011; Aitken et al. 2013). Secondly, the control was effectively placebo in both clinical trials, that is, it was the same drug set at a very low, non-therapeutic, dosage. Thirdly, although the EMA and NICE approved the product for use in 2012 for a sub-group of cystic fibrosis patients (described below), the U.S. FDA denied marketing authorisation in 2013, based on the same clinical trial results, citing concerns over the high level of discontinuation with treatment in the clinical trials and the failure to achieve effects that were statistically significant. The location and scale parameters for the logistic distribution are derived from a recent study investigating the relationship between costs and other factors on approval decisions made by NICE (Dakin et al., 2014).

It should be noted that the application is illustrative and is not intended to be a comment on the efficacy or cost-effectiveness of the technology in question. Table 1 summarises the main parameter values, together with their sources. A description of how the parameter values are derived is contained in Appendix B.

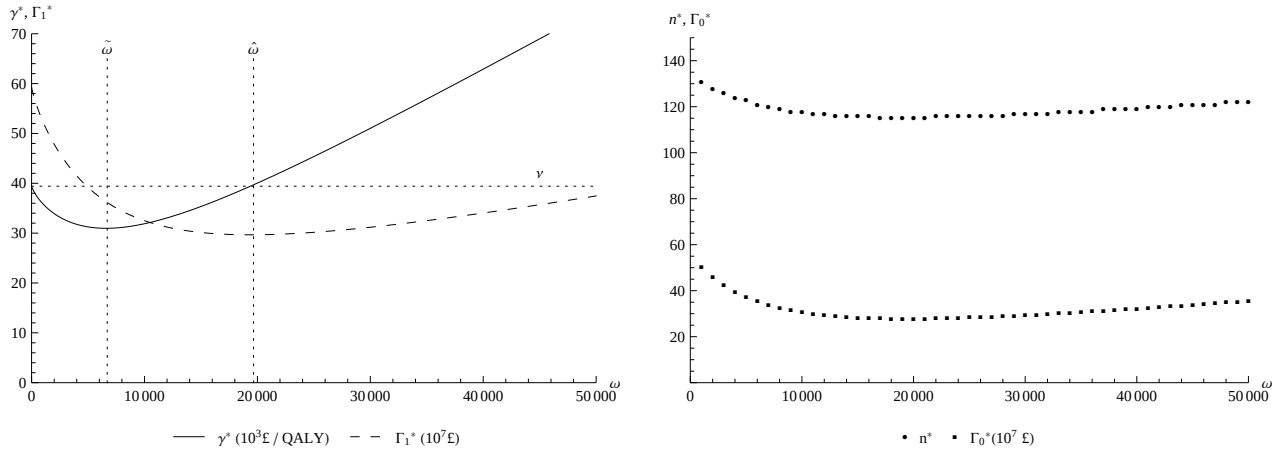
5.1 The role of uncertainty

Figure 4(a) shows the U-shaped nature of the optimal ICER (price) and expected Stage 1 profit as a function of ω. As expected, for $\omega \longrightarrow 0$, the optimal ICER tends to the mean of the distribution (£39,417 per QALY), whereas the minimum of Γ_1^* corresponds to the value of ω such that $\gamma^* = \nu$ (Proposition 1). For the specific parameters of our calibration, both optimal price and optimal expected Stage 1 profit are decreasing in ω for $\omega < \tilde{\omega} = 6{,}604$, optimal price is increasing and optimal profit decreasing for $\tilde{\omega} < \omega < \hat{\omega}$, and both are increasing for $\omega > \hat{\omega} = 19{,}381$. Figure

Parameter	Definition	Source	Value
1. μ_0	Expected value of prior beliefs concerning μ_X	Bilton et al. (2011)	85.0mL
2. σ_0	Standard deviation of prior beliefs concerning μ_X	Bilton et al. (2011)	16.1mL
3. I_0	Fixed cost of carrying out clinical trial	Assumption	£10,000,000
4. d	Marginal cost of one pairwise allocation	Assumption	£50,000
5. c	Estimated cost of one year's course of mannitol for patient who responds, and adheres to, treatment	NICE (2012a)	£6,041
6.	Estimated cost of placebo	NICE (2012b)	£0
7a. ICER	Incremental cost-effectiveness ratio (using rhDNase)	NICE (2012b)	£47,095/QALY
7b. ICER	Incremental cost-effectiveness ratio (not using rhDNase)	NICE (2012b)	£41,074/QALY
7c. ICER	Incremental cost-effectiveness ratio (not using rhDNase, rapidly declining lung function)	NICE (2012b)*	£29,999/QALY*
8. ν	Location parameter of logistic distribution	Dakin et al. (2014)	£39,417/QALY
9. ω	Scale parameter of logistic distribution	Dakin et al. (2014)	£11,230/QALY
10. σ_X	Population standard deviation of incremental effectiveness	Bilton et al. (2011)	190.5mL
11.	Fixed annual prevalence of patients to be treated	NICE (2012a)	10,000
12.	Market exclusivity horizon	EU legislation	10 years
13. k	Size of the population to treat with the new technology	11. and 12.	100,000
14. I_1	Fixed cost of production	Assumption	£10,000,000
15. b	Marginal cost of production	Assumption	£0
16. z_α	Critical value for RA threshold	NICE (2012b)	1.96

Table 1: Parameter values and sources used for the application (baseline case).

NOTES: *Reported as being under £30000 per QALY



(a) Optimal ICER (price) and optimal expected Stage 1 profit as a function of ω.

(b) Optimal sample size and optimal expected Stage 0 profit as a function of ω.

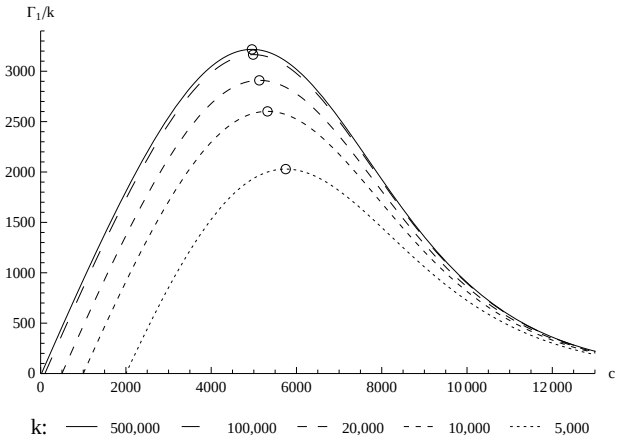
Figure 4: The role of uncertainty.

4(b) shows how the non-monotonic response of the optimal Stage 1 price and profit with respect to changes in ω (Figure 4(a)) feeds-back on the determination of n^* at Stage 0. Hence, n^* and Γ_0^* are first decreasing and then increasing in ω.

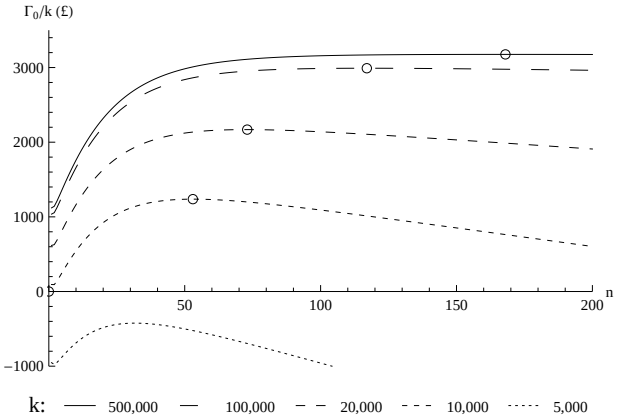
The parameter ω could be seen as a policy parameter from the perspective of the HCI. NICE, for example, might reduce ω by narrowing the declared range of the maximum values of ICER accepted (£20,000 - £30,000), or by formally stating how specific characteristics of the technology or the disease (e.g. life threatening conditions) have an impact on the decision. Although a full welfare analysis is beyond the scope of the present work, the results obtained so far provide some interesting insights. For example, the value of ω calibrated using results from the analysis of NICE's decision by Dakin et al. (2014) (11,230) lies between $\tilde{\omega}$ and $\hat{\omega}$. For the specific case under consideration, a reduction of ω to any value between 6,604 and 11,230 would have the following implications: a lower price (Figure 4(a)), a stronger incentive to invest in R&D via Γ_0^* (Figure 4(a)) and more precision on the estimate of the effectiveness via n^* (Figure 4(b)).

Another interesting question is whether, and to what extent, a lack of transparency on the true cost-effectiveness threshold ($\omega > 0$) can shift rents from the HTP to the HCI. In the formal limit case of $\omega = 0$, and assuming the HTP's beliefs about the threshold are correct in expectation, the threshold will then be equal to the mean ν. Assuming $\nu\bar{x} > c_p(k)$, the HTP's optimal price choice in Stage 1 is $c^* = \nu\bar{x}$. With the parameter values of our application, the optimal sample size for this special case is $n^* = 135$, and the corresponding optimal profit $\Gamma_0^* =$ £575,000,000. In comparison, for the situation where ω equals the value calibrated from NICE's actual decisions ($\omega =$ 11,230), $n^* = 117$ and $\Gamma_0^* =$£299,000,000.

An interesting extension would be to estimate the Expected Value of Perfect Information about the cost-effectiveness threshold, which takes into account the fact that the threshold, while allowing for better HTP decisions once obtained, is still uncertain during the HTP's planning phase.



(a) Stage 1 expected profit per patient to benefit (Γ_1/k) as a function of the HTP's proposed Stage 1 price, c for different values of k. Circles indicate maxima.



(b) Expected profit at Stage 0 (Γ_0/k) as a function of sample size, n, for different values of k. Circles indicate maxima.

Figure 5: The role of the size of the population to treat.

5.2 The role of population size

Figure 5(a) is useful to highlight the main implication of introducing a cost $c_p(k) > 0$. The results of Section 4 showed that the optimal price setting policy is independent of the size of the population to treat when $c_p(k) = 0$ because the optimal profit per patient (Γ_1^*/k) would be independent of k. Figure 5(a) shows that this is no longer the case when costs are accounted for in Stage 1. In particular, c^* is decreasing in k, meaning that, for a comparatively rare disease, it is optimal to propose a higher price. This, in turn, leads to a lower probability of acceptance and lower expected profits per patient.[2]

Fixing ω at the baseline value, Figure 5(b) shows the Stage 0 profit per patient for different values of the population size as a function of n.[3] The figure shows that n^* is increasing in k. In increasing order (that is, as k increases in Figure 5(b)), the optimal sample sizes for the Stage 0 decision are $n^* = 0$, 53, 73, 117 and 168, respectively. The probability of RA acceptance under the prior, $\mathcal{P}$ in Eq. (13), is also strictly increasing in k and may be computed for each specific optimal sample size. Performing this calculation yields values of $\mathcal{P}$ equal to 0, 0.864, 0.934, 0.983 and 0.995, respectively.

From the policy perspective, the main concern about orphan diseases is the lack of incentives for the firm to undertake R&D projects that could benefit those patients. In Section 4.2.2 we

[2]The economic intuition for the effect of k on c^* is straightforward. Consider two drugs with very different population sizes, but common fixed costs of production $I_1 > 0$. For both drugs, an increase in c increases expected revenues if the technology is eventually adopted, but also reduces the probability of adoption. Absent fixed investment costs, both terms would be proportional to k and the marginal condition would not be affected. But with $I_1 > 0$, what is left to the firm producing the drug for a less common disease is less. Therefore, the marginal cost due to the reduction in the probability of adoption is less. This leads to a higher value of the optimal price.

[3]Figure 5(b) shows profits per patient and not total profits for the sake of clarity. Note that the maximization problem is unaffected.

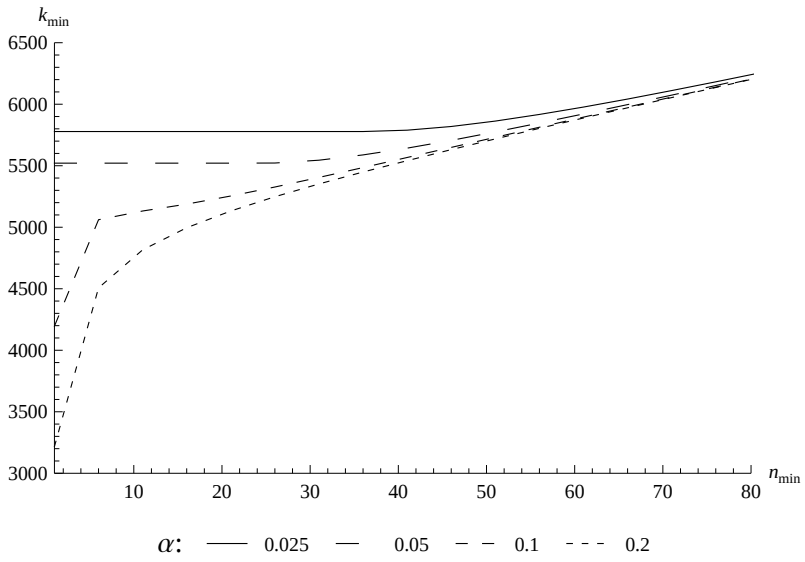


Figure 6: Minimum patient population to benefit (k_{min}) as a function of RA's minimum sample size (n_{min}) for different values of α.

defined k_{min} as the minimum population size such that the HTP would find it profitable to start the project. Figure 5(b) shows that, for the set of parameters used in the calibration, k_{min} is between 5,000 and 10,000.

The analysis presented so far shows that some of the parameters relevant in Stage 1 and which might be, to some extent, under the control of the HCI or the RA may be crucial in providing incentives to invest in R&D. We conclude the discussion of our application with an attempt to investigate quantitatively the role of two parameters characterizing Stage 0: α and n_{min}. Figure 6 shows k_{min} as a function of n_{min} for some different values of α, with $5 \leq n_{\text{min}} \leq 80$. As expected, for a given value of n_{min}, k_{min} decreases in the significance level, α, because a stricter policy by the RA (a lower α) requires, other things being equal, larger samples, which pay less in terms of expected profit when the population to treat is small. For a given value of α, k_{min} is non-decreasing in n_{min} because, when the latter is a binding constraint, an increase means that larger values of k are needed to make non-negative profits. The flat parts of the curves correspond to regions where $n^* > n_{\text{min}}$. Overall, the figure suggests that any policy consideration on the impact of statistical requirements on the incentive to invest in R&D should take both of these parameters into account. In quantitative terms, for the set of parameters used, the impact of increasing α from 2.5% to 20% is to almost halve the value of k_{min} when n_{min} is very small.

6 Discussion and Conclusions

Historically, economic considerations have played a secondary role to the demonstration of safety and efficacy in the drug-approval process. However, the increasing need for regulators to assess the economic implications of their decisions implies that integration between economic and clin-

ical considerations is much greater nowadays. To the best of our knowledge, the two-stage model that we propose is the first to present a full analysis of how regulation of access to the market interacts with the reimbursement decision of a health care insurer, and how the incentives thereby created encourage, or discourage, investment in R&D for new pharmaceutical products.

Our main results relate to how the degree of uncertainty surrounding the true value of the health care insurer's maximum willingness to pay for one unit of effectiveness impacts optimal profit, price and sample size. In particular, it is shown that, for reasonable functional forms describing the distribution of the true value of the insurer's willingness to pay, optimal profit, price and sample size are U-shaped functions of the uncertainty parameter. Compared with the case of perfect knowledge, this implies that introducing a small amount of uncertainty reduces the expected return of the R&D investment as well as the optimal sample size of the trial. However, it also reduces the price proposed for the new technology, and therefore the value of its ICER. The policy implication is that introducing uncertainty on the reimbursement decision may result in a less precise estimate of a new treatment's effectiveness, while at the same time reducing the impact on the insurer's budget. However, the U-shaped nature of the relationships implies that, at higher levels of uncertainty, a marginal increase in the uncertainty parameter can *increase* optimal profits, price and sample size. An interesting implication is that there exists a range of values of the uncertainty parameter over which a reduction in uncertainty benefits the firm, by increasing the expected value of the R&D investment, the insurer, by reducing the price to reimburse, and patients, by increasing the chance that a firm decides to invest in a marginal project.

Concerning incentives that can be provided at the development stage, it has been suggested that this opportunity for regulators might have been under-explored so far (Clarke et al., 2014). Our model provides a framework to investigate this and, in principle, to study the substitutability of incentives at the commercialization and the development stage. Our application includes a tentative estimate of the impact of a change in the significance level (α) of the statistical test, used by the regulatory authority to approve a new drug, on the minimum size of the population that ensures non negative expected profit from an investment in R&D. There is a strong convention within RAs that the type I error rate should be controlled at 5% 2-sided, that is, that the one-sided level, α, should be 0.025. However, the FDA has stressed that this rule is not written in stone and actual FDA decisions for rare diseases confirm this (Sasinowski, 2012). Our results on the consequences of different choices of α are therefore practically relevant.

We conclude with a discussion of a number of limitations of the model and opportunities for future research. For example, it is assumed that there is only one authority which controls access to the market – the RA – and one which decides on reimbursement – the HCI. Although key decisions tend to be concentrated in a limited number of RAs in the real world (e.g. the FDA in the US and the EMA in Europe), this is not the case for insurers.

Regarding reimbursement decisions, our model is based on a cost per unit of effectiveness criterion. However, not all insures use such an approach. For example, multiple HCIs are active in the US, and US legislation bans the formal use of cost per QALY for insurance decisions. Both the concept of quality-adjustment of life, and of setting a price on the value of a life (year) are far from uncontroversial. The model used in this article could potentially be extended to allow the sponsor gain to be dependent on decisions from a multitude of RAs and HCIs. More-

over, decisions made in different countries may not be independent, such as when reference pricing mechanisms are adopted. Taking this into account would raise a number of interesting and challenging questions related to strategic interactions and a provider's optimal sequence of reimbursement decisions. Another valuable extension would be the formal modelling of price negotiations at Stage 1.

One could also relax the assumption that the incremental cost of the new technology only depends on the difference between prices. A better technology may, for example, also reduce other health care costs, which would introduce dependency between incremental cost and effectiveness. Methods similar to those used by Kikuchi and Gittins (2009) and Kikuchi et al. (2008) (see Section 2) could be used to model such a relationship.

Although it is acknowledged that the drug discovery and development process extends well beyond the remit of this paper (Pennings and Sereno, 2011), the part of the process that we consider is crucial because of the size of its costs, which are estimated to be around 50% of the total cost of clinical development (Pharmaceutical Research and Manufacturers of America, 2014), and the high probability of failure (estimated to be around 50% in Phase III). Nevertheless, the recursive nature of the solution to the model could permit earlier stages in the drug development process to be added.

Finally, our model has assumed that the RA and HCI refer to a common measure of effectiveness. Things get more complicated when RAs and HCIs focus on distinctly different variables: RAs often prefer an objective, 'hard', endpoint, while HCIs may look more at patient-reported quality-of-life. Recently, the EMA has invited HCIs to increase the alignment. In an extension, we could therefore assume the existence of two different, but correlated, response variables, one for each stage of the model. An interesting question would be the degree to which a lack of alignment between RA and HCI objectives could disincentivise drug development.

Acknowledgements

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A Proofs

A.1 Stage 1

Proofs of comparative static results (Eq. 10 and Eq. 11):

- *Results for* Γ_1^*: Since $\gamma^*(\nu,\omega) > 0$ and $0 < F_Y < 1$, that $\frac{\partial\Gamma_1^*}{\partial k}$ and $\frac{\partial\Gamma_1^*}{\partial\bar{x}}$ are positive is immediate from Eq. (7). By the Envelope Theorem,

$$\frac{\partial\Gamma_1^*}{\partial\nu} = \frac{\partial\Gamma_1}{\partial\nu}\Big|_{c=c^*} = kc^*\left(\frac{1}{\omega}\right) f_T\left(\frac{c^*/\bar{x}-\nu}{\omega}\right) > 0.$$

- *Results for* c^*: Partial differentiation of Eq. (6) immediately gives $\frac{\partial c^*}{\partial k} = 0$ and $\frac{\partial c^*}{\partial\bar{x}} = \gamma^*(\nu,\omega) > 0$. Since γ^* satisfies the first order condition, differentiation of Eq. (9) gives

$$\frac{\partial\gamma^*}{\partial\nu} r_Y(\gamma^*;\nu,\,\omega\,) + \gamma^*\left(\frac{\partial r_Y}{\partial\gamma}(\gamma^*;\nu,\,\omega\,)\frac{\partial\gamma^*}{\partial\nu} + \frac{\partial r_Y}{\partial\nu}(\gamma^*;\nu,\,\omega\,)\right) = 0 \iff$$
$$\frac{\partial\gamma^*}{\partial\nu} = -\frac{\gamma^*\frac{\partial r_Y}{\partial\nu}(\gamma^*;\nu,\,\omega\,)}{r_Y(\gamma^*;\nu,\,\omega\,) + \gamma^*\frac{\partial r_Y}{\partial\gamma}(\gamma^*;\nu,\,\omega\,)}.$$

  By assumption **A2**, $\frac{\partial r_Y}{\partial\gamma} > 0$. Since $\gamma^* > 0$ always holds, the denominator of the fraction above is positive and the sign of $\frac{\partial\gamma^*}{\partial\nu}$ equals the sign of $-\frac{\partial r_Y}{\partial\nu}$. But $\frac{\partial r_Y}{\partial\nu}$ is negative, so that $\frac{\partial\gamma^*}{\partial\nu}$ and hence $\frac{\partial c^*}{\partial\nu}$ is positive.

□

Proof of Proposition 1:
Let $g(\gamma\,;\nu,\,\omega\,) = \gamma r_Y(\gamma\,;\nu,\,\omega\,)$. As previously noted, by Assumption **A2**, $g(\gamma\,;\nu,\,\omega\,)$ is strictly increasing in γ, and $g(\gamma^*(\nu,\,\omega\,)\,;\nu,\,\omega\,) = 1$, since γ^* satisfies the first order condition. But this means that, for any γ, $\gamma \lessgtr \gamma^*(\nu,\,\omega\,)$ if and only if $g(\gamma\,;\nu,\,\omega\,) \lessgtr 1$. In particular, for $\gamma = \nu$,

$$\nu \lessgtr \gamma^*(\nu,\,\omega\,) \iff \gamma r_Y(\nu\,;\nu,\,\omega\,) \lessgtr 1 \iff \nu r_T(0)/\omega \lessgtr 1 \iff \nu r_T(0) \lessgtr \omega.$$

Hence, for any fixed $\nu > 0$, there exists a value of the scale parameter $\hat{\omega} = \nu r_T(0)$ such that the optimal ICER is less than ν if and only if $\omega < \hat{\omega}$. This observation may be used to characterise the response of Γ_1^* to changes in ω. For, by the Envelope Theorem applied to Eq. (7) and the rotation result for F_Y in Eq. (3),

$$\frac{\partial\Gamma_1^*}{\partial\omega} = \frac{\partial\Gamma_1}{\partial\omega}\Big|_{c=c^*} = -k\bar{x}\gamma^*\frac{\partial F_Y}{\partial\omega}(\gamma^*;\nu,\,\omega\,) \gtrless 0 \iff \gamma^* \gtrless \nu \iff \omega \gtrless \hat{\omega}.$$

□

Proof of Proposition 2:
By making use of the substitution $\gamma = \nu + \omega t$, we see that solving the first order necessary condition in Eq. (9) for $\gamma > 0$ is equivalent to solving the following transformed problem for $t > -\nu/\omega$,

$$(\nu + \omega t) r_T(t)/\omega = 1 \iff -\nu/\omega = t - 1/r_T(t) \iff \psi(t) = -\nu/\omega,$$

where $\psi(t) \equiv t - 1/r_T(t)$. By assumption **A2**, $\psi(t)$ is strictly increasing. This implies that its inverse ψ^{-1} is well-defined and that the solution to the equation above may be written as $t^* = \psi^{-1}(-\nu/\omega)$. The corresponding solution for the original problem is then $\gamma^* = \nu + \omega\psi^{-1}(-\nu/\omega)$. Fixing ν, differentiation with respect to ω yields

$$\frac{\partial \gamma^*}{\partial \omega}(\omega) = \psi^{-1}(-\nu/\omega) + \frac{\nu/\omega}{\psi'\left(\psi^{-1}(-\nu/\omega)\right)}.$$

Now, since the change of variable $\theta = \psi^{-1}(-\nu/\omega) \iff \psi(\theta) = -\nu/\omega$ defines a strictly increasing mapping of $\omega \in (0, \infty)$ onto $\theta \in (-\infty, \psi^{-1}(0))$, $\frac{\partial \gamma^*}{\partial \omega}(\omega)$ is strictly increasing if and only if $\theta \mapsto \theta - \frac{\psi(\theta)}{\psi'(\theta)}$ is strictly increasing. Differentiation with respect to θ results in the sufficient condition

$$1 - \frac{\psi'(\theta)^2 - \psi(\theta)\psi''(\theta)}{\psi'(\theta)^2} > 0 \iff \psi(\theta)\psi''(\theta) > 0.$$

Since $\psi(\theta) = \psi(\psi^{-1}(-\nu/\omega)) = -\nu/\omega < 0$ when $\nu > 0$, we obtain the sufficient condition $\psi''(\theta) < 0$ for $\theta \in (-\infty, \psi^{-1}(0))$. Because $m(\theta) = \theta - \psi(\theta)$, this is equivalent to $m''(\theta) > 0$.

□

A.2 Stage 0

Proof of Proposition 3:
Let $\zeta(n) = \mathbb{E}\Big[\, \bar{X} \mid \bar{X} > h(n) \,\Big] \mathcal{P}(\, \bar{X} > h(n)\,)$, so that $\Gamma_0 = \eta^*(k, \nu, \omega)\zeta(n) - (I_0 + dn)$. By the Envelope Theorem,

$$\frac{\partial \Gamma_0^*}{\partial \omega} = \frac{\partial \Gamma_0}{\partial \omega}\Big|_{n=n^*} = \zeta(n^*)\frac{\partial \eta^*(k, \nu, \omega)}{\partial \omega}. \tag{24}$$

Since $\zeta(n^*)$ is always positive and the sign of $\frac{\partial \eta^*}{\partial \omega}$ equals the sign of $\frac{\partial \Gamma_1^*}{\partial \omega}$ (for any fixed but arbitrary $\bar{x}$), part (a) follows from Proposition 1.

By the Implicit Function Theorem,

$$\frac{\partial n^*}{\partial \omega} = -\left(\frac{\partial^2 \Gamma_0}{\partial n^2}\right)^{-1} \frac{\partial^2 \Gamma_0}{\partial \omega \partial n}\Big|_{n=n^*}. \tag{25}$$

By assumption, $\frac{\partial^2 \Gamma_0}{\partial n^2}\Big|_{n=n^*} < 0$, and hence the sign of $\frac{\partial n^*}{\partial \omega}$ equals the sign of

$$\frac{\partial^2 \Gamma_0}{\partial \omega \partial n}\Big|_{n=n^*} = \frac{\partial^2}{\partial \omega \partial n}\left(\eta^* \zeta - (I_0 + dn)\right)\Big|_{n=n^*} = \frac{\partial \eta^*(k, \nu, \omega)}{\partial \omega}\frac{\partial \zeta(n^*)}{\partial n}. \tag{26}$$

By definition, n^* solves the first order necessary condition, implying $\frac{\partial \zeta(n^*)}{\partial n} = d/\eta^*(k, \nu, \omega) > 0$. Therefore, the sign of $\frac{\partial n^*}{\partial \omega}$ equals the sign of $\frac{\partial \eta^*}{\partial \omega}$ and part (b) follows from Proposition 1.

□

B Sources of parameter values for application

We briefly summarise the results of the two clinical studies considered (Bilton et al. (2011); Aitken et al. (2013)) and the NICE health technology appraisal as it relates to the estimates of cost-effectiveness.

- *The Phase III trials*. Bilton et al. (2011) compared 400 mg of mannitol twice daily with placebo for 324 subjects aged 6 years or over, randomised 3:2 to mannitol and control. The subjects were based in Europe, Australia and New Zealand. At 26 weeks, upon conclusion of the double-blind stage of the study, the authors reported a significant improvement in forced expiratory volume in one second (FEV_1) in subjects receiving mannitol compared with control. Aitken et al. (2013) compared the same dosage of mannitol to placebo for 192 patients aged 6 years or over, again randomised 3:2. Patients were recruited from North America, South America and Europe. The authors reported a statistically significant improvement in FEV_1 for the mannitol group compared with control during the double-blind stage of the study (the first 26 weeks). Both studies included open label periods, running for 26 weeks after the double-blind stage had concluded, intended to collect more data on adverse reactions. The studies also collected data on quality of life, together with other secondary outcome measures.

- *The NICE Health Technology Appraisal's assessment of cost-effectiveness.* Cost-effectiveness was assessed in the manufacturer's submission to NICE using a Markov model comparing treatment with and without mannitol and populated with data from the clinical trials (NICE, 2012a). The NICE technology appraisal calculates ICERs according to subgroups defined according to whether or not patients were using an alternative treatment, rhDNase. The baseline results for the estimated ICER are split by this classification: that for mannitol compared to treatment without mannitol in the rhDNase group is £47,095 per QALY and that for the group not using rhDNase is £41,074. The report summarises the results of various sensitivity analyses which resulted in changes in these estimates and concluded that the high reported ICERs (between £50,000 and £80,000 per QALY) for patients taking rhDNase meant that the treatment could not be recommended for them because it was not cost-effective; the ICER for those not on rhDNase because they were ineligible, intolerant, or because of inadequate response was considered to be above £30,000 per QALY. However, for those in the latter group whose lung function is decreasing rapidly, the ICER was considered to be under £30,000 per QALY (two reported estimates are £27,700 and £30,100 per QALY). The NICE appraisal committee therefore concluded that mannitol could be considered a cost-effective use of NHS resources for this sub-group only.

Although the trials overlapped in calendar time, we assume a hypothetical scenario in which the first trial reported before the second. We take the perspective of an HTP using information from the first trial to decide whether or not to go ahead with the second trial. This permits us to use the results of the first trial to define some of the parameter values at the start of the second trial, including the prior mean, μ_0, and variance, σ_0^2.

Bilton et al. (2011) report a statistically significant improvement in FEV_1 compared with placebo ($p < 0.001$) in the first trial. Averaged across the post-randomisation visits, the point estimate of $\bar{x}$ is reported to be 85.03mL with a 95% confidence interval of (53.5mL,116.6mL) (Bilton et al., 2011, page 1073, section entitled 'Efficacy'). It is therefore assumed that $\mu_0 =$ 85.03mL for the start of the second Phase III trial (Aitken et al., 2013).

The 95% confidence interval reported by Bilton et al. is used to obtain an estimate of σ_X, the standard deviation of the difference between effects in the treatment and control arms. Assume that $\sigma_t = \sigma_c \equiv \sigma$, that is, the sampling variances of the two trial arms are equal. Then, referencing Table 1 of Bilton et al. (2011), the sample sizes of $n_t = 177$ (number of subjects in treatment arm) and $n_c = 118$ (number of subjects in control arm), an estimate of σ may be obtained by rearranging the standard error formula for two independent means when the variance is known (this being one of the assumptions of the model solved in Section 3):

$$\sigma = \text{SE}(\bar{X}) \left(\sqrt{1/n_t + 1/n_c} \right)^{-1}, \tag{27}$$

where $\text{SE}(\bar{X}) = (116.6 - 85.03)/1.96 = 16.10$, obtained from the 95% confidence interval. Solving Eq. (27) yields an estimate of $\sigma = 135.5$. The standard deviation of the difference is therefore $\sigma_X = \sqrt{2} \times 135.5 = 191.63$. Alternatively, we may assume a sample size equivalent to approximately $n = 140$ pairwise allocations and calculate σ_X directly as $\sigma_X = SE(\bar{X})\sqrt{n} = 16.10 \times \sqrt{140} = 190.5$. The standard deviation for the prior is simply taken to be the standard error, $\sigma_0 = SE(\bar{X}) = 16.10$.

The calibration of the values for ν and ω in Eq. (22) merit some discussion. The values in units of £/QALY are taken from Dakin et al. (2014), who estimate a number of different regression models for past NICE appraisal decisions and find that the reported ICER was the major factor influencing the probability of acceptance (no other factor, other than the type of condition, was found to have a statistically significant effect on NICE's decision). For the model with the highest prediction accuracy, Dakin et al. (2014) report that the ICER values corresponding to probabilities of NICE recommendations of 0.25, 0.50 and 0.75 were £51,754, £39,417 and £27,047 per QALY, respectively (Table III, model 4 in Dakin et al. (2014)). The pairs (0.5, 39,417) and (0.75, 51,754), when inserted into Eq. (22), give two equations for ν and ω which can be solved to yield the following estimates: $\nu =$ £39,417/QALY and $\omega =$ £11,230/QALY. Now, the unit of the incremental efficacy $\bar{x}$ is not QALYs, but FEV_1 mL. Hence, when performing computations within the model it is first necessary to convert the willingness to pay into units of £/mL. Calibration gives a conversion factor of $s = 0.0018$ QALYs/mL.

We assume 10,000 patients treated per year, and a time horizon of 10 years, which is the length of the exclusivity period allowed in the European Union for rare diseases. This implies $k =$ 100,000 in our baseline scenario.

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