Late-Stage Pharmaceutical R&D for Rare Diseases under Two-Stage Regulation

Sebastian Jobjörnsson,* Martin Forster,† Paolo Pertile,‡
Carl-Fredrik Burman§

May 23, 2015

Abstract

We study the impact of pharmaceutical regulation on the incentives to invest in late stage R&D, with a focus on rare diseases. A Bayesian health technology provider faces a two-stage decision problem in which it must first choose the optimal sample size for a Phase III trial. Conditional upon obtaining Regulatory Authority approval, the provider then chooses the optimal price to propose to a health care insurer in the presence of uncertainty surrounding the true value of the insurer's willingness to pay for health gain. Optimal policy rules and rewards are derived, together with a comparative static analysis, and we present an application of the model in the field of cystic fibrosis. Results confirm that the size of the population to treat has a very large impact on the firm's decision to invest in R&D. We discuss the role of a number of policy parameters as possible incentive mechanisms. A particularly interesting role is that of the uncertainty surrounding the insurer's willingness to pay. We show that, for reasonable functional forms, a situation with a small amount of uncertainty on the cost-effectiveness threshold, in comparison with one where this is known with certainty, implies more uncertainty on the true clinical effectiveness, due to a reduction in the clinical trial's optimal sample size, and weaker incentives for R&D investment, due to lower expected profits. However, these impacts are non-monotonic in the degree of uncertainty.

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

*Department of Mathematical Sciences, Chalmers University of Technology, SE-412 96, Gothenburg, Sweden. e-mail: jobjorns@chalmers.se

†Department of Economics and Related Studies, University of York, Heslington, York YO10 5DD, U.K.. e-mail: mf8@york.ac.uk.

‡Department of Economics, University of Verona, 37129 Verona, Italy. e-mail: paolo.pertile@univr.it.

§Department of Mathematical Sciences, Chalmers University of Technology, SE-412 96, Gothenburg, Sweden; Advanced Analytics Centre, AstraZeneca R&D, SE-431 83 Molndal, Sweden. e-mail: carl-fredrik.burman@astrazeneca.com

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 regulatory 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 demonstrated efficacy 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. For the second, interest in risk-sharing agreements has been growing in recent years (Pita Barros, 2011; Towse and Garrison, 2010; Cook et al., 2008). Such agreements can take several forms, but what is common to all of them is that part of what is paid by the health care insurer must be paid back if the true effectiveness of the treatment is below a defined threshold (performance-based agreements), or the total cost to the insurer is higher than a pre-specified amount (financial-based agreements).

Somewhat surprisingly, however, at the same time as health care insurers have been growing more concerned about technology-induced growth of health care expenditures, suppliers of innovations have been experiencing some negative trends, including 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., 2013). Empirical evidence that tighter regulation leads to a delay in the adoption of innovations, and a weaker incentive for the industry to invest in R&D, has also been provided (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 provide incentives for investments 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 investments is that predicted sales are 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.

In 1983, in an attempt to address such disincentives, the United States introduced the 'Orphan Drug Act'. A recent review of the impact of the Act (Braun et al., 2010) concluded that 247 drugs for over 200 different diseases had received FDA approval since its inception. The European Commission has also taken a number of steps to stimulate research into rare diseases. In 2000, regulations for orphan drugs were introduced to the EU, including Regulation (EC) No 141/2000, which grants exclusivity in the market for new drugs for a period of 10 years. This has led to over 850 orphan drug designations and around 60 marketing approvals (The Committee for Orphan Medicinal Products and the European Medicines Agency Scientific Secretariat, 2011). The EUROPLAN project promotes national strategies for tackling rare diseases.[1] At the level of statistical methodology, recent EU 'Framework' Programmes have funded a number of initiatives intended to develop general statistical methods to improve clinical trials for small population groups.

A new drug needs to pass two key regulatory steps 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. Because, at least for the majority of innovations, most 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 to this decision has been increasing in recent years. As a result, Phase III clinical trials, which previously aimed only to assess effectiveness, are often accompanied by an economic evaluation. However, there can exist a lack of transparency on the precise role played by cost-effectiveness results in determining adoption decisions. Even the National Institute for Health and Care Excellence (NICE) in the UK, which is probably one of the most transparent institutions in this respect, does not refer to a single value for the cost-effectiveness threshold when making its decisions, but to a range of between £20,000 and £30,000 per Quality-Adjusted-Life-Year gained (McCabe et al., 2008).

The aim of this paper is to provide a unified framework for the analysis of these two regulatory stages, and so to study how late-stage R&D incentives for the pharmaceutical industry depend on interactions among parameters and policy variables at each stage. We then investigate how these incentives may affect decisions to invest in rare diseases. We use a Bayesian decision-theoretic model for a health technology provider operating within a defined jurisdiction (such as at the country level) and define its optimal sampling and pricing policies over two stages. In Stage 0, the health technology provider decides whether to run a trial and, if it does so, the trial's sample size. If, based on the results of the trial, the regulatory authority (RA) for the jurisdiction deems the treatment to be effective at a predefined level of statistical significance, the provider may apply for reimbursement by a health care insurer in Stage 1. This involves proposing a price for the new product which, together with the evidence on effectiveness provided by the trial, sets the level of the incremental cost-effectiveness ratio upon which the health care insurer bases its decision about whether or not to reimburse the cost of the new technology.

Although it is acknowledged that the drug discovery and development process extends well beyond the remit of this paper (Pennings and Sereno, 2011), our focus on late-stage incentives

[1] http://www.europlanproject.eu/

on R&D, starting with the Phase III trial, is a crucial part of a drug development project because of the size of its costs, which are estimated to be around 50% of the total cost of clinical development (Parmaceutical Research and Manufacturers of America, 2014) and the very high probability of failure (estimated to be around 50% in Phase III). Hence the late stage incentives that are the focus of this paper may be expected to influence earlier decisions relating to drug discovery and development, even though they are not formally modelled here.

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, affect optimal pricing policies, expected profit and sample sizes. We show that moving from a situation of no uncertainty on the cost-effectiveness threshold to one with some uncertainty leads to lower prices, lower expected profit, a lower probability of the trial taking place, and a smaller sample size if it does. This implies that the presence of uncertainty on the cost-effectiveness decision (Stage 1) can shift rents from the firm to the insurer, and increase uncertainty on the true effectiveness of the innovation due to the reduction in the optimal sample size. However, the impact of such uncertainty is non-monotonic.

Concerning the focus on rare diseases, 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. This is influenced by regulatory parameters in both Stage 0 and Stage 1, and a calibrated model of a rare diseases is used to study the interaction between parameters such as the level of the Type I error that characterises the RA's decision and the level of the expected value of the incremental cost-effectiveness ratio (ICER) threshold that is set by the insurer.

Section 2 of this paper presents a brief summary of the literature that is relevant to this work. Section 3 presents the model, which is solved in Section 4 first in general form and then assuming a specific probability distribution for the random variable related to the insurer's willingness to pay for health gain. Section 5 presents the application. Section 6 discusses some of the main results, the limitations of the work and provides conclusions.

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 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 behaviour 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, noting the disincentive that exists to Phase III development for rare conditions, in which there is a low chance that expected revenues can cover development costs. 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. During Stage 1, the firm makes a decision about whether to run a trial for a particular drug, paying a R&D cost. In Stage 2, the entrants to the market compete for customers. The firm's reward is profit in Stage 2 minus the cost paid to enter the market. Each trial has a probability $\pi \in (0, 1)$ of success and it is assumed that entrants take an equal share of the market premium. 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 (NMEs) 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. However, it has been argued that more should be done to remove hurdles related to the development stage by improving the definition of 'rarity' with reference to how feasible it will be to commission trials with appropriate power to detect a clinically relevant effect (Clarke et al., 2014).

The above models are important precursors to ours and contain many common elements and ideas. However, none of them explicitly combine the optimal choice of a trial's sample size with explicit modelling of a price-setting rule at Stage 1, in the presence of uncertainty surrounding the health care insurer's willingness to pay.

3 The model

We take the perspective of a Health Technology Provider (HTP) which is 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 the market considers the evidence concerning the drug's efficacy, where 'evidence' is defined as being the point estimate of incremental effectiveness, together with its standard error. This stage of the process is defined as being 'Stage 0'. If RA approval is granted, the HTP aims to have the drug reimbursed by a Health Care Insurer (HCI) by proposing a price for the treatment of a single patient. This stage of the process is defined as 'Stage 1'. The HTP's choice variables are therefore the following: 1. whether or not to commission a trial (a 'Stage 0' decision); 2. the sample size of the trial, should it be commissioned (also a 'Stage 0' decision) and 3. the price the HTP proposes to the HCI, should the HTP seek to have the drug reimbursed (a 'Stage 1' decision).

Let μ_X be the incremental effectiveness (assumed unknown to all agents) of the new treatment versus standard in the population. We assume that the control group is treated with placebo.[2] We ignore differences in costs which are not directly related to the cost of the pharmaceutical product, implying that the incremental cost coincides with the price of the new drug.

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

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

where n is the sample size of the trial and σ_X is twice the residual standard deviation,[3] assumed known to all agents. From the perspective of the start of Stage 0, $\bar{X}$ is a random variable. When discussing the HTP's optimal pricing rule in Stage 1, conditional upon the trial having concluded, we shall use $\bar{x}$ to denote the realised value of $\bar{X}$ that resulted from the trial.

3.1 The Regulatory Authority

Conditional upon meeting a requirement for a minimum sample size for the trial, $n_{\min} > 0$, 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). Approval for the new treatment will be granted if and only if the point estimate $\bar{x}$ is such that:

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

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 either reimbursed to patients or directly paid by the HCI.

3.2 The Health Care Insurer

The HCI's aim is to ensure that only innovations that are deemed to be 'good value for money' are reimbursed. This requires comparing $\bar{x}$ from the Phase III trial with the incremental cost of the innovation. The incremental cost equals the HTP's proposed price for providing the treatment to a single patient, defined as $c > 0$. It is assumed that the HCI only adopts technologies whose ICER ($c/\bar{x}$) is below a defined threshold. As was noted in Section 1 there exists uncertainty surrounding this value.

Conditional upon the point estimate $\bar{x} > 0$ resulting from the trial, from the perspective of the HTP, the uncertainty surrounding the HCI's ICER threshold is modelled as a continuous random

[2] This may be ethically justified when there is no approved treatment, or when the new treatment is given as an add-on to existing standard treatment, situations that are commonly found for rare diseases.

[3] Note that a sample size of n means that $n/2$ differences can be observed.

variable, V, with location (or mean) parameter $\nu > 0$, scale (or dispersion) parameter $\omega > 0$ and cumulative distribution function $F_V(v; \nu, \omega)$. From the perspective of the HTP, the probability, P, $0 < \mathrm{P} < 1$, that the new treatment is reimbursed by the HCI is defined as:

$$\mathrm{P}(c; \bar{x}, \nu, \omega) = 1 - F_V\left(\frac{c}{\bar{x}}; \nu, \omega\right). \tag{3}$$

F_V is assumed to be $\mathcal{C}^{(2)}$ in all its arguments, where $\mathcal{C}^{(m)}$ denotes the class of functions that are m times continuously differentiable. By the standard properties assumed for F_V it follows that:

$$\frac{\partial \mathrm{P}}{\partial c} < 0; \quad \frac{\partial \mathrm{P}}{\partial \bar{x}} > 0, \quad \frac{\partial \mathrm{P}}{\partial \nu} > 0. \tag{4}$$

Moreover, in order to show the existence of a unique optimal pricing policy, we assume that, for finite values of ω:

$$\lim_{c \to \infty} c\mathrm{P} = 0. \tag{5}$$

The parsimonious definition of P, which depends only on the price proposed by the HTP and the point estimate of effectiveness to arise from the trial, means that the HCI's acceptance decision does not depend on the strength of evidence concerning the result of the trial (because n is not an argument of P), nor does it depend on whether or not the disease is a rare one (because k is not an argument of P). The implications of relaxing these assumptions are considered in Section 6.

3.3 The Health Technology Provider's Problem

The HTP's problem is solved by backward induction within a Bayesian decision-theoretic framework (Raiffa and Schlaifer, 1961; DeGroot, 1970). At the beginning of Stage 0, the HTP decides whether it should enter Phase III clinical testing. The cost of performing the trial is assumed to be $I_0 + dn$, where $I_0 > 0$ is a 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. By running the Phase III trial with a sample size n, the HTP can use the prior predictive distribution for $\bar{X}$ to view the optimal Stage 1 profit as a function of the Stage 0 choice of sample size. Viewed from the 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 $\bar{x}$ is known, if Eq. (2) is satisfied and RA approval granted, the HTP moves to Stage 1 and proposes the price, c, to the HCI. The HCI will adopt the new technology with probability $\mathrm{P}(c; \bar{x}, \nu, \omega)$ defined by Eq. (3). If the technology is not adopted, the HTP makes no profit. Otherwise, the Stage 1 profit is $k(c - c_p(k))$, where k is the size of the population to treat with the new technology and $c_p(k) \equiv I_1/k + b > 0$ 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 profit function may be written as

$$\Pi_1(c; k, \bar{x}, I_1, b, \nu, \omega) = k(c - c_p(k))\mathbf{1}_{\text{HCI adopts}},$$

where $\mathbf{1}_E$ is the indicator function, equal to 1 if the event E is realized and 0 otherwise. Hence expected Stage 1 profit becomes:

$$\Gamma_1(c; k, \bar{x}, I_1, b, \nu, \omega) = \mathbb{E}\left[\Pi_1(c; k, \bar{x}, I_1, b, \nu, \omega)\right] = k(c - c_p(k))\mathrm{P}(c; \bar{x}, \nu, \omega). \tag{6}$$

4 The HTP's optimal policy

4.1 The HTP's Stage 1 pricing rule

Given RA approval, the HTP solves the problem

$$\Gamma_1^*(k, \bar{x}, I_1, b, \nu, \omega) \equiv \max_{c>0} \Gamma_1(c; k, \bar{x}, I_1, b, \nu, \omega). \tag{7}$$

The assumptions made to date ensure that a solution to Eq. (7) exists [4] and the first order necessary condition (FONC) defining the optimal choice of c is:

$$k\mathrm{P}(c; \bar{x}, I_1, b, \nu, \omega) + k[\,c - c_p(k)]\,\frac{\partial \mathrm{P}(c; \bar{x}, I_1, b, \nu, \omega)}{\partial c} = 0. \tag{8}$$

The first term on the LHS of Eq. (8) is the marginal benefit to the HTP of increasing c: the expected additional total profit flow from a one unit increase in c. The second term is the marginal cost, the total Stage 1 profit weighted by the lower probability of acceptance that a higher price implies.

Since P is differentiable, any solution to Eq. (7) must also satisfy Eq. (8). Depending on the precise form of P, it may be the case that, although an optimal price exists, it is not unique. We therefore impose a sufficient condition on P to ensure that the FONC has at most one solution:[5]

$$\frac{\partial}{\partial c}\left(\frac{\mathrm{P}}{\frac{\partial \mathrm{P}}{\partial c}}\right) \geq A > -1, \text{ for some constant } A. \tag{10}$$

[4] To see this, define c^+ to be any price such that $c^+ > c_p(k)$, with corresponding expected profit $\Gamma_1^+ > 0$. By Eq. (5) it is the case that:

$$\lim_{c\to\infty} \Gamma_1 = \lim_{c\to\infty} k(c - c_p(k))\mathrm{P} = 0^+,$$

so that there must exist a positive number c_R such that $\Gamma_1 < \Gamma_1^+$ whenever $c > c_R$. Noting also that $\Gamma_1 < 0$ unless $c \geq c_p(k)$, it follows that any solution to

$$\max_{c_p(k) \leq c \leq c_R} \Gamma_1(c; k, \bar{x}, I_1, b, \nu, \omega)$$

also solves Eq. (7). The latter problem must have a solution, since P is $\mathcal{C}^{(2}$ given the assumption on F_V.

[5] By Eq. (4), $\partial \mathrm{P}/\partial c \neq 0$, meaning that Eq. (8) may be rewritten as

$$\frac{\mathrm{P}}{\frac{\partial \mathrm{P}}{\partial c}} + (c - c_p(k)) = 0. \tag{9}$$

Since existence of a maximum in (7) has already been established, we know that (9) is satisfied in at least one point. But, by (10), the left hand side of (9) is differentiable with respect to c, with derivative $\geq A + 1 > 0$. Therefore, the left hand side is strictly increasing in c, so that (9) can be satisfied in at most one point, implying that there is a unique, common solution to the FONC and (7).

This optimal Stage 1 policy is therefore:

$$c^* = c^*(k, \bar{x}, I_1, b, \nu, \omega). \tag{11}$$

Finally, the assumptions placed on P up to this point are sufficient to show that c^* is $\mathcal{C}^{(1)}$ in all of its arguments (see section A.1 of the appendix). This permits us to derive the following comparative static results.

Proposition 1 (**Stage 1 Optimal Profit Comparative Statics).**

The partial derivatives of expected optimal Stage 1 profit satisfy:

$$\frac{\partial \Gamma_1^*}{\partial \bar{x}} > 0, \quad \frac{\partial \Gamma_1^*}{\partial \nu} > 0, \quad \frac{\partial \Gamma_1^*}{\partial k} > 0.$$

Proofs: See Section A.2 of the Appendix.

Proposition 2 (**Stage 1 Optimal Price Comparative Statics).**

The partial derivative of the optimal pricing policy with respect to k satisfies:

$$\frac{\partial c^*}{\partial k} < 0.$$

Further, letting

$$e_{Pc} = c\left(\frac{\frac{\partial \mathrm{P}}{\partial c}}{P}\right)$$

be the price elasticity of the probability of reimbursement by the HCI, under the additional assumptions that P *satisfies*

$$\left.\frac{\partial e_{Pc}}{\partial \bar{x}}\right|_{c=c^*} > 0, \quad \left.\frac{\partial e_{Pc}}{\partial \nu}\right|_{c=c^*} > 0, \tag{12}$$

the partial derivatives of the optimal pricing policy with respect to $\bar{x}$ and ν satisfy:

$$\frac{\partial c^*}{\partial \bar{x}} > 0, \quad \frac{\partial c^*}{\partial \nu} > 0.$$

Proofs: See Section A.4 of the Appendix.

The economic intuition for the effect of k on c^* in Proposition 2 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 (respectively, the first and second terms in Eq. (8)). Absent fixed investment costs, both terms would be proportional to k and the marginal condition would not be affected. But with $I_1 > 0$, the change of the second term is no longer proportional, because what is left to the HTP once fixed costs are covered is lower for rare diseases than for common ones. Hence, when $I_1 > 0$, the marginal cost of increasing c is smaller the smaller is

k, implying that it is optimal to set a higher price. This, in turn, implies that as long as k does not appear in the HCI's decision function, technologies targeting small populations have a lower probability of being adopted (via the result for $\partial P/\partial c$ in Proposition 1).

Finally, we note that clear-cut comparative static results for the effect of ω on c^* and Γ_1^* are not easily obtainable. This matter is explored in more detail in sections 5 and 6.

4.2 The HTP's Stage 0 optimal choice of sample size

From the perspective of the start of Stage 0, define $\Gamma_0(n; c^*(\bar{X}; k, I_1, b, \nu, \omega), I_0, d)$ as the expected reward of running a Phase III trial with an sample size n and pricing optimally during Stage 1 according to the policy defined in Eq. (11). Since, from the perspective of Stage 0, $\bar{X}$ is a random variable, Stage 1 reward depends on the optimal choice of c^* via the realisation of $\bar{X}$. The Stage 0 optimal choice of n must therefore be computed using the predictive distribution for $\bar{x}$, defined as $f_n(\bar{x})$. 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:

$$\Gamma_0^*(n; c^*(\bar{x}; \cdot), I_0, d) \equiv \max_n \left\{ \mathbb{E}\Big[\Gamma_1^*(\, c^*(\bar{x}; \cdot)\,) \,|\, \bar{x} > h(n) \Big] \mathcal{P}(\bar{x} > h(n)) - (I_0 + dn) \right\} \tag{13}$$

$$= \left\{ \int_{h(n)}^{\infty} \Gamma_1^*(k, \bar{x}, I_1, b, \nu, \omega) f_n(\bar{x})\, \mathrm{d}\bar{x} - (I_0 + dn) \right\} \tag{14}$$

$$\text{subject to } n \geq n_{\min},$$

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

$$\mathcal{P}(\bar{x} > h(n)) = 1 - \Phi(h(n)), \tag{15}$$

where $\Phi(h(n))$ is the CDF of the prior predictive distribution.

The FONCs for the optimal choice of n, defined as n^*, are the following:

$$\frac{\partial \Gamma_0(\cdot)}{\partial n}\Big|_{n^*} \leq 0,\ n^* - n_{\min} \geq 0,\ (n^* - n_{\min}) \frac{\partial \Gamma_0(\cdot)}{\partial n}\Big|_{n^*} = 0, \tag{16}$$

where the first derivative with respect to n is best interpreted with reference to Eq. (13):

$$\frac{\partial \Gamma_0(\cdot)}{\partial n} = \frac{\partial \mathbb{E}\Big[\Gamma_1^*(\, c^*(\bar{x}; \cdot)) | \bar{x} > h(n)\Big]}{\partial n} \mathcal{P}(\bar{x} > h(n)) + \mathbb{E}\Big[\Gamma_1^*(c^*(\bar{x}; \cdot)) | \bar{x} > h(n)\Big] \frac{\partial \mathcal{P}(\bar{x} > h(n))}{\partial n} - d. \tag{17}$$

Assuming that the n^* that results from the solution to the FONCs yields a unique positive value of Γ_0^*, the HTP's optimal choice of n is best interpreted by considering Γ_0^* as a function of $\bar{x}$ and studying the effect of changing n on the predictive distribution for $\bar{x}$. Figure 1 shows the

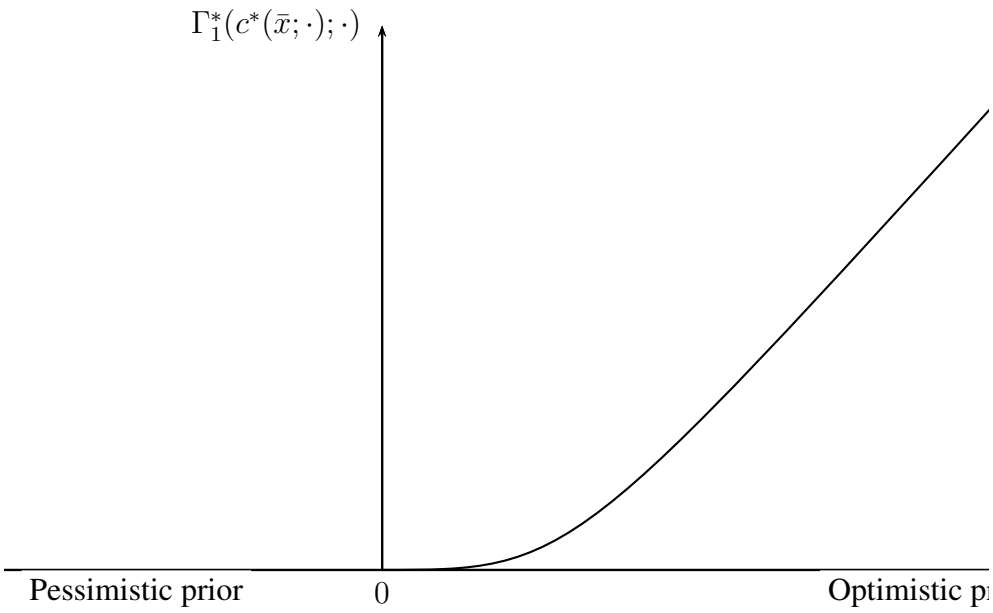


Figure 1: Optimal choice of sample size at Stage 0 given possible scenarios for the prior predictive distribution

scenario for which Γ_1^* is a strictly convex function of $\bar{x}$, approaching linearity at high and low values of $\bar{x}$, which is the case studied in section 5, where a logistic functional form is chosen for P.

There are three broad scenarios for the HTP, given the prior on μ_X:

1. 'Pessimistic prior': in this scenario, μ_0 is negative and far from any range for $\bar{x}$ which leads to positive expected rewards at Stage 1 (see Figure 1). By referring to Eq. (17), the marginal benefit of sampling is negative because $\mathcal{P}$ is close to zero and $\partial\mathcal{P}/\partial n < 0$ (increasing the sample size increases the HTP's belief of a bad result in the trial). As a result, no trial is commissioned because the net marginal benefit of sampling in Eq. (17) is negative.

2. 'Optimistic prior': in this scenario, μ_0 is positive and maps to Γ_0^* via the linear part of Γ_1^*. The HTP sets $n^* = n_{\min}$ so as to satisfy the RA's requirement for a minimum sample size. The marginal benefit of increasing n above $n_{\min}$ is negative because $\partial\mathbb{E}[\cdot]/\partial n = 0$ in Eq. (17) (increasing n does not change $\bar{x}$ and does not change Stage 0 expected profit because Γ_1^* is linear on the support $\bar{x}$) and $\partial\mathcal{P}(\cdot)/\partial n = 0$ (the HTP already believes that the probability of acceptance at $n = n_{\min}$ is equal to one).

3. Between 'Pessimistic' and 'Optimistic priors': in this scenario, the predictive distribution for $\bar{x}$ maps, at least in part, via the strictly convex part of Γ_1^*, to Γ_0^*. In this scenario, the

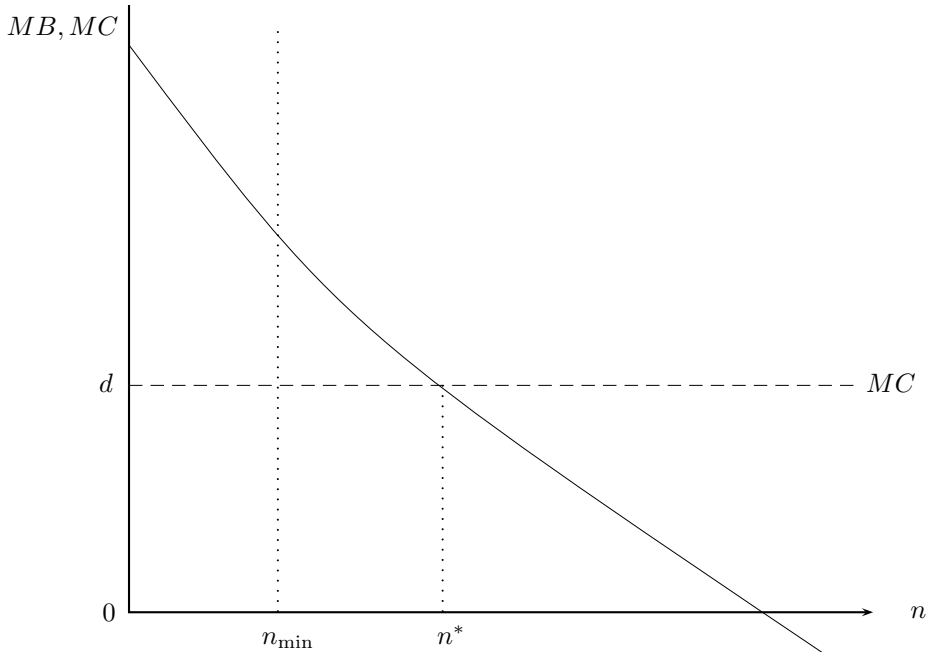


Figure 2: Determination of Stage 0 optimal sample size using Eqs. (16) and (17)

aforementioned constituent elements of Eq. (17) are not equal to zero and there can exist an optimal sample size that is equal to, less than, or greater than, $n_{\min}$. If either of the former two result, then $n^* = n_{\min}$ and the first derivative is not equal to zero. If the latter, the first derivative in the FONC is equal to zero and $n > n_{\min}$. This scenario is illustrated using Figure 2, which plots the first two terms of Eq. (17) – the marginal benefits of sampling – and the marginal cost, d. For this particular scenario, there exists a unique expected utility-maximising value of n^*. We study this scenario in more detail in section 5.

Finally, we state two quite intuitive comparative static results for Stage 0.

Proposition 3 (**Stage 0 Optimal Profit Comparative Statics).**

The partial derivatives of the optimal Stage 0 expected profit with respect to k and ν satisfy:

$$\frac{\partial \Gamma_0^*}{\partial k} > 0, \quad \frac{\partial \Gamma_0^*}{\partial \nu} > 0.$$

Proofs: See Section A.3 of the Appendix.

Since $\Gamma_0^*(k = 0) < 0$, 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:

$$k_{\min} = \min \left\{ k \,\|\Gamma_0^*(k, \cdot) > 0 \right\}. \tag{18}$$

This definition is required for some of the analysis of the incentives to invest in trials for rare diseases that is presented in Sections 5 and 6.

4.3 A logistic model for the probability of acceptance

In order to illustrate the general framework and to prepare the ground for the application, this section considers a specific functional form for P, which assumes that the HTP describes its uncertainty about the HCI's willingness to pay, V, by a logistic density with mean parameter ν and scale parameter ω. The logistic density is chosen for two reasons. Firstly, it has been used in a recent report assessing how estimates of cost-effectiveness and other variables affect NICE decisions (Dakin et al., 2014). Secondly, its functional form is convenient for deriving first order necessary conditions and analysing the comparative static results with respect to ω. Given that $\bar{x}$ has been observed in the trial, reimbursement will occur if and only if $c/\bar{x} \leq V$, implying that Eq. (3) is:

$$\mathrm{P}(c;\bar{x},\nu,\omega) = \left(1+\exp\left(\frac{c/\bar{x}-\nu}{\omega}\right)\right)^{-1}. \tag{19}$$

It is easily verified that P as defined above satisfies all the general requirements stated in Section 3.2, together with the additional assumptions on the elasticity derivatives in Eq. (12).

By inserting the definition in Eq. (19) into the Stage 1 FONC (Eq. (8)) and rearranging terms, one obtains the following equation for the optimal choice of c^*:

$$c^* = c_p(k) + \bar{x}\omega\left(1+\exp\left(\frac{\nu - c^*/\bar{x}}{\omega}\right)\right).$$

A unique solution to this equation may be obtained in terms of the so called LambertW function.[6] Denoting this function by W, the optimal Stage 1 price and expected profit are given by

$$c^* = c_p(k) + \bar{x}\omega\left[1+W\left(\exp\left(\frac{\nu - c_p(k)/\bar{x}}{\omega}-1\right)\right)\right], \tag{20}$$

$$\Gamma_1^* = k\bar{x}\omega W\left(\exp\left(\frac{\nu - c_p(k)/\bar{x}}{\omega}-1\right)\right). \tag{21}$$

Propositions 1 and 2 showed that c^* and Γ_1^* both respond monotonically to changes in k, $\bar{x}$ and ν, but it was noted that the effect of changes on ω on optimal policies and rewards was less clear-cut. The effect of the dispersion parameter, ω, on these values is more complicated. By using the properties of the LambertW function, the following limit results may be shown using Eqs. (20) and (21):

$$\lim_{\omega\to 0}(c^*,\Gamma_1^*) = \begin{cases} (c_p(k),0) & \text{if } \bar{x}\nu \leq c_p(k) \\ (\bar{x}\nu, k(\bar{x}\nu - c_p(k))) & \text{if } \bar{x}\nu > c_p(k) \end{cases}, \quad \lim_{\omega\to\infty}(c^*,\Gamma_1^*) = (\infty,\infty). \tag{22}$$

As $\omega \to 0$, the HTP's uncertainty about the true value of V approaches certainty. Hence, the first limit result just states that, as the HTP becomes certain that $V = \nu$, the optimal pricing rule is

[6] http://mathworld.wolfram.com/LambertW-Function.html

to set the price to the maximum that will imply an adoption decision, provided that this ensures non-negative profits ($c^* \geq c_p(k)$).

The second limit result states that, as the HTP's uncertainty about the true value of V grows without bounds, so will the optimal price and corresponding expected profit.

By differentiating Eqs. (20) and (21) w.r.t ω, for constants $\beta_c \approx 5.8696$ (found numerically) and $\beta_{\Gamma_1} = 2$ it is the case that:

$$\begin{gathered}
\frac{\partial c^*}{\partial \omega} < 0 \text{ if } \omega < \breve{\omega}_c, \quad \frac{\partial \Gamma_1^*}{\partial \omega} < 0 \text{ if } \omega < \breve{\omega}_{\Gamma_1}, \\
\frac{\partial c^*}{\partial \omega} = 0 \text{ if } \omega = \breve{\omega}_c, \quad \frac{\partial \Gamma_1^*}{\partial \omega} = 0 \text{ if } \omega = \breve{\omega}_{\Gamma_1}, \\
\frac{\partial c^*}{\partial \omega} > 0 \text{ if } \omega > \breve{\omega}_c, \quad \frac{\partial \Gamma_1^*}{\partial \omega} > 0 \text{ if } \omega > \breve{\omega}_{\Gamma_1}, \\
\text{where : } \breve{\omega}_c = \frac{\nu - c_p(k)/\bar{x}}{\beta_c}, \quad \breve{\omega}_{\Gamma_1} = \frac{\nu - c_p(k)/\bar{x}}{\beta_{\Gamma_1}}.
\end{gathered}$$

Hence, we may distinguish two qualitatively different cases. If $\bar{x}\nu \leq c_p(k)$, then both the optimal price and the optimal expected Stage 1 profit are strictly increasing in ω. On the other hand, if $\bar{x}\nu > c_p(k)$, both c^* and Γ_1^* are first decreasing and then increasing in ω. Moreover, in this case, the optimal price has a strict global minimum at $\breve{\omega}_c$ and the optimal profit has a strict global minimum at $\breve{\omega}_{\Gamma_1}$. Further, if $\bar{x}\nu > c_p(k)$, then, by the envelope theorem,

$$\frac{\partial \Gamma_1^*(\omega)}{\partial \omega} = \left(\frac{\partial \Gamma_1}{\partial \omega}\right)\Bigg|_{c=c^*(\omega)} = \left(k(c - c_p(k))\left(\frac{\partial \mathrm{P}}{\partial \omega}\right)\right)\Bigg|_{c=c^*(\omega)} = 0 \implies c^*(\omega) = \bar{x}\nu,$$

since $c^*(\omega) > c_p(k)$ always holds and $\partial \mathrm{P}/\partial \omega = 0$ only if $c = \bar{x}\nu$ for the logistic model. Hence it follows that:

$$c^*(\breve{\omega}_{\Gamma_1}) = c^*\left(\frac{\nu - c_p(k)/\bar{x}}{\beta_{\Gamma_1}}\right) = \bar{x}\nu = \lim_{\omega \to 0} c^*(\omega).$$

This analysis shows that, changes in ω imply changes both in the optimal price paid by the insurer and the expected profit for the company. Hence, not only is the expected value of the cost-effectiveness threshold able to shift rents between the HCI and the HTP, as previously shown in the literature (Jena and Philipson (2008)), but the uncertainty surrounding it can also have such an effect. Moreover, in what can reasonably be considered the most likely situation, that is, one where the parameters are such that the HTP would make positive profit with a known cost-effectiveness threshold, the optimal expected profit is non-monotonic in ω. The results also have clear policy implications for Stage 1 decisions, because they show that the degree of transparency of the HCI's adoption decision may influence the rent enjoyed by the HTP. However, the non-monotonicity of the relationship makes essential the practical question of whether at levels of ω consistent with an HCI's observed decision pattern the optimal price and expected profit functions are increasing or decreasing in ω. We shall address this point in Section 5.

5 Application

We implement the model using evidence from the recent NICE health technology appraisal of mannitol dry powder (Bronchitol) for inhalation for treating cystic fibrosis (NICE, 2012b). Cystic fibrosis 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). It affects approximately 9,600 adults in the U.K. (NICE, 2012a) and 30,000 in the U.S. (Food and Drug Administration, 2013).

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.

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.

We briefly summarise the results of the two clinical studies and the NICE health technology appraisal as it relates to the estimates of cost-effectiveness. Table 1 summarises the main parameter values that are taken from these documents to parameterise the model, together with their sources. A summary of how the parameter values are derived is contained in Appendix B.

- *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.

The functional form of P used in the application is given by Eq. (19). The calibration of the values for ν and ω in that formula 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. (19), 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 $k = 100{,}000$.

5.1 Stage 1

To explore some of the features of the HTP's optimal Stage 1 pricing policy, it is neccessary to condition upon a particular value of $\bar{x}$. For the purposes of illustration, we assume that $\bar{x}$ is equal to the point estimate to emerge from the first study and that this is also the HTP's prior (and predictive) mean as it considers whether or not to commission the second study. This Stage 1

Parameter	Definition	Source	Value
1. μ_0	Expected value of prior incremental effectiveness	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)	£6041
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
9. ω	Scale parameter of logistic distribution	Dakin et al. (2014)	£11,230
10. σ_X	Population standard deviation of incremental effectiveness		190.5
11.	Fixed annual prevalence of patients to be treated	NICE (2012a)	10,000
12. T	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

analysis therefore assumes a point estimate $\bar{x}$ that is equal to the mean of the HTP's predictive distribution for $\bar{x}$, $\bar{x} \approx 85.03$mL (refer to Section B).

Fixing k at its baseline value of 100,000, Figure 3 shows Γ_1 versus c for some different values of ω. There are two common intersection points, where all curves meet regardless of the specific value of ω. One appears when c is set equal to the production cost $c_p(k) = 100$, so that $\Gamma_1 = 0$. The other occurs when $c = \nu\bar{x}s \approx 6030$, that is, the ICER equals the expected value of the distribution of the cost-effectiveness threshold, since this choice will always make $\mathrm{P} = 1/2$ regardless of the value of ω. The circles in Figure 3 mark the optimal price-profit pairs (c^*, Γ_1^*) for each value of ω.

The non-monotonic dependence of optimal price and optimal expected profit on ω which was analysed in Section 4.3 is clearly visible by tracing the path of the circles as ω increases. In particular, since $\bar{x}\nu > c_p(k)$ for the baseline values of the simulation, there exists a strict global minimum for the optimal price at $\breve{\omega}_c = \{(s\,\nu - c_p(k)/\bar{x})/\beta_c\} \times (1/s) \approx 6604$ and there exists a strict global minimum for the optimal Stage 1 profit at $\breve{\omega}_{\Gamma_1} = \{(s\nu - c_p(k)/\bar{x})/\beta_{\Gamma_1}\} \times (1/s) \approx 19381$. An interesting implication is that, for values of ω between 6604 and 19381, a reduction in ω means a lower optimal price and a higher Stage 1 expected profit, due to the higher probability of adoption. Hence, both the HTP and the HCI are better-off with reduced uncertainty on the true value of the cost-effectiveness threshold within this range.

In the perspective of assessing the role of the size of the population to treat, it is not only interesting to study the total expected profit Γ_1, but also the expected profit per-patient Γ_1/k. The results of Section 4.3 provide quick answer for some limit case. For the specific combination of parameter values used, as $k \to \infty$, Eqs. (20) and (21) imply that $c^* \to 4949$ and $\Gamma_1^*/k \to 3230$, with a corresponding limit value of P equal to 0.653. Figure 4(a) shows Γ_1/k versus c for some finite values of k. The figure shows that, as k falls, the optimal price rises but the the total expected profit and the expected profit per-patient falls.

5.2 Stage 0

We now consider the full model, that is, we consider the decision of an HTP which has observed the results of the first trial and which is considering whether to commission a second trial.

Fixing k at the baseline value in Table 1, Figure 4(b) shows how the non-monotonic response of the optimal Stage 1 price and profit with respect to changes in ω determine of n^* at Stage 0. For example, n^* for $\omega =$ 50,000 is larger than the corresponding value for $\omega =$ 25,000, but smaller than that for $\omega =$ 5,000. For the parameter values corresponding to our baseline case, as ω increases from a small value, the optimal sample size and the optimal Stage 0 profit first decrease, reach their minimum values and then increase.

Fixing ω at the baseline value, Figure 4(c) shows the Stage 0 profit per patient for different values of the population size as a function of n.[7] The figure shows that n^* is increasing in k. In increasing order (that is, as k increases in Figure 4(c)), the optimal sample sizes for the Stage 0 decision are $n^* =$ 0, 53, 73, 117 and 168, respectively. The probability of RA acceptance under

[7]Figure 4(c) shows profits per patients and not total profits for the sake of clarity in the illustration. Note that the maximization problem is unaffected.

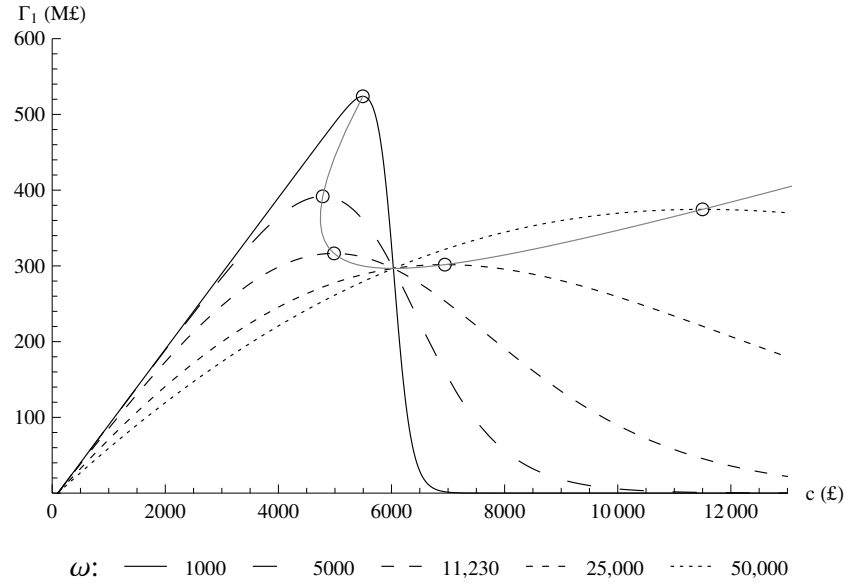
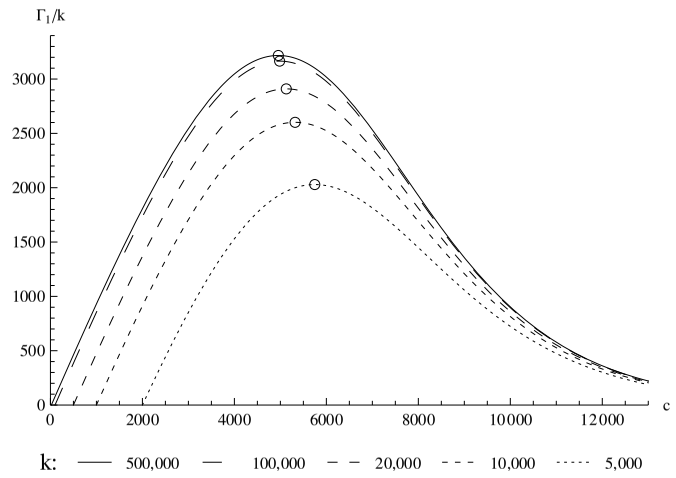


Figure 3: Optimal Stage 1 expected profit (Γ_1) as a function of the HTP's proposed price, c, given various values of uncertainty on the HCI's willingness to pay, ω.

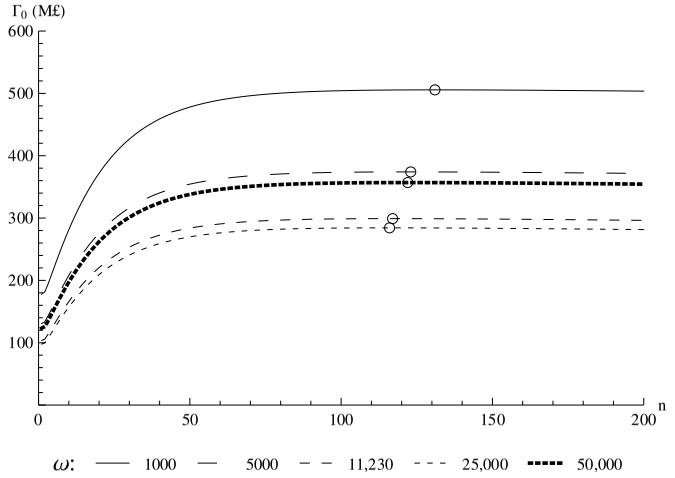
the prior, $\mathcal{P}$ in Eq. (15), is also strictly increasing in k and may be computed for each specific optimal sample size. Performing this calculation yields values of $\mathcal{P}$ equal to 0, 0.864, 0.934, 0.983 and 0.995, respectively. Finally, Figure 4(c) shows that for the set of parameters used in the calibration, the value of k_{min} is between 5,000 and 10,000.

5.3 Dependence of k_{min} on the RA parameters α and $n_{\min}$

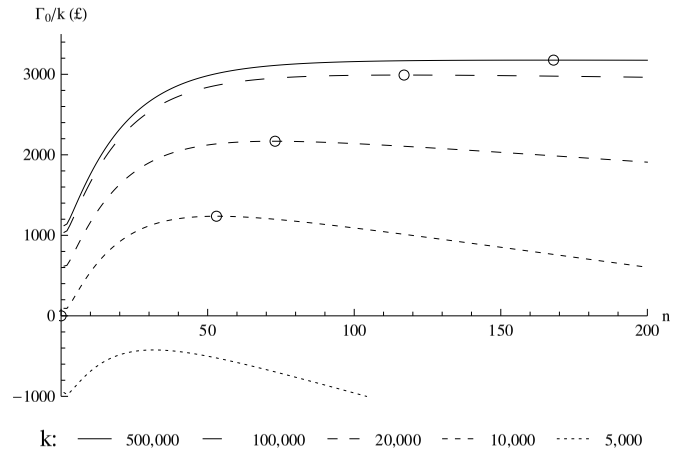
In this section we will take a brief look at how the parameters α and $n_{\min}$, defining the behaviour of the RA, influence the value of k_{min}, the minimum population size required for the HTP to invest in a trial. Figure 4(d) shows k_{min} as a function of $n_{\min}$ for some different values of α, with $5 \leq n_{\min} \leq 80$. As expected, 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 $n^* > n_{\min}$. 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 k_{min} is very small.



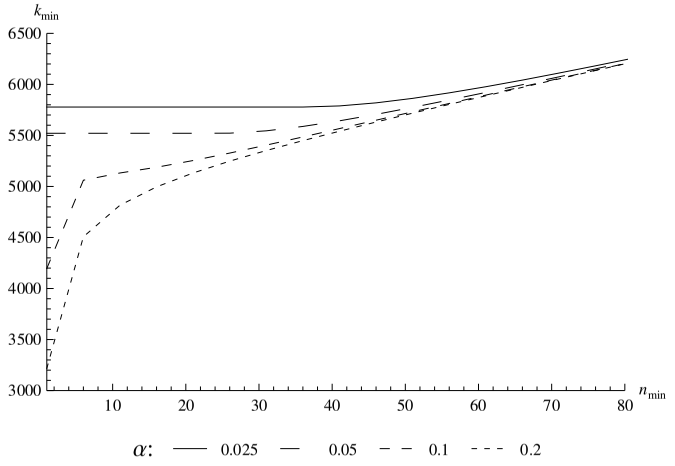
(a) Stage 1 expected profit per patient to benefit (Γ_1/k) as a function of the HTP's proposed Stage 1 price, c for different values of k.



(b) Expected profit at Stage 0 (Γ_0) as a function of sample size, n, for different values of ω.



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



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

Figure 4: Results of sensitivity analyses from the application of Section 5

5.4 The role of uncertainty on the cost-effectiveness threshold

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. Figures 3 and 4(b) show that uncertainty on the HTP's cost-effectiveness threshold has a large impact on the optimal price setting policy, profit and choice of sample size for the HTP. Although a full welfare analysis is beyond the scope of the present work, the results obtained so far provide some interesting insights.

The combination of the analytical results in Section 4.3 with those of the calibration imply that, with a logistic distribution, moving from a situation of no uncertainty on the cost-effectiveness threshold to one with some uncertainty reduces c^*, Γ_0^* and n^*. Hence, for this particular case, more uncertainty on the cost-effectiveness threshold implies more uncertainty on the true effectiveness of the treatment, due to the smaller size of the trial. Moving to a higher range of values of ω, it is interesting to observe that, for the application under consideration, if NICE reduced ω from 11,230 to 5,000 the impact would be: a lower price (Figure 3), a stronger incentive to invest in R&D via Γ_0^* (Figure 4(b)) 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. Provided that $\nu\bar{x} > c_p(k)$, the HTP's optimal price choice in Stage 1 is $c^* = \nu\bar{x}$. If instead $\nu\bar{x} \leq c_p(k)$, then no price is proposed, so Stage 1 profits equal zero. Hence, the optimal Stage 0 sample size is found by solving

$$\max_{n \geq n_{\min}} \left\{ \int_{h(n)}^{\infty} k \max(\nu\bar{x} - c_p(k), 0) f_n(\bar{x}) \, \mathrm{d}\bar{x} - (I_0 + dn) \right\}.$$

With parameter values as in the application of Section 5, the optimal sample size for this special case was found to be $n^* = 135$, with an optimal profit of £575,000,000. In comparison, for the situation where ω equals the value calibrated from NICE's actual decisions, $\omega =$ £11,230/QALY, $n^* = 117$ 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.

6 Discussion and Conclusions

Historically, clinical trials were mainly designed with the objective of obtaining registration by demonstrating effectiveness and safety of the new drug, with economic evaluation playing a secondary role. The increasing need for regulators to assess the economic implications of their decisions implies that integration between these two types of evaluation is much greater nowadays.

To the best of our knowledge, the two-stage model that we propose is the first to investigate how regulation of access to the market interacts with the decision by health care insurers on whether to reimburse a new pharmaceutical.

Results confirm that the size of the population to treat has a very large impact on the decision by a firm to invest in R&D for a specific disease. At the stage where a decision on the reimbursement of the new product is made, the optimal price increases when the population size decreases, which in turn implies a lower probability of acceptance for orphan drugs. As a result, it is the case that both total profit and profit per patient are smaller, the rarer is the disease. These results carry over to the decision about whether to undertake R&D investment: there exists a smaller expected profit and a higher probability that not undertaking R&D investment at all is optimal. The possibility that the RA requires a minimum sample size to consider the application reinforces this result, because this is more likely to be binding for a rare disease.

In our framework, a number of policy variables have an impact on these decisions and could be used as incentive mechanisms. Some of them have to do with the commercialization stage (Stage 1), others with the development stage (Stage 0). The decision by the European Commission to grant exclusivity in the market for new orphan drugs for a period of 10 years is an incentive related to the former. Similarly, consistent with some results of the literature (Jena and Philipson, 2008) one could think of setting higher cost-effectiveness thresholds for rare diseases. In our analysis, we pay particular attention to the role of the degree of uncertainty around the true value of these thresholds, rather than to their level. We show that, for reasonable functional forms, introducing a small amount of uncertainty reduces the maximum expected return of the R&D investment for the firm with respect to the case of no uncertainty. Moreover, the optimal trial sample size is also reduced. The policy implication is that introducing uncertainty on the reimbursement decision may result in a less precise estimate of the new treatment's effectiveness. However, the result is not monotonic and the sign of the impact on both expected profit and optimal sample size changes to positive for higher levels of uncertainty. This result holds independently of the size of the population to treat. Interestingly, for our application, results suggest that by reducing, but not eliminating, the degree of uncertainty by some amount from our estimate of the current degree of uncertainty on the true value of the threshold, NICE could obtain a lower price, a stronger incentive to invest in R&D for the industry and more precision in the estimate of the effectiveness.

Concerning incentives that can be provided at the development stage, it has been suggested that this opportunity 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.

Although the calibration seems to suggest that the model can predict pretty well price and sample size setting policy by the firm, it also comes with a number of limitations. For example, it is assumed that there is only one authority deciding on market access – the RA – and one deciding 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 true for

insurers.

RA rules are similar in the two main regions, US and EU, and there is a relatively well established practice on the requirements of efficacy, in that it is normally required that two Phase III trials demonstrate efficacy of a new drug. However, it is not uncommon to see decisions based on only one trial, as we assume, for example, if trial results are complemented by sufficiently strong evidence of efficacy from Phase II, if a large mortality trial is performed, if the patient population is small or if the drug already has already been shown to be efficacious for a similar indication. Moreover, relaxing this assumption would not change our results.

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.

Regarding commercialisation, our model is based on NICE's approach, which is clearly stated as dependent on cost per QALY. Reasons to focus on this system are that it is relatively well described and understood, that empirical data on NICE decisions is readily available, and that NICE's paradigm and decisions are influential for other HCIs. In contrast, 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. Moreover, decisions made in different countries may not be independent, for example when reference pricing mechanisms are adopted. Taking this into account would raise a number of interesting and challenging questions related to strategic interactions and the optimal sequence of reimbursement decisions from the perspective of the company, as well as increasing the potential size of the market. Another valuable extension would be allowing for further rounds of negotiations in case of rejection.

Ideally, one would also get rid of 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. This would mean that incremental cost and effectiveness are not independent. Methods similar to those used by Kikuchi and Gittins (2009) and Kikuchi et al. (2008) (see Section 2) could be used to incorporate such a relationship.

Finally, it has been assumed that the increase in QALYs is proportional to the increase in efficacy. This proportionality may be reasonable, but may depend on the scale on which efficacy is measured. For example, QALY benefit is normally linked more directly to average survival time, or time to progression, than to the hazard ratio (which is the standard efficacy variable in oncology trials). In this case, the variables are merely measuring the same thing (survival) in different ways. 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. In an extension, we could therefore assume that two different, but correlated, response variables are in focus in the two different stages of the model. An interesting research question is to what extent such a lack of alignment between RAs and HCIs could disincentivise drug development. Recently, the EMA has invited HCIs to increase the alignment.

Future research will aim to remove these and to address some related issues that have not been studied here. Underlying the concern for the lack of incentives to invest in R&D for orphan diseases is an equity argument, i.e. the idea that people should not have fewer chances to be treated because their disease is rare.[8] One way to incorporate the rarity of the disease into the model would be to allow the size of the population to directly affect directly the probability of adoption. A natural extension would be to study the equity-efficiency trade-off, if any, that is, whether improving incentives to invest in rare diseases in comparison with more common ones, keeping the budget constant, has a price in terms of total expected health benefit in the population.

Acknowledgements

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no 602552.

[8]The EU's statement on this matter is: 'patients suffering from rare conditions should be entitled to the same quality of treatment as other patients; it is therefore necessary to stimulate the research, development and bringing to the market of appropriate medications by the pharmaceutical industry (European Union (2000)).

A Proofs

A.1 c^* is $\mathcal{C}^{(1)}$

In order to establish that $c^*(k, \bar{x}, \nu, \omega) \in \mathcal{C}^{(1)}$ the implicit function theorem (Rudin, 1976, p. 224) may be applied. The theorem requires that $\mathrm{P} \in \mathcal{C}^{(2)}$ and $c_p(k) \in \mathcal{C}^{(1)}$, which we have assumed explicitly. Further, it must be verified that

$$\left.\frac{\partial^2 \Gamma_1}{\partial c^2}\right|_{c=c^*} \neq 0.$$

The first and second order partial derivatives of Γ_1 w.r.t. c are given by

$$\begin{aligned}\frac{\partial \Gamma_1}{\partial c} &= k\left(\mathrm{P} + (c - c_p(k))\frac{\partial \mathrm{P}}{\partial c}\right)\\ \frac{\partial^2 \Gamma_1}{\partial c^2} &= k\left(\frac{\partial \mathrm{P}}{\partial c} + \frac{\partial \mathrm{P}}{\partial c} + (c - c_p(k))\frac{\partial^2 \mathrm{P}}{\partial c^2}\right).\end{aligned}$$

By definition, c^* solves the FONC, implying

$$(c^* - c_p(k)) = -\left.\left(\frac{\mathrm{P}}{\frac{\partial \mathrm{P}}{\partial c}}\right)\right|_{c=c^*}. \tag{23}$$

It follows that

$$\left.\frac{\partial^2 \Gamma_1}{\partial c^2}\right|_{c=c^*} = k\left.\left(\frac{\partial \mathrm{P}}{\partial c} + \frac{\left(\frac{\partial \mathrm{P}}{\partial c}\right)^2 - \mathrm{P}\frac{\partial^2 \mathrm{P}}{\partial c^2}}{\frac{\partial \mathrm{P}}{\partial c}}\right)\right|_{c=c^*} = k\left.\left[\frac{\partial \mathrm{P}}{\partial c}\left(1 + \frac{\partial}{\partial c}\left(\frac{\mathrm{P}}{\frac{\partial \mathrm{P}}{\partial c}}\right)\right)\right]\right|_{c=c^*} < 0, \tag{24}$$

where the last inequality follows from (4) and (10).

A.2 Proposition 1 (Stage 1 Optimal Profit Comparative Statics)

Γ_1^* is $\mathcal{C}^{(1)}$ since c is $\mathcal{C}^{(1)}$. Hence, it follows from the envelope theorem, as given in (Varian, 1992, p. 490), that

$$\frac{\partial \Gamma_1^*}{\partial k} = \left.\left(\frac{\partial \Gamma_1}{\partial k}\right)\right|_{c=c^*} = \left.\left((c - c_p(k))\mathrm{P} - k\frac{\partial c_p(k)}{\partial k}\mathrm{P}\right)\right|_{c=c^*} > 0,$$

since $c^* > c_p(k)$ and, by assumption, $\mathrm{P} > 0$ and $\frac{\partial c_p(k)}{\partial k} < 0$. For any other variable y ($\bar{x}$ or ν) the corresponding result is

$$\frac{\partial \Gamma_1^*}{\partial y} = \left.\left(\frac{\partial \Gamma_1}{\partial y}\right)\right|_{c=c^*} = \left.\left(k(c - c_p(k))\left(\frac{\partial \mathrm{P}}{\partial y}\right)\right)\right|_{c=c^*}.$$

Hence, the sign of $\frac{\partial \Gamma_1^*}{\partial y}$ equals the sign of $\left.\left(\frac{\partial \mathrm{P}}{\partial y}\right)\right|_{c=c^*}$ and Proposition 1 follows.

A.3 Proposition 3 (Stage 0 Optimal Profit Comparative Statics)

For these results, $\Gamma_0^* > 0$ denotes the optimal profit corresponding to a unique optimal choice $n^* > n_{\min}$ in an open set of values for k, ν and ω. By the envelope theorem, Leibniz's rule and the corresponding results for Γ_1^*, partial differentiation of Γ_0 w.r.t. k and ν gives

$$\frac{\partial \Gamma_0^*}{\partial k} = \left(\frac{\partial \Gamma_0}{\partial k}\right)\bigg|_{n=n^*} = \left(\int_{h(n)}^{\infty} \frac{\partial(\Gamma_1^*)}{\partial k} f_n(\bar{x})\,\mathrm{d}\bar{x}\right)\bigg|_{n=n^*} > 0,$$
$$\frac{\partial \Gamma_0^*}{\partial \nu} = \left(\frac{\partial \Gamma_0}{\partial \nu}\right)\bigg|_{n=n^*} = \left(\int_{h(n)}^{\infty} \frac{\partial(\Gamma_1^*)}{\partial \nu} f_n(\bar{x})\,\mathrm{d}\bar{x}\right)\bigg|_{n=n^*} > 0.$$

A.4 Proposition 2 (Stage 1 Optimal Price Comparative Statics)

By differentiating (23) w.r.t. y (= k, $\bar{x}$ or ν) and rearranging terms, we obtain

$$\frac{\partial c^*}{\partial y} = \left(\frac{\frac{\partial c_p(k)}{\partial y} - \frac{\partial}{\partial y}\left(\frac{\mathrm{P}}{\frac{\partial \mathrm{P}}{\partial c}}\right)}{1 + \frac{\partial}{\partial c}\left(\frac{\mathrm{P}}{\frac{\partial \mathrm{P}}{\partial c}}\right)}\right)\bigg|_{c=c^*}. \tag{25}$$

Hence, by (10), the sign of $\frac{\partial c^*}{\partial y}$ is equal to the sign of the numerator in Eq. (25). If $y = k$, then $\frac{\partial c^*}{\partial k} < 0$ since $\frac{\partial c_p(k)}{\partial k} < 0$ and P by assumption does not depend on k. For any other y (= $\bar{x}$ or ν), since $c_p(k)$ only depends on k, the numerator is reduced to

$$-\frac{\partial}{\partial y}\left(\frac{\mathrm{P}}{\frac{\partial \mathrm{P}}{\partial c}}\right)\bigg|_{c=c^*} = -\frac{\partial}{\partial y}\left(\frac{c}{e_{Pc}}\right)\bigg|_{c=c^*} = -c^*\frac{\partial}{\partial y}\left(\frac{1}{e_{Pc}}\right)\bigg|_{c=c^*} = c^*\left(\frac{\frac{\partial e_{Pc}}{\partial y}}{e_{Pc}^2}\right)\bigg|_{c=c^*},$$

which must be positive by (12) and the fact that $c^* > c_p(k)$.

B Sources of parameter values for application

Both Phase III trials use as their primary outcome the improvement in FEV_1. The trials overlapped in time, with the second one (Aitken et al. 2013) starting as the first (Bilton et al. 2011) was concluding.

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):

$$\sigma = \text{SE}(\bar{X}) \left(\sqrt{1/n_t + 1/n_c} \right)^{-1}, \tag{26}$$

where $\text{SE}(\bar{X}) = (116.6 - 85.03)/1.96 = 16.10$, obtained from the 95% confidence interval. Solving Eq. (26) 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, $\sigma_0 = SE(\bar{X}) = 16.10$.

References

Acemoglu, D. and Linn, J. (2004). Market size in innovation: theory and evidence from the pharmaceutical industry. *The Quarterly Journal of Economics*, 119(3):1049–1090.

Aitken, M., Bellon, G., Boeck, K. D., et al. (2013). Long-term inhaled dry powder manniitol in cystic fibrosis. an international randomized study. *Americal Journal of Respiratory and Critical Care Medicine*, 185(6):645–652.

Berger, J. O. (1993). *Decision Theory and Bayesian Analysis*. Springer Series in Statistics, New York, second edition.

Bilton, D., Robinson, P., Cooper, P., et al. (2011). Inhaled dry powder mannitol in cystic fibrosis: an efficacy and safety study. *European Respiratory Journal*, 38:1071–1080.

Braun, M., Farag-El-Massah, S., Xu, K., and Coté, T. (2010). Emergence of orphan drugs in the United States: a quantitative assessment of the first 25 years. *Nature Reviews. Drug Discovery*, 9:519–522.

Clarke, J. T., Coyle, D., Evans, G., Martin, J., and Winquist, E. (2014). Toward a functional definition of a 'rare disease' for regulatory authorities and funding agencies. *Value in Health*, 17(8):757–761.

Cook, J., Vernon, J., and Mannin, R. (2008). Pharmaceutical risk-sharing agreements. *Pharmacoeconomics*, 26:551–6.

Dakin, H., Devlin, N., Feng, Y., Rice, N., O'Neill, P., and Parkin, D. (2014). The influence of cost-effectiveness and other factors on NICE decisions. *Health Economics*.

Danzon, P., Towse, A., and Mestre-Ferrandiz, J. (2015). Value-based differential pricing: efficient prices for drugs in a global context. *Health Economics*, 24(3):294–301.

Danzon, P. M. and Epstein, A. J. (2008). Effects of regulation on drug launch and pricing in interdependent markets. NBER Working Papers 14041, National Bureau of Economic Research, Inc.

Danzon, P. M., Wang, Y. R., and Wang, L. (2005). The impact of price regulation on the launch delay of new drugs - evidence from twenty-five major markets in the 1990s. *Health Economics*, 14(3):269–292.

DeGroot (1970). *Optimal Statistical Decisions*. McGraw-Hill, New York, First edition.

DiMasi, J. A., Hansen, R. W., and Grabowski, H. G. (2003). The price of innovation: new estimates of drug development costs. *Journal of Health Economics*, 22(2):151–185.

Dimitri, N. (2012). R & D investments for neglected diseases can be sensitive to the economic goal of pharmaceutical companies. *Drug Discovery Today*, 17(15/16):818–823.

Dranove, D. and Meltzer, D. (1994). Do important drugs reach the market sooner? *RAND Journal of Economics*, 25(3):402–423.

Eichler, H.-G., Abadie, E., Breckenridge, A., Flamion, B., Gustafsson, L. L., Leufkens, H., Rowland, M., Schneider, C. K., and Bloechl-Daum, B. (2011). Bridging the efficacy-effectiveness gap: a regulator's perspective on addressing variability of drug response. *Nature Reviews. Drug Discovery*, 10(7):495–506.

European Union (2000). Regulation on orphan medicines. EC/141/2000.

Filson, D. (2012). A Markov-perfect equilibrium model of the impacts of price controls on the performance of the pharmaceutical industry. *RAND Journal of Economics*, 43(1):110–138.

Food and Drug Administration (1998). Guidance for industry providing clinical evidence of effectiveness for human drug and biological products. Rockville, MD. Available from `http://www.fda.gov/downloads/Drugs/.../Guidances/ucm078749.pdf`.

Food and Drug Administration (2013). Pulmonary-Allergy Drugs Advisory Committee Meeting, January 30, 2013. NDA# 202049: mannitol inhalation powder (proposed name Bronchitol) for oral inhalation sponsored by Pharmaxis for the management of cystic fibrosis (CF) in patients aged 6 years and older to improve pulmonary function.

Gittins, J. and Pezeshk, H. (2000). A behavioural Bayes method for determining the size of a clinical trial. *Drug Information Journal*, 34:355–363.

Golec, J., Hegde, S., and Vernon, J. A. (2010). Pharmaceutical R&D spending and threats of price regulation. *Journal of Financial and Quantitative Analysis*, 45(01):239–264.

Jena, A. B. and Philipson, T. (2008). Cost-effectiveness analysis and innovation. *Journal of Health Economics*, 27(5):1224–1236.

Kikuchi, T. and Gittins, J. (2009). A behavioural Bayes method to determine the sample size of a clinical trial considering efficacy and safety. *Statistics in Medicine*, 28:2293–2306.

Kikuchi, T., Pezeshk, H., and Gittins, J. (2008). A Bayesian cost-benefit approach to the determination of sample size in clinical trials. *Statistics in Medicine*, 27:68–82.

Kyle, M. K. (2007). Pharmaceutical price controls and entry strategies. *The Review of Economics and Statistics*, 89(1):88–99.

Levaggi, R., Moretto, M., and Pertile, P. (2013). The dynamics of pharmaceutical regulation and R&D investments. Working Papers 13/2013, University of Verona, Department of Economics.

Magazzini, L., Pammolli, F., and Riccaboni, M. (2013). Market structure, sunk costs and entry in pharmaceutical R & D. Available from: http://www.eea-esem.com/files/papers/eea-esem/2013/1570/MPR_ESEM.pdf.

McCabe, C., Claxton, K., and Culyer, A. J. (2008). The NICE cost-effectiveness threshold. What it is and what it means. *Pharmacoeconomics*, 26(9):733–744.

NICE (2012a). Mannitol dry powder for inhalation for treating cystic fibrosis. Costing statement. NICE technology appraisal guidance 266. London.

NICE (2012b). Mannitol dry powder for inhalation for treating cystic fibrosis. Technology Appraisal Guidance 266. London.

OECD (2013). Health at a glance 2013: OECD indicators. Technical report, OECD.

Orphanet (2014). Prevalence of rare diseases. Listed in alphabetical order of disease or group of diseases. Available from www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf.

Pammolli, F., Magazzini, L., and Riccaboni, M. (2011). The productivity crisis in pharmaceutical R&D. *Nature Reviews. Drug Discovery*, 10(6):428–438.

Pennings, E. and Sereno, L. (2011). Evaluating pharmaceutical R & D under technical and economic uncertainty. *European Journal of Operational Research*, 212:374–385.

Pharmaceutical Research and Manufacturers of America (2014). 2014 biopharmaceutical research industry profile. PhRMA: Washington DC. http://www.phrma.org/sites/default/files/pdf/2014_PhRMA_PROFILE.pdf.

Pita Barros, P. (2011). The simple economics of risk sharing agreements between the NHS and the pharmaceutical industry. *Health Economics*, 20(4):461–470.

Pratt, J., Raiffa, H., and Schlaifer, R. (1995). *Introduction to Statistical Decision Theory*. MIT Press, Cambridge, Mass., Second edition.

Raiffa, H. and Schlaifer, R. (1961). *Applied Statistical Decision Theory*. Harvard University Graduate School of Business Administration, Boston, First edition.

Rudin, W. (1976). *Principles of Mathematical Analysis*. McGraw Hill, Third edition.

Sasinowski, J. J. (2012). Quantum of effectiveness evidence in FDA's approval of orphan drugs: cataloguing FDA's flexibility in regulating therapies for persons with rare disorders. *Drug Information Journal*, 46(2):238–263.

Scannell, J. W., Blanckley, A., Boldon, H., and Warrington, B. (2012). Diagnosing the decline in pharmaceutical R&D efficiency. *Nature Reviews. Drug Discovery*, 11(3):191–200.

The Committee for Orphan Medicinal Products and the European Medicines Agency Scientific Secretariat (2011). European regulation on orphan medicinal products: 10 years of experience and future perspectives. *Nature Reviews. Drug Discovery*, 10:341–349.

Towse, A. and Garrison, L. (2010). Can't get no satisfaction? Will pay for performance help? Toward an economic framework for understanding performance-based risk sharing agreements for innovative medical products. *Pharmacoeconomics*, 28:93–102.

Varian, H. R. (1992). *Microeconomic Analysis*. Norton & Company, Inc., Third edition.

Vernon, J. A. (2005). Examining the link between price regulation and pharmaceutical R&D investment. *Health Economics*, 14(1):1–16.

Weisbrod, B. A. (1991). The health care quadrilemma: An essay on technological change, insurance, quality of care, and cost containment. *Journal of Economic Literature*, 29(2):523–552.

Willan, A. R. (2008). Optimal sample size determinations from an industry perspective based on the expected value of information. *Clinical Trials*, 5:587–594.

Willan, A. R. and Eckermann, S. (2010). Optimal clinical trial design using value of information methods with imperfect implementation. *Health Economics*, 19:549–561.