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

Sebastian Jobjörnsson,<sup>\*</sup> Martin Forster,<sup>†</sup> Paolo Pertile,<sup>‡</sup>  
Carl-Fredrik Burman<sup>§</sup>

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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 concerning 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 of 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:** Pharmaceutical Pricing and Reimbursement; Rare Diseases; Optimal Sample Size

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

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

<sup>‡</sup>Corresponding author. Department of Economics, University of Verona, 37129 Verona, Italy. e-mail: paolo.pertile@univr.it .

<sup>§</sup>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 effort has been targeted towards the process by which new health 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, 2016). 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 delays 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 sam-

63 ple. Hence, disincentives for research into rare diseases may be found at both commercialisation,  
64 and development, stages.

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

73 This paper presents a unified, Bayesian decision-theoretic framework to investigate late-stage  
74 R&D incentives for the pharmaceutical industry in the presence of these two, exogenous, reg-  
75 ulatory stages. We model a health technology provider operating within a defined jurisdiction  
76 (such as at the country level) and define its optimal sampling and pricing policies in a two stage  
77 problem. In the first stage, the provider decides whether to run a Phase III trial and, if it does so,  
78 the trial's sample size. In making its decision, the provider knows that, should the regulatory au-  
79 thority which reviews the trial evidence deem the treatment to be effective at a predefined level of  
80 statistical significance, the provider may apply for reimbursement by a health care insurer in the  
81 second stage. This involves proposing a price for the new product which, when combined with  
82 the evidence on effectiveness provided by the trial, determines the incremental cost-effectiveness  
83 ratio upon which the health care insurer bases its reimbursement decision.

84 To the best of our knowledge, our model is the first to present a full analysis of how the 'dou-  
85 ble hurdle', in the form of the regulatory authority and the health care insurer, affects optimal  
86 price, expected profit, the 'go/no go' decision for a Phase III clinical trial, and the trial's sample  
87 size. A key result is that the degree of uncertainty surrounding the true value of the insurer's  
88 maximum willingness to pay for a unit increase in effectiveness has a non-monotonic impact on  
89 the optimal price of the innovation, the firm's optimal expected profit and the optimal sample  
90 size chosen for the Phase III clinical trial. We identify three ranges for the uncertainty parameter,  
91 in which increases in uncertainty have different effects. In the 'low uncertainty' range, increases  
92 in uncertainty result in lower prices, lower expected profits and a smaller trial sample size. In  
93 the 'high uncertainty' range, the situation is reversed: greater uncertainty leads to higher prices,  
94 higher expected profits and a larger trial sample size. Intuitively, when there exists low uncer-  
95 tainty, the mass of the probability distribution for willingness to pay is concentrated around its  
96 expected value. Price and profits fall following a small increase in uncertainty because a price  
97 reduction maintains the probability of adoption at a comparatively high level, while causing a  
98 relatively small reduction in the value of revenues conditional upon adoption. In contrast, when  
99 there exists high uncertainty, price and profits rise following an increase in uncertainty because  
100 a price rise has little impact on the probability of adoption but increases the reward in the event  
101 that adoption takes place.

102 For 'intermediate uncertainty', prices are increasing, expected profits decreasing and sample  
103 size decreasing in the degree of uncertainty. This implies that there exists a range of values  
104 of the uncertainty parameter – the 'intermediate uncertainty' range – over which a reduction  
105 in uncertainty benefits the firm, the insurer and patients. Subsequent analysis considers how the

106 regulatory framework may influence a health technology provider’s incentive to invest in projects  
107 which are deemed by the provider to be ‘marginal’, that is, ones for which the expected profit is  
108 close to zero, by looking at the incentive to research treatments for rare diseases. In particular, we  
109 characterise the minimum size of a population to treat such that the firm is incentivised to invest  
110 in the development of a new drug. In an application using published data from trials of a new  
111 treatment for cystic fibrosis, defined as a rare disease by the Orphanet register of rare diseases  
112 (Orphanet, 2014), we show how parameters and regulatory policies in both periods, such as the  
113 level of the Type I error that characterises the regulatory authority’s decision and the uncertainty  
114 surrounding the level of the payer’s maximum willingness to pay for one effectiveness unit, can  
115 affect the incentives to invest.

116 Section 2 presents a brief summary of the literature. Section 3 presents the model. Sections  
117 3.1 to 3.3 provide a non-technical introduction to the model, and additional technical elements  
118 that are required to obtain the main propositions are introduced in Section 3.4. Theoretical results  
119 for optimal policies at the regulatory and pricing stages are presented in Section 4. Those wishing  
120 to skip the technical material and the formal solution of the optimisation problem may omit  
121 Sections 3.4 and 4 and move directly to the application, which is presented in a self-contained  
122 manner in Section 5. Section 6 discusses the main results, avenues for future research, and  
123 concludes.

## 124 **2 Background**

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

136 Acemoglu and Linn (2004) consider the effect of the potential size of markets on pharma-  
137 ceutical innovation and entry of new drugs. The authors derive an equilibrium condition for the  
138 levels of R&D effort and show that, the greater is the market size, the more profitable it is to sup-  
139 ply the drug and so the greater will be the research effort required to gain market-leader position.  
140 Magazzini et al. (2013) consider the effects of R&D sunk cost and market size on a pharmaceu-  
141 tical company’s decision to enter a clinical trial. They present a two-stage model with a number  
142 of firms which can enter one or more therapeutic submarkets and compete for customers. In  
143 line with Acemoglu and Linn, the authors predict that, the greater is the market size, the higher  
144 is the total R&D investment. With lower success rates and a higher cost per trial, fewer firms  
145 enter clinical testing. Further, an increase in sunk R&D expenditures lowers the number of trials

146 and firms. Pennings and Sereno (2011) present a real options model evaluating pharmaceutical  
147 R&D under what they term ‘technical’ and ‘economic’ uncertainty. They recognise the risk of  
148 failure (for example, due to safety issues) during drug development, but do not model clinical  
149 trial design or pricing. Dranove and Meltzer (1994) are concerned with the time for new medical  
150 entities to be approved in the US and conclude that, since the 1950s, more important drugs reach  
151 the market sooner than less important ones.

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

### 156 3 The model

157 We take the perspective of a Health Technology Provider (HTP) considering whether to com-  
158 mission a Phase III clinical trial to evaluate the efficacy of a new drug. Let  $\mu$  be the expected  
159 value of the incremental effectiveness of the new treatment versus standard in the population  
160 (assumed unknown to all agents). For simplicity we assume that the trial is placebo-controlled,  
161 an assumption which may be justified when there exists no approved treatment, or when the new  
162 treatment is given as an add-on to existing standard treatment. The HTP has a prior distribution  
163 on  $\mu$ , defined by a normal random variable with mean  $\mu_0$  and variance  $\sigma_0^2$ .

164 It is assumed that the  $n$  responses observed in the trial are used to calculate the sample mean  
165  $X$ , an unbiased and consistent estimator of  $\mu$ :

$$X | \mu \sim \mathcal{N}\left(\mu, \frac{\sigma^2}{n}\right), \quad (1)$$

166 where  $\sigma$  is assumed known to all agents. We use the convention that upper case denotes a random  
167 variable (e.g., at the start of the planning horizon,  $X$  is a random variable) and lower case denotes  
168 its realisation (e.g., once the trial has concluded,  $x$  denotes the realisation of  $X$ ).

169 The HTP knows that, if a clinical trial is commissioned, upon its completion, a Regulatory  
170 Authority (RA) in charge of granting access to a market with  $N$  patients considers the trial’s ev-  
171 idence concerning the drug’s incremental effectiveness, together with its standard error. There is  
172 no threat of entry which challenges the market size  $N$ , and so it is assumed that  $N$  is known with  
173 certainty by the HTP. We call this stage – establishment of prior, trial commissioning, conduct,  
174 reporting and RA assessment – ‘Stage 0’.

175 If RA approval is granted, the HTP tries to have the new drug reimbursed by a Health Care  
176 Insurer (HCI) by proposing a price,  $p > 0$ , for the treatment of a single patient in the market.  
177 This stage is called ‘Stage 1’. In proposing the price, the HTP does not know the value of the  
178 HCI’s maximum willingness to pay (WTP) for an additional unit of effectiveness, i.e. the cost-  
179 effectiveness threshold. Rather, the uncertainty concerning the HCI’s maximum WTP, from the  
180 perspective of the HTP, is modelled as a random variable so that, in seeking a higher price for the  
181 drug, the HTP faces a trade-off: a higher proposed price offers the potential for higher profits,  
182 but it reduces the probability that the drug is reimbursed by the HCI.

183 The HTP’s choice variables may be summarised as follows: 1. the Stage 0 decision concern-  
 184 ing whether or not to commission a trial and, if a trial is commissioned, what its sample size,  $n$ ,  
 185 should be; 2. in the event that RA approval is granted, the Stage 1 decision of proposing a price  
 186 to the HCI. The HTP’s ‘planning horizon’, over which optimisation takes place, comprises both  
 187 Stages 0 and 1.

188 The optimal Stage 1 pricing policy depends on the estimate of incremental effectiveness that  
 189 results from the clinical trial, which is a random variable from the perspective of Stage 0. Hence  
 190 the problem must be solved recursively. The Stage 1 problem is solved first to yield an optimal  
 191 pricing policy conditional upon  $x$ . Then the Stage 0 problem is solved, using the HTP’s beliefs  
 192 about the realisation of  $X$  that will result from the clinical trial, to determine whether or not  
 193 to commission the trial, as well as its optimal sample size, accounting for the optimal Stage 1  
 194 pricing policy.

### 195 3.1 The Regulatory Authority

196 Conditional upon meeting a requirement for a minimum sample size,  $n_{\min}$ , for the trial, the RA’s  
 197 decision is based upon classical frequentist statistical criteria, so that the new treatment is re-  
 198 quired to show superiority to placebo at a given one-sided level of statistical significance,  $\alpha$ ,  
 199 where  $\alpha$  is conventionally taken to be 2.5% (Food and Drug Administration, 1998). Hence ap-  
 200 proval for the new treatment will be granted if and only if  $n \geq n_{\min}$  and the observed value of  
 201 incremental effectiveness,  $x$ , exceeds a critical value,  $x_{\text{crit}}(n) > 0$ , defined as:

$$x_{\text{crit}}(n) \equiv \frac{z_{\alpha}\sigma}{\sqrt{n}}, \quad (2)$$

202 where  $z_{\alpha}$  is the standard normal  $Z$ -value corresponding to the one-sided significance level,  $\alpha$ .  
 203 If this condition is not satisfied, the treatment is rejected by the RA and is not taken forward to  
 204 Stage 1. If the condition is satisfied, the HTP proceeds to Stage 1 and proposes a price to the  
 205 HCI.

### 206 3.2 The Health Care Insurer

207 The HCI aims to ensure that only innovations that are deemed to be ‘good value for money’ are  
 208 reimbursed. It compares  $x$  with the price,  $p$ , proposed by the HTP, using the incremental cost  
 209 effectiveness ratio (ICER). We ignore differences in costs which are not directly related to the  
 210 cost of the drug, implying that the ICER considered by the HCI is  $p/x$ . The drug is approved if  
 211 this proposed ICER is less than, or equal to, the HCI’s maximum WTP for an additional unit of  
 212 effectiveness.

213 From the perspective of the HTP, the value of the HCI’s maximum WTP is uncertain and  
 214 is modelled using a continuous random variable,  $W$ , with cumulative distribution function  $F_W$ .  
 215 We assume that  $F_W$  belongs to a location-scale family of random variables, meaning that we can  
 216 characterise any member in terms of the pair  $(m, s)$ , where  $m$  is the expected value (location) of  
 217  $W$  and the scale,  $s$ , can be considered a measure of its uncertainty, or spread. This assumption  
 218 is commonly applied in economic models of decision making under risk (Meyer, 1987) and

219 covers a wide class of distributions, including the uniform, normal and logistic. It is sufficiently  
 220 general to contain members that can be used to approximate uncertainty concerning WTP; it is  
 221 sufficiently simple to allow for a convenient and easily understandable parameterisation.

### 222 **3.3 The Health Technology Provider’s problem**

223 At the beginning of Stage 0, the HTP must decide whether or not it should enter Phase III clinical  
 224 testing and, if it does, the optimal sample size for the trial. The cost of performing the trial is  
 225 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  
 226 of increasing the sample size by one unit.

227 Once the trial has taken place and  $x$  is known, if RA approval is granted, the HTP’s Stage 1  
 228 problem is to propose a price,  $p$ , to the HCI. For the purposes of subsequent analysis we note that,  
 229 since  $x$  is known in Stage 1, an increase (decrease) in  $p$  always implies an increase (decrease) in  
 230 the ICER. We assume that the fixed cost of commercialising the drug, together with the marginal  
 231 production cost, equal zero. This is plausible if production costs are negligible relative to R&D  
 232 costs, which is true for most pharmaceuticals (Newhouse, 2004; Barton and Emanuel, 2005). In  
 233 Section 5 we relax this assumption using a calibrated application.

234 The HCI will adopt the new drug with probability  $1 - F_W(p/x; m, s)$ , which may be inter-  
 235 preted as the individual expected demand function,  $D_W(\cdot) = 1 - F_W(p/x; m, s)$ . If the drug  
 236 is not approved for reimbursement, the HTP makes zero profits. Define  $\theta \equiv (N, x, m, s)$ . If  
 237 the HCI approves the drug for reimbursement, profits are  $Np$ , implying that the Stage 1 expected  
 238 profit function is:

$$\Gamma_1(p; \theta) = Np [1 - F_W(p/x; m, s)]. \quad (3)$$

239 As already noted, the HTP’s problem is solved recursively. Firstly, it establishes an optimal  
 240 Stage 1 pricing policy as a function of  $x$ , taking into account uncertainty concerning maximum  
 241 WTP. It then uses this policy and its prior on  $\mu$  to solve the Stage 0 problem, make the ‘go/no go’  
 242 decision for the clinical trial, and decide the trial’s optimal sample size. At Stage 0, uncertainty  
 243 on  $\mu$  is encoded using a normal prior density with mean  $\mu_0$  and standard deviation  $\sigma_0$ , so that the  
 244 prior predictive distribution for  $X$  that is used to compute the expected profit over the two stages  
 245 is normal with mean  $\mu_0$  and standard deviation  $\sqrt{\sigma_0^2 + \sigma^2/n}$  (Pratt et al., 1995).

246 In order to derive the main theoretical results of Section 4, it is necessary to state a number  
 247 of assumptions concerning the probability distribution  $F_W$ . These are dealt with in Section 3.4.  
 248 The reader wishing to skip these more technical aspects and the formal solution to the model  
 249 may move directly to the application in Section 5.

### 250 **3.4 Characterisation of the distribution for WTP**

251 Following the ideas in Meyer (1987), Van den Berg (2007) and Johnson and Myatt (2006), we  
 252 introduce the following assumptions on the probability distribution for  $W$ .

#### 253 **A1 (Location-scale family)**

254 Let  $T$  be a random variable with zero mean and finite variance. Assume that the cumulative



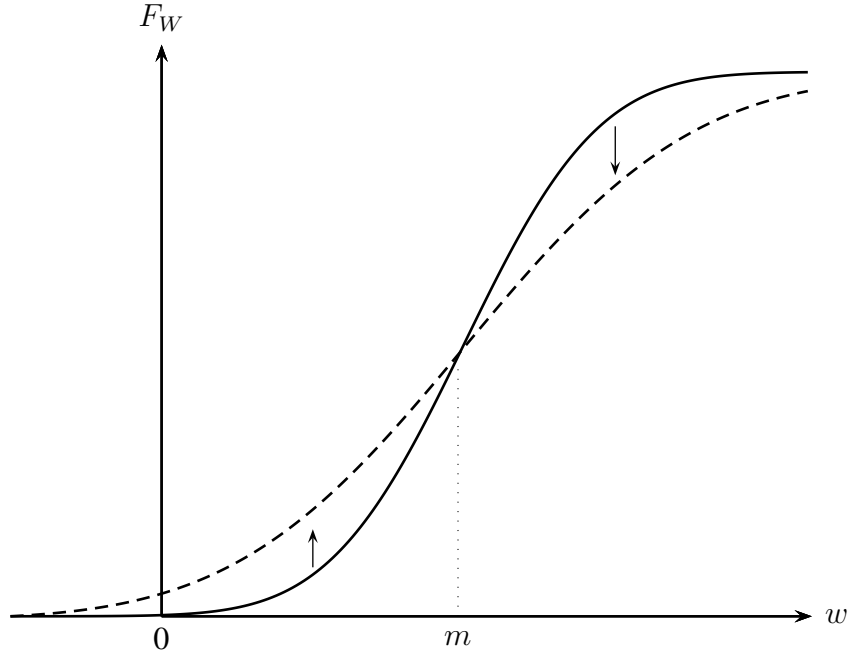


Figure 1: An increase in the uncertainty concerning maximum WTP,  $s$ , rotates its cumulative distribution function,  $F_W$ , around its location parameter,  $m$ .

255 distribution function of  $T$ ,  $F_T$ , is twice continuously differentiable with probability density  
 256 function  $f_T$ . The cumulative distribution function of the HCI's maximum willingness to  
 257 pay,  $F_W$ , is assumed to belong to a location-scale family of random variables defined by  
 258  $F_W(w) = F_T((w - m) / s)$ , where  $m$  is the location parameter and  $s$  the scale parameter.

259 **A2 (Increasing hazard function).**

260 The hazard function of  $T$ ,  $r_T(t) = f_T(t)/(1 - F_T(t))$ , is an increasing function for  $t \in \mathbb{R}$ .

261 Assumption **A1** permits us uniquely to define any member of the family describing maximum  
 262 WTP in terms of the pair  $(m, s)$ , separating the location and scale properties from the shape of the  
 263 distribution, which is determined by  $F_T$ . It is required to define the existence of an optimal price,  
 264 as well as to obtain comparative statics results. As shown in Figure 1, the assumption implies that  
 265 an increase in  $s$  rotates  $F_W$  around the location parameter  $m$  such that  $F_W$  increases/decreases  
 266 according to whether  $w$  is less than/greater than  $m$ . That is:

$$w \gtrless m \iff \frac{\partial F_W}{\partial s} \lesseqgtr 0. \quad (4)$$

267 Intuitively, an increase in  $s$  implies that the density is moved from the centre of the distribution  
 268 to the tails, while ensuring that the distribution functions cross only once, at  $m$ . The economic  
 269 interpretation is that, following an increase in  $s$ , the expected demand function,  $D_W(\cdot) = 1 -$

270  $F_W(v; m, s)$ , decreases for values of the ICER that are below  $m$  and increases for values that  
 271 are above  $m$ .

272 Assumption **A2** is required to show that the optimal price is unique for every combination  
 273 of the location and scale parameters and may therefore be considered to be a function of  $m$   
 274 and  $s$ . It may best be interpreted by referring to the concept of increasing duration dependence  
 275 borrowed from the survival analysis literature. Let us define the ICER as  $v = p/x$ , so that  
 276  $D_W = 1 - F_W(v; m, s)$  is the probability that the HCI accepts a proposed ICER equal to  $v$ . If  
 277 the HTP increases the ICER by a small amount,  $\Delta$ , the probability of acceptance,  $D_W$ , decreases  
 278 by approximately  $D'_W(v) \Delta$ . Given acceptance of the technology at  $v$ , the conditional probability  
 279 that the technology is rejected due to this price increase is therefore  $\Delta(-D'_W(v)/D_W(v))$  and is  
 280 increasing in  $v$ . Thus,  $r_W(v) = -D'_W(v)/D_W(v)$  can also be interpreted as the marginal risk of  
 281 rejection.

## 282 4 Optimal Stage 0 and 1 policies

283 The Stage 1 problem may be thought of as a monopolist's pricing problem, in which marginal  
 284 cost is equal to zero and there exists a true, fixed, maximum willingness to pay for the new drug.  
 285 This WTP is unknown to the HTP, who therefore places a probability distribution upon it. The  
 286 problem is also similar in nature to models such as those of independent private value auctions  
 287 (Van den Berg, 2007). In this section, we outline the optimal solution for each stage: first, we  
 288 derive the HTP's optimal Stage 1 pricing policy as a function of the estimate of effectiveness  
 289 from the trial. Then we solve for the optimal Stage 0 sample size.

### 290 4.1 Optimal Stage 1 policy

291 At the start of Stage 1,  $x$  is known, whereas  $p$  is to be chosen optimally by the HTP. The Stage  
 292 1 maximisation problem may be considered from the perspective of the optimal choice of the  
 293 ICER,  $v$ , by writing Eq. (3) as follows:

$$294 \Gamma_1^*(\boldsymbol{\theta}) \equiv \max_{v > 0} N x v [1 - F_W(v; m, s)]. \quad (5)$$

294 The optimal ICER is the value  $v = v^*(m, s)$  which solves the first order necessary condition:

$$1 - F_W(v; m, s) - v f_W(v; m, s) = 0, \quad (6)$$

295 or, equivalently,

$$v = \frac{1}{r_W(v; m, s)}, \quad (7)$$

296 which is a simplified version of the standard monopolist's inverse elasticity rule for a single  
 297 product in the presence of zero marginal production cost (Tirole, 1988). By Assumption **A1**, an  
 298 optimal solution to the maximisation problem in Eq. (5) exists and satisfies Eq. (6) because the  
 299 profit function  $\Gamma_1(v; \boldsymbol{\theta})$  is a differentiable function of the ICER,  $v$ , on the interval  $(0, \infty)$  and  
 300 the term  $v[1 - F_W(\cdot)]$  in Eq. (5) tends to zero as  $v$  tends to infinity, owing to the assumption

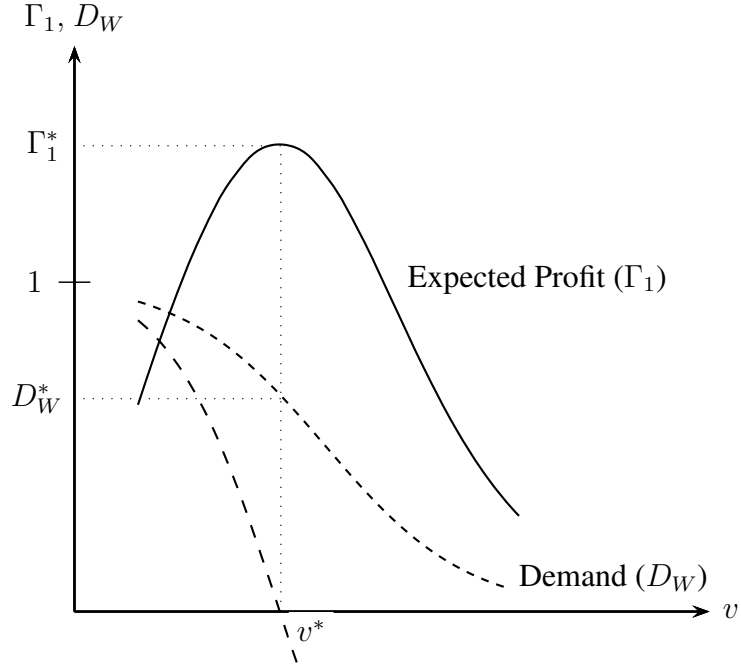


Figure 2: Expected profit function (Eq. (5), continuous line), expected demand function  $D_W(\cdot) \equiv 1 - F_W(v; m, s)$  (short dash) and the LHS of Eq. (6) (long dash) showing the optimal choice of the ICER,  $v^*$ .

301 that  $T$  has a finite mean (Van den Berg, 2007). Assumption **A2** implies that  $1/r_W(v; m, s)$  is  
 302 decreasing in  $v$ , so that the solution  $v^*(m, s)$  of Eq. (7) must be unique.

303 Figure 2 plots the expected profit function,  $\Gamma_1$ , the expected demand function (short dash),  
 304 and the LHS of Eq. (6) (long dash) and shows the determination of the optimal ICER,  $v^*$ . Note  
 305 that, according to Assumption **A1**, an increase in  $s$  rotates  $F_W$  clockwise (Figure 1) and the  
 306 expected demand function counter-clockwise (Figure 2), both around  $m$ . The change in the  
 307 slope of the expected demand function following an increase in  $s$  affects  $v^*$  through Eq. (6).

308 As is clear from comparison of Eqs. (5) and (6),  $N$  and  $x$  affect the level of optimal profits,  
 309 but not the optimal choice of the ICER. This provides two simple, but important, expressions for  
 310 optimal price and profits in terms of the optimal ICER,  $v^*$ , which are required to solve the Stage  
 311 0 problem. They show that the optimal price is independent of the population size, while being  
 312 strictly increasing in the effect size,  $x$ :

$$p^*(x, m, s) = x v^*(m, s), \quad (8a)$$

$$\Gamma_1^*(\theta) = x N \rho^*(m, s), \quad (8b)$$

$$\text{where } \rho^*(m, s) \equiv v^*(m, s) [1 - F_W(v^*(m, s); m, s)]$$

313 The following comparative statics expressions for optimal price (ICER) and profit with respect

314 to  $N$ ,  $x$  and  $m$  are formally derived in Appendix A.1:

$$(i) \quad \frac{\partial \Gamma_1^*}{\partial N} > 0; \quad (ii) \quad \frac{\partial \Gamma_1^*}{\partial x} > 0; \quad (iii) \quad \frac{\partial \Gamma_1^*}{\partial m} > 0; \quad (9a)$$

$$(iv) \quad \frac{\partial p^*}{\partial N} = 0; \quad (v) \quad \frac{\partial p^*}{\partial x} = v^*(m, s) > 0; \quad (vi) \quad \frac{\partial p^*}{\partial m} \geq 0. \quad (9b)$$

315 The results for  $N$  and  $x$  have been discussed above. For  $m$ , the best way to interpret the result is  
 316 to refer to Figure 2: an increase in  $m$  shifts  $D_W$  to the right, raising the probability of acceptance  
 317 at  $v^*$ . The HTP may therefore obtain higher expected profits than before, at a higher price,  
 318 because a marginal increase in  $v$  raises expected revenue while the demand, or probability of  
 319 acceptance, remains above  $D_W^*$ .

320 We next consider results for the response of optimal profit and price to changes in the scale  
 321 parameter,  $s$ , highlighting their importance for this work by stating them as propositions. Both  
 322 Assumptions **A1** and **A2** are needed in the proofs.

323 **Proposition 1 (Effect of uncertainty surrounding the HCI's maximum willingness to pay**  
 324 **on Stage 1 optimal expected profit).** *Optimal Stage 1 profit is a U-shaped function of the un-*  
 325 *certainty surrounding the HCI's maximum willingness to pay for one unit of effectiveness,  $s$ .*  
 326 *The function has a global minimum at  $\hat{s} = m r_T(0)$ . Moreover, the optimal ICER proposed by*  
 327 *the HTP will be lower/higher than  $m$  according to whether  $s$  is lower/higher than  $\hat{s}$ , that is,*  
 328  $m \lesseqgtr v^*(m, s) \iff \hat{s} \lesseqgtr s$ .

329 *Proof:* See Appendix A.1.

330  
 331 Note that, in Proposition 1, a result for the value of  $v^*$  relative to  $m$  is stated in terms of the  
 332 value of  $s$  relative to  $\hat{s}$ . Proposition 2 extends this partial result to a full characterisation of the  
 333 response of the optimal price (and hence the optimal ICER),  $p^*$ , to changes in  $s$ . Proposition  
 334 2 states a sufficient condition which, by ensuring that  $\partial v^*/\partial s$  is a strictly increasing function  
 335 of  $s$  and that  $\lim_{s \rightarrow 0} v^*(m, s) = m$  may be proved, implies a U-shape also for  $v^*$  as a function  
 336 of  $s$ . The proposition requires that an assumption be placed on the Mill's ratio, defined as the  
 337 reciprocal of the hazard function ( $M(t) = 1/r_T(t)$ ), which holds for common distributions such  
 338 as the normal and the logistic.

339 **Proposition 2 (Effect of uncertainty surrounding the HCI's maximum willingness to pay**  
 340 **on Stage 1 optimal expected price).** *If the Mill's ratio,  $M$ , satisfies  $M'' > 0$ , then the optimal*  
 341 *price is a U-shaped function of the uncertainty surrounding the HCI's maximum WTP for one*  
 342 *unit of effectiveness,  $s$ , with a global minimum at some  $\tilde{s} < \hat{s}$ .*

343 *Proof:* See Appendix A.1.

344  
 345 The economic intuition for these results is as follows. When the uncertainty surrounding  
 346 the true value of the HCI's maximum WTP is relatively small ('low uncertainty'), the mass of  
 347 the distribution of  $W$  is concentrated around its expected value. Hence, if  $s$  increases, a small  
 348 reduction in the proposed price keeps the probability of adoption by the HCI comparatively high,

349 while causing just a small reduction in the value of revenues conditional upon adoption. Hence  
 350  $p^*$  decreases with  $s$ . On the other hand, if  $s$  is very large ('high uncertainty'), a small reduction  
 351 in  $p$  affects the probability of adoption only marginally. Hence, if  $s$  increases, it is optimal to  
 352 increase  $p^*$ , to maximise the reward in the event of adoption taking place.

353 Concerning the relative size of the intervals defining low, intermediate and high uncertainty,  
 354 Proposition 1 defines the value of  $\hat{s}$  as a function of  $m$  and the hazard function for the standardised  
 355 distribution chosen to model maximum WTP ( $\hat{s} = mr_T(0)$ ). As is shown in Appendix A.1, the  
 356 position of  $\tilde{s}$  relative to  $\hat{s}$  may also be defined by making reference to this hazard function, using  
 357 results from Proposition 2. A numerical computation shows that  $\hat{s}/\tilde{s} = 2.935$  for the standard  
 358 logistic distribution that is chosen for the application of Section 5.

359 Propositions 1 and 2 have important policy implications, because they imply that, for  $s$  suf-  
 360 ficiently large ( $s > \hat{s}$ ), reductions in uncertainty surrounding the HCI's maximum WTP for one  
 361 unit of effectiveness (e.g. by the HCI being more explicit about the decision process that leads to  
 362 adoption/rejection decisions) induce the HTP to propose lower prices and accept lower expected  
 363 profits. When there is low uncertainty ( $s < \tilde{s}$ ), the same policy would lead to the opposite re-  
 364 sult, that is, higher prices and higher expected profits. Interestingly, for intermediate values of  
 365 uncertainty ( $\tilde{s} < s < \hat{s}$ ), both parties would benefit from greater transparency, because optimal  
 366 prices would be reduced and optimal expected profits increased. The reason is that, with less  
 367 uncertainty, it is optimal for HTPs to propose lower prices, but the increase in the probability of  
 368 acceptance that this would imply is such that expected profits would be higher. Figure 4(a) of the  
 369 application shows the three regions of  $s$  for which these various effects may be observed.

370 As the uncertainty surrounding the value of the HCI's maximum willingness to pay decreases  
 371 towards 0 the expected demand function  $D_W$  converges towards a step function that equals one  
 372 when  $v < m$  and zero when  $v > m$ . In this formal limit case, it is clear that the optimal behaviour  
 373 of the HTP is to choose a price just at the limit of what the HCI will accept, so that  $v^* = m$ . This  
 374 suggests that  $\lim_{s \rightarrow 0} v^*(m, s) = m$  and, further, that, as  $s \rightarrow 0$ , any change in  $m$  is matched by  
 375 an equal change in  $v^*$ .

## 376 4.2 Optimal Stage 0 policy

377 At the start of Stage 0, the HTP is in possession of the following information which allows it to  
 378 make an optimal 'go/no go' decision for the Phase III clinical trial, and to choose the optimal  
 379 sample size of the trial if the decision is 'go': 1. it has a prior distribution on expected incremental  
 380 effectiveness, as described at the start of Section 3; 2. it therefore knows, for any sample size  $n$ ,  
 381 the prior predictive distribution for the point estimate of incremental effectiveness,  $X$ , that will  
 382 result from the Phase III trial (see Section 3.3); 3. it has solved the Stage 1 problem, which has  
 383 established the optimal pricing policy and expected reward as a function of the point estimate,  $x$ ,  
 384 that results from the trial (Eqs. (8a) and (8b)).

385 In this section, we explain how the prior predictive distribution for  $x$  and the optimal Stage 1  
 386 policy may be used to establish the expected reward at Stage 0 for any choice of sample size  $n$   
 387 and hence the optimal Stage 0 'go/no go' and sample size decisions.

### 388 4.2.1 Optimal sample size determination

389 From the perspective of the start of Stage 0, define  $\Gamma_0(n; \cdot)$  as the expected reward of running a  
 390 Phase III trial with a sample size  $n$  and pricing optimally during Stage 1 according to the policy  
 391 of Eq. (8a) to give the reward in Eq. (8b). In Stage 0, the estimate of incremental effectiveness  
 392 that will result from the trial is a random variable,  $X$ . Hence so are the optimal prices and  
 393 rewards, since both are linear functions of the realisation of  $X$  (see Eqs. (8a) and (8b)).

394 The Stage 0 optimal choice of  $n$  uses the prior predictive density for  $X$  to weight the Stage 1  
 395 rewards and calculate the expected total reward for the project as a function of  $n$ . Because, from  
 396 Eq. (8b),  $\Gamma_1^*$  is linear in  $x$ , optimal Stage 0 expected profits,  $\Gamma_0^*$ , may be written as:<sup>1</sup>

$$\Gamma_0^*(\cdot) \equiv \max_n \left\{ N \rho^*(m, s) \mathbb{E} \left[ X \mid X > x_{\text{crit}}(n) \right] \mathcal{P}(X > x_{\text{crit}}(n)) - (I_0 + dn) \right\}, \quad (10)$$

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

397  $\mathcal{P}$  is the probability that the realisation of  $x$  from the trial exceeds the RA's lower acceptance  
 398 threshold,  $x_{\text{crit}}(n)$ . Since the prior predictive distribution for  $X$  is normal with mean  $\mu_0$  and  
 399 standard deviation  $\sigma_p(n) = \sqrt{\sigma_0^2 + \sigma^2/n}$ , it follows that

$$\mathcal{P}(X > x_{\text{crit}}(n)) = 1 - \Phi \left( \frac{x_{\text{crit}}(n) - \mu_0}{\sigma_p(n)} \right), \quad (11)$$

400 where  $\Phi$  denotes the CDF of the standard normal distribution.

401 Changing the sample size,  $n$ , has two effects on expected rewards: firstly, increasing  $n$  re-  
 402 duces the standard deviation of the predictive distribution,  $\sigma_p$ ; secondly, increasing  $n$  lowers the  
 403 acceptance threshold,  $x_{\text{crit}}$ . As a result, changes in  $n$  change both the conditional expected value  
 404 of  $X$  and the conditional probability,  $\mathcal{P}$ , in Eq. (10).

405 For an interior solution,  $n^* > n_{\text{min}}$  and  $\partial \Gamma_0^*(\cdot) / \partial n = 0$ , implying that the following condition  
 406 holds:

$$\frac{N \rho^*(m, s) \mathbb{E}[X \mid X > x_{\text{crit}}(n)] \mathcal{P}(X > x_{\text{crit}}(n))}{n} \left( e_{\mathbb{E}[\cdot], n} + e_{\mathcal{P}(\cdot), n} \right) = d. \quad (12)$$

407 The left hand side of this expression is the marginal benefit (MB) of sampling at Stage 0, ac-  
 408 counting for the optimal pricing policy and optimal expected reward at Stage 1. The right hand  
 409 side is the marginal cost (MC). The marginal benefit expression is best interpreted by breaking  
 410 it into two parts. The term that is not in parentheses measures the expected Stage 1 reward at  
 411 the (Stage 0) *study-subject* level; the expected contribution made to profits of one study subject  
 412 recruited to the trial. The term in parentheses is the elasticity of the Stage 1 expected reward with  
 413 respect to  $n$  (by a standard result for the elasticity of a product, this is equal to the sum of the two

---

<sup>1</sup>This is because expected revenue at Stage 0 is  $\int_{x_{\text{crit}}(n)}^{\infty} x f_X N \rho^*(m, s) dx$ , where  $f_X$  is the pdf of the prior predictive distribution. Eq. (10) follows because  $N \rho^*(m, s)$  is a constant and  $\int_{x_{\text{crit}}(n)}^{\infty} f_X x dx = \mathbb{E} \left[ X \mid X > x_{\text{crit}}(n) \right] \mathcal{P}(X > x_{\text{crit}}(n))$ .

414 elasticities that appear in parentheses). These elasticities capture the two aforementioned effects  
 415 of  $n$  on the conditional expectation and the probability of acceptance, respectively.

416 The per-study-subject expected reward will be strictly positive because  $x_{\text{crit}}(n_{\min})$  can never  
 417 be less than zero. Hence the sign of the marginal benefit function is determined by the signs and  
 418 sizes of the two elasticities. Since both  $\mathbb{E}[X | X > x_{\text{crit}}(n)] > 0$  and  $\mathcal{P}(x > x_{\text{crit}}(n)) > 0$ , the  
 419 sign of each elasticity depends solely on the sign of the partial derivative that each contains. In  
 420 general, marginal benefit may be an increasing, or decreasing, function of  $n$ . There will exist a  
 421 unique optimal value of  $n^* > n_{\min}$  if there is a single point where Eq. (12) is satisfied and the  
 422 marginal benefit function is falling. This situation is illustrated in Figure 3.

423 Although a full characterisation of the Stage 0 optimality condition is hard to obtain because  
 424 of the aforementioned effects of changes in  $n$ , it is possible to state the main Stage 0 result, which  
 425 concerns the comparative statics results for Stage 0 expected profits and optimal sample size with  
 426 respect to  $s$  for the case of a unique  $n^* > n_{\min}$ .

427 **Proposition 3 (Effect of uncertainty surrounding the HCI's maximum willingness to pay on**  
 428 **Stage 0 optimal expected profits and optimal sample size).** (a) *If  $F_W$  satisfies the assumptions*  
 429 *of Section 3 and optimal profit,  $\Gamma_0^*$ , is as defined in Eq. (10), then an increase in uncertainty*  
 430 *increases/decreases Stage 0 profits according to whether  $s$  is greater than or less than  $\hat{s}$  as*  
 431 *defined in Proposition 1:*

$$\frac{\partial \Gamma_0^*}{\partial s} \begin{matrix} \geq \\ < \end{matrix} 0 \iff s \begin{matrix} \geq \\ < \end{matrix} \hat{s}. \quad (13)$$

432 (b) *Suppose  $F_W$  satisfies the assumptions of Section 3 and that there exists a unique  $n^*(N, m, s) >$*   
 433  *$n_{\min}$  which solves Eq. (10). Suppose further that the conditions required for applying the implicit*  
 434 *function theorem in the computation of  $\partial n^*/\partial s$  are fulfilled. Then the optimal sample size is*  
 435 *increasing/decreasing in the level of uncertainty according to whether  $s$  is greater than or less*  
 436 *than  $\hat{s}$ :*

$$\frac{\partial n^*}{\partial s} \begin{matrix} \geq \\ < \end{matrix} 0 \iff s \begin{matrix} \geq \\ < \end{matrix} \hat{s}. \quad (14)$$

437

438 *Proof:* See Appendix A.2.

439

440 Using the same methods of proof, it is possible to derive comparative static results for optimal  
 441 profits with respect to  $N$  and  $m$  under the assumptions of Proposition 3(a) which lead to Eq. (13):

$$(i) \quad \frac{\partial \Gamma_0^*}{\partial N} > 0; \quad (ii) \quad \frac{\partial \Gamma_0^*}{\partial m} > 0. \quad (15)$$

442 Further, under the assumptions of Proposition 3(a) and (b) which lead to Eq. (14), it is possible  
 443 to derive the comparative static results for optimal sample size with respect to  $N$  and  $m$ :

$$(i) \quad \frac{\partial n^*}{\partial N} > 0; \quad (ii) \quad \frac{\partial n^*}{\partial m} > 0. \quad (16)$$

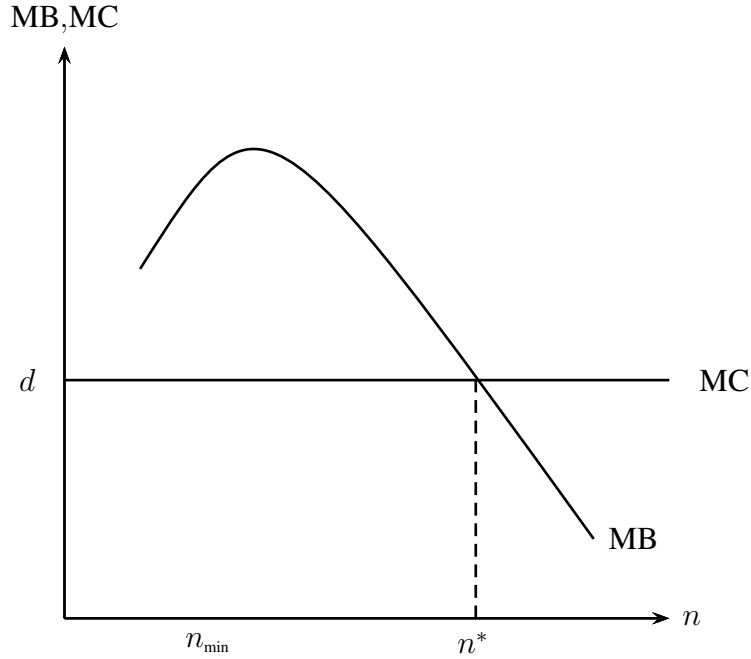


Figure 3: Determination of an interior solution for the optimal sample size at Stage 0 (Eq. (12)).

444 Two policy implications follow from these results. First, an increase in  $m$ , the expected value  
 445 of maximum WTP, not only increases the expected profit of the project, but also the optimal  
 446 sample size of the trial. Second, since the optimal sample size,  $n^*$ , is an increasing function of  
 447 the population size,  $N$ , it will be optimal to select lower sample sizes for rare diseases and there  
 448 will exist a lower bound on population size below which no trial will be optimal. This matter is  
 449 considered next, in the context of the optimal investment decision.

#### 450 4.2.2 Optimal investment decision

451 The dynamic efficiency implications of the regulatory framework that were discussed in Section  
 452 1, that is, the incentives for investment in R&D, can be assessed by considering whether or not the  
 453 HTP chooses to invest in the Phase III trial at the start of Stage 0. Having derived the condition  
 454 for the optimal sample size, the condition for the optimal investment decision is straightforward.  
 455 The project will be started if and only if  $\Gamma_0^*(\cdot) > 0$ .

456 Since  $\Gamma_0^*(N = 0; \cdot) < 0$  and given Eq. (15(i)), this allows us to define the minimum size  
 457 of a population to treat, such that the expected profit of investing in the development of a new  
 458 treatment is non-negative:

$$N_{\min} = \min \{ N \mid \Gamma_0^*(N, \cdot) \geq 0 \}. \quad (17)$$

459 This equation defines a ‘marginal project’ from the perspective of the market size for the drug  
 460 and is required for some of the analysis of the incentives to invest in trials for rare diseases that  
 461 is presented in Section 5.



## 5 Application

The main theoretical results of Section 4 can be summarised as follows:

- Assuming Stage 1 is reached, which occurs if the RA approves the new drug, both optimal price and optimal expected profit are at first decreasing, and then increasing, in the degree of uncertainty surrounding the HCI's maximum WTP for one unit of effectiveness. The minimum point of the HTP's optimal price function lies to the left of the minimum point of the Stage 1 optimal expected profit function.
- In Stage 0, both optimal sample size and expected profit over the two stages are first decreasing, and then increasing, in the degree of uncertainty surrounding the HCI's maximum WTP.

The economic intuition for these results has been stated in the paragraphs immediately following Proposition 2. In this section, we provide a calibrated application of the theoretical model, which we believe is important for a number of reasons. Firstly, it illustrates the U-shaped nature of the optimal price, profit and sample size functions that were described in Propositions 1–3. Secondly, it permits us to use published data to provide tentative estimates of the quantitative impact of changes in some key parameters on optimal values. Thirdly, we generalise the model proposed in the theoretical analysis a little. The numerical results obtained in this section are valid for the specific setting under consideration and cannot be easily extended to different applications. However, the quantitative nature of the numerical results is consistent with the theoretical findings of Section 4. Those wishing to apply the framework in their own settings are referred to the code that is released as part of the Online Supplementary Material.

For the model to be operationalised, a functional form for  $F_W$ , the CDF of the HCI's maximum WTP, must be specified. We use the logistic distribution, which satisfies all of the assumptions of Section 3.4 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), which we refer to in deriving the values of the location and scale parameters.

Throughout Sections 3 and 4, we assumed that there was no cost to produce or commercialise the drug if it were to be 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 a parameter representing the production cost per patient treated,  $c_p(N) \equiv I_1/N + b$ , where  $I_1 \geq 0$  is a fixed investment cost and  $b \geq 0$  is a constant marginal cost of production. With this assumption, the Stage 1 expected profit function (Eq. (3)) may be written as

$$\Gamma_1(p; \tilde{\theta}) = N(p - c_p(N)) [1 - F_W(p/x; m, s)], \quad (18)$$

where  $\tilde{\theta} \equiv (N, x, m, s, I_1, b)$ . For the parameter values which we choose for the simulation, the qualitative nature of our main results agree with the theoretical results. In particular, we observe a U-shaped optimal Stage 1 profit and optimal price function, provided that  $m > c_p(N)/x$

499 (this is a reasonable condition, since it simply requires that the price that the HTP would choose  
500 if HCI's maximum willingness to pay for one effectiveness unit is  $m$  for sure, exceeds  $c_p(N)$ ).<sup>2</sup>

501 We study the recent NICE health technology appraisal of mannitol dry powder (Bronchitol)  
502 for inhalation for treating cystic fibrosis (NICE, 2012b), which is deemed to be a rare disease  
503 according to the Orphanet register of rare diseases, with a prevalence of approximately 12.6 per  
504 100,000 in Europe (Orphanet, 2014).

505 The technology is chosen for a number of reasons. Firstly, the status of cystic fibrosis as  
506 a rare disease means that the R&D decision could potentially be considered to be a 'marginal  
507 project', that is, one with a market size  $N$  that is close to the minimum population size required  
508 for investment to be deemed profitable,  $N_{\min}$  (refer to Eq. (17)). Secondly, high quality data  
509 on the clinical effectiveness, costs and QALYs upon which NICE made its recommendations  
510 are available in the NICE report itself and the publications reporting the results of the two key  
511 Phase III clinical trials (Bilton et al. (2011) and Aitken et al. (2013)). Thirdly, the control was  
512 effectively placebo in both clinical trials, that is, it was the same drug set at a very low, non-  
513 therapeutic, dosage. Finally, although the EMA and NICE approved the product for use in 2012  
514 for a sub-group of cystic fibrosis patients (described below), the U.S. FDA denied marketing  
515 authorisation in 2013, based on the same clinical trial results, citing concerns over the high level  
516 of discontinuation with treatment in the clinical trials and the failure to achieve effects that were  
517 statistically significant.

518 Although the trials reported by and overlapped in calendar time, we assume a hypothetical  
519 scenario in which the first trial (Bilton et al., 2011) reported before the second (Aitken et al.,  
520 2013). This permits us to use results from the first trial to assign values to the parameters of the  
521 model, including the prior mean,  $\mu_0$ , and variance,  $\sigma_0^2$  for expected incremental effectiveness. We  
522 take the perspective of a HTP using information from the first trial to decide whether or not to go  
523 ahead with the second trial. Full details on the calculations that are used to inform the parameter  
524 values are contained in Appendix B.

525 Table 1 summarises the main parameter values, together with their sources. It should be  
526 noted that the application is illustrative and is not intended to be a comment on the efficacy or  
527 cost-effectiveness of the technology in question.

## 528 **5.1 The role of uncertainty**

529 Figure 4(a) shows the U-shaped nature of the optimal ICER (price) and expected Stage 1 profit as  
530 functions of the uncertainty parameter,  $s$ , and the three regions representing 'low', 'intermediate'  
531 and 'high' uncertainty, within which the responses of price and profits to increases in  $s$  differ:

- 532 • The 'low uncertainty' range is defined as the region to the left of the minimum point on

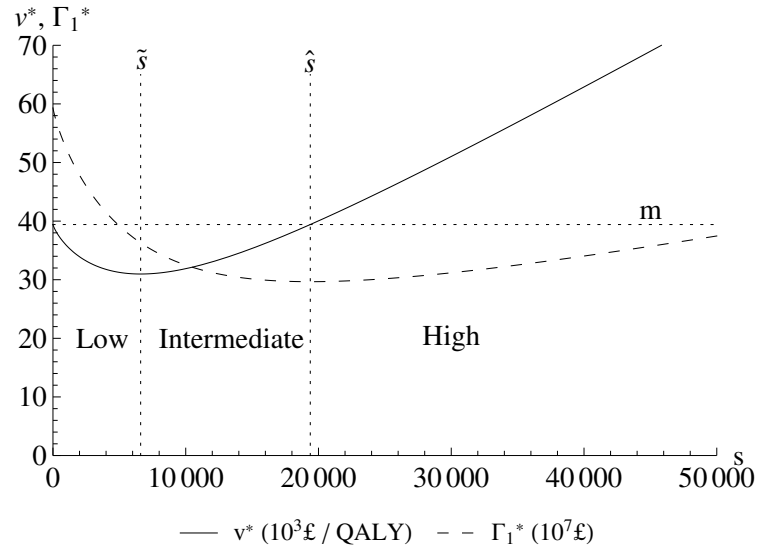
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<sup>2</sup>When introducing fixed and variable production costs, the optimal price is no longer independent of  $N$  but decreasing in it. The derivation of  $\hat{s}$  from Proposition 1, needs to be adjusted as follows:  $\hat{s} = (m - c_p(N)/x)r_T(0)$ . Moreover, the simple result describing the position of  $\hat{s}$  relative to  $\bar{s}$  following Proposition 2 no longer holds, and the optimal ICER is no longer independent of  $x$ . This, in turn, implies that optimal Stage 1 profit is no longer linear in  $x$ , which complicates the theoretical analysis of the optimal Stage 0 policy. Nevertheless, given the parameter values that we choose, the U-shaped behaviour of  $\Gamma_0^*$  and  $n^*$  with respect to  $s$  that was derived for the case  $c_p(N) = 0$  is still observed.

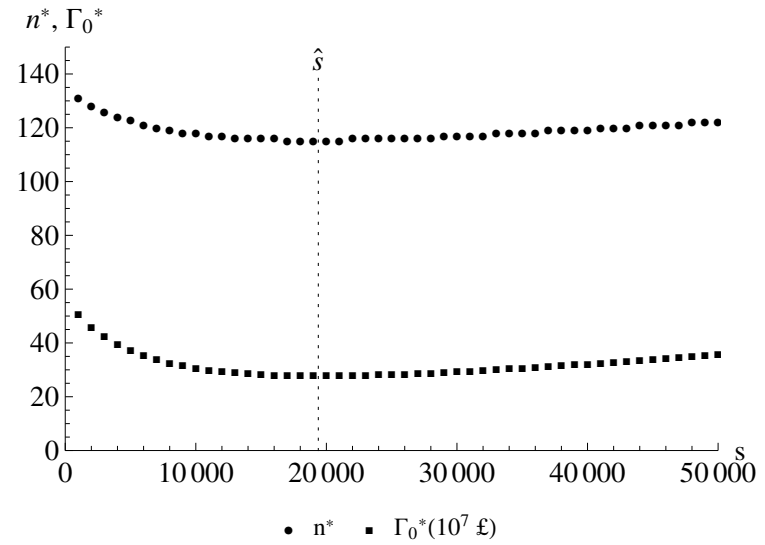
Parameter	Definition	Source	Value
1. $\mu_0$	Expected value of prior beliefs concerning $\mu$	Bilton et al. (2011)	85.0mL
2. $\sigma_0$	Standard deviation of prior beliefs concerning $\mu$	Bilton et al. (2011)	16.1mL
3. $I_0$	Fixed cost of carrying out clinical trial	Assumption	£10,000,000
4. $d$	Marginal cost of one pairwise allocation	Assumption	£50,000
5. $p$	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. $m$	Location parameter of logistic distribution	Dakin et al. (2014)	£39,417/QALY
9. $s$	Scale parameter of logistic distribution	Dakin et al. (2014)	£11,230/QALY
10. $\sigma$	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. $N$	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. $z_\alpha$	Critical value for RA threshold	NICE (2012b)	1.96

Table 1: Parameter values and sources used for the application.

NOTES: \*Reported as being under £30,000 per QALY



(a) Optimal ICER and optimal expected Stage 1 profit as functions of the uncertainty parameter,  $s$ . The computations were performed assuming that  $x = \mu_0$ .



(b) Optimal sample size and optimal expected Stage 0 profit as functions of the uncertainty parameter,  $s$ . Optimal values are computed numerically.

Figure 4: Optimal Stage 1 ICER and profit and optimal Stage 0 sample size and profit as functions of the uncertainty parameter,  $s$ .

533 the optimal ICER function,  $\tilde{s} = \text{£}6,604/\text{QALY}$ . As  $s \rightarrow 0$ , the optimal ICER tends to  
 534 the expected value of maximum WTP for one effectiveness unit ( $m = \text{£}39,417/\text{QALY}$ ).  
 535 In this region, both optimal price and optimal expected Stage 1 profits are decreasing in  
 536 uncertainty  $s$ .

- 537 • The ‘high uncertainty’ range is defined as the region to the right of  $\hat{s} = \text{£}19,382/\text{QALY}$ ,  
 538 the value of the uncertainty parameter which minimises  $\Gamma_1^*$  and which sets the optimal  
 539 value of the ICER equal to the expected value of maximum WTP,  $m$ , of the HCI (see  
 540 Proposition 1). In this region, both optimal price and optimal expected Stage 1 profit are  
 541 increasing in uncertainty  $s$ .

- 542 • The ‘intermediate uncertainty’ range is defined as the region lying between  $\tilde{s}$  and  $\hat{s}$ . In this  
 543 region, optimal price is increasing in  $s$  and optimal expected Stage 1 profit is decreasing in  
 544  $s$ .

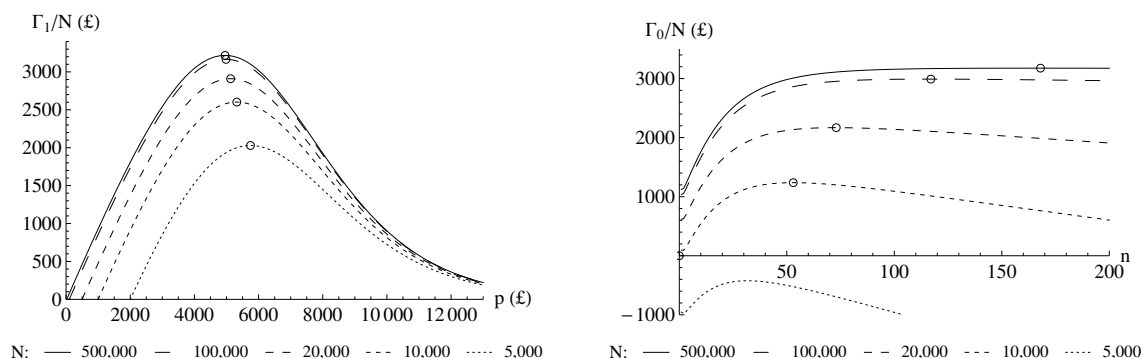
545 Figure 4(b) shows how these non-monotonic Stage 1 responses feed-back to the determina-  
 546 tion of optimal sample size,  $n^*$ , at Stage 0. Both  $n^*$  and  $\Gamma_0^*$  are first decreasing, then increasing  
 547 in  $s$ , with the minimum of the two functions occurring at  $\hat{s}$ .

548 Although a full welfare analysis is beyond the scope of the present work, the results obtained  
 549 so far provide some interesting insights. For example, the value of  $s$  calibrated using results from  
 550 the analysis of NICE’s decision by Dakin et al. (2014) ( $\text{£}11,230$  per QALY) lies between the two  
 551 threshold values previously reported ( $\text{£}6,604$  and  $\text{£}19,382$  per QALY). Hence for the specific  
 552 case under consideration, a reduction of  $s$  to any value between these two values would have the  
 553 following implications: a lower price (Figure 4(a)), a stronger incentive to invest in R&D via  
 554 expected Stage 0 profits (Figure 4(b)) and more precision on the estimate of the effectiveness via  
 555  $n^*$  (Figure 4(b)).

556 Another interesting question is whether, and to what extent, a lack of transparency on the  
 557 true cost-effectiveness threshold ( $s > 0$ ) can shift rents from the HTP to the HCI. In the formal  
 558 limit case of  $s = 0$  per QALY, if  $mx > c_p(N)$ , the HTP’s optimal price in Stage 1 is  $p^* = mx$ .  
 559 With the parameter values of our application, and assuming that  $m$  is equal to the true value  
 560 of the HCI’s maximum WTP, the optimal sample size for this special case is  $n^* = 135$ , and  
 561 the corresponding optimal profit  $\Gamma_0^* = \text{£}575,000,000$ . In comparison, for the situation where  $s$   
 562 equals the value calibrated from NICE’s actual decisions ( $s = \text{£}11,230$  per QALY),  $n^* = 117$   
 563 and  $\Gamma_0^* = \text{£}299,000,000$ . An interesting extension would be to estimate the Expected Value of  
 564 Perfect Information about the cost-effectiveness threshold.

## 565 5.2 The role of market size

566 The results of Section 4 showed that the optimal price setting policy is independent of the size  
 567 of the population to treat when  $c_p(N) = 0$  because the optimal profit per patient would be  
 568 independent of  $N$ . Figure 5(a) shows that this is no longer the case when costs  $c_p(N) > 0$  are  
 569 accounted for in Stage 1. In particular, the optimal price is decreasing in the population size,



(a) Stage 1 expected profit per patient to benefit, ( $\Gamma_1/N$ ), as a function of the HTP's proposed Stage 1 price,  $p$ , for different values of  $N$ . Circles indicate maxima.

(b) Expected profit at Stage 0, ( $\Gamma_0/N$ ), as a function of sample size,  $n$ , for different values of  $N$ . Circles indicate maxima.

Figure 5: Expected profits at the per patient level as a function of price/sample size for various sizes of the market.

570 meaning that, for a comparatively rare disease, it is optimal to propose a higher price. This, in  
 571 turn, leads to a lower probability of acceptance and lower expected profits per patient.<sup>3</sup>

572 Fixing  $s$  at £11,230/QALY, Figure 5(b) shows the expected profit per patient at Stage 0 for  
 573 different values of the market size as a function of sample size.<sup>4</sup> The figure shows that the optimal  
 574 sample size increases with the size of the population. In increasing order (that is, as  $N$  increases  
 575 in Figure 5(b)), the optimal sample sizes for the Stage 0 decision are  $n^* = 0, 53, 73, 117$  and  
 576  $168$ , respectively. The probability of RA acceptance under the prior, is also strictly increasing  
 577 in  $N$  and may be computed for each specific optimal sample size. Performing this calculation  
 578 yields values of probability of adoption equal to  $0, 0.864, 0.934, 0.983$  and  $0.995$ , respectively.

579 From the policy perspective, the main concern about orphan diseases is the lack of incentives  
 580 for the firm to undertake R&D projects that could benefit those patients. In Section 4.2.2 we  
 581 defined  $N_{\min}$  as the minimum market size such that the HTP would find it profitable to start the  
 582 project. Figure 5(b) shows that, for the set of parameters used in the calibration,  $N_{\min}$  is between  
 583  $5,000$  and  $10,000$ .

584 The analysis presented so far shows that some of the parameters relevant in Stage 1 and which  
 585 might be, to some extent, under the control of the HCI may be crucial in providing incentives  
 586 to invest in R&D. We conclude the discussion of our application with an attempt to investigate  
 587 quantitatively the role of two parameters characterising Stage 0:  $\alpha$  and  $n_{\min}$ . Figure 6 shows  $N_{\min}$

<sup>3</sup>The economic intuition for the effect of  $N$  on  $p^*$  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  $p$  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  $N$  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.

<sup>4</sup>Figure 5(b) shows profits per patient, and not total profits, for the sake of clarity. Note that the maximisation problem is unaffected.

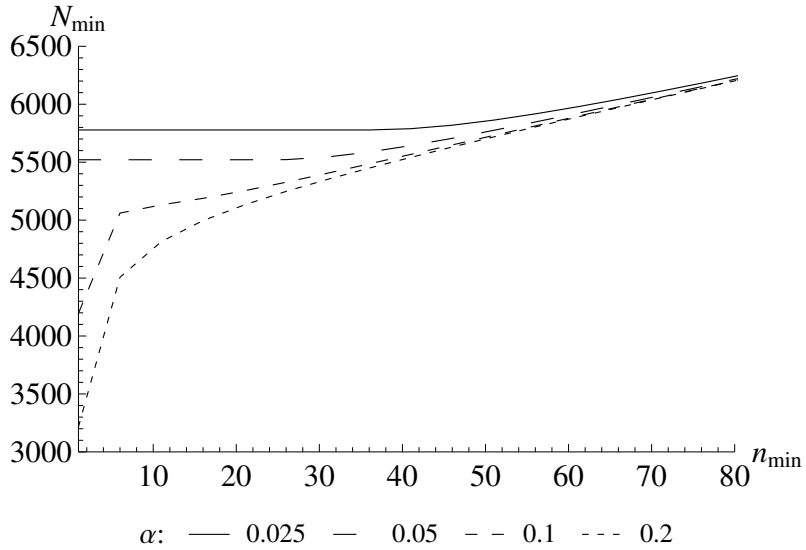


Figure 6: Minimum patient population to benefit ( $N_{\min}$ ) as a function of RA's minimum sample size ( $n_{\min}$ ) for different values of  $\alpha$ .

588 as a function of  $n_{\min}$  for some different values of  $\alpha$ , with  $5 \leq n_{\min} \leq 80$ . As expected, for a given  
589 value of  $n_{\min}$ ,  $N_{\min}$  decreases in the significance level,  $\alpha$ , because a stricter policy by the RA (a  
590 lower  $\alpha$ ) requires, other things being equal, larger samples, which pay less in terms of expected  
591 profit when the population to treat is small (refer to the per study-subject reward that appeared  
592 in the first order necessary condition for the optimal choice of the sample size in Eq. (12)). For a  
593 given value of  $\alpha$ ,  $N_{\min}$  is non-decreasing in  $n_{\min}$  because, when the latter is a binding constraint,  
594 an increase means that a larger market is required to make non-negative profits. The flat parts of  
595 the curves correspond to regions where  $n^* > n_{\min}$ . Overall, the figure suggests that any policy  
596 consideration on the impact of statistical requirements on the incentive to invest in R&D should  
597 take both of these parameters into account. In quantitative terms, for the set of parameters used,  
598 the impact of increasing  $\alpha$  from 2.5% to 20% is to almost halve the value of  $N_{\min}$  when  $n_{\min}$  is  
599 very small.

## 600 6 Discussion and conclusions

601 Historically, economic considerations have played a secondary role to the demonstration of safety  
602 and efficacy in the drug-approval process. However, the increasing need for regulators to assess  
603 the economic implications of their decisions implies that integration between economic and clin-  
604 ical considerations is much greater nowadays. To the best of our knowledge, the two-stage model  
605 that we propose is the first to present a full analysis of how regulation of access to the market  
606 interacts with the reimbursement decision of a health care insurer, and how exogenous incentives  
607 within the regulatory framework either encourage, or discourage, investment in R&D for new  
608 pharmaceutical products.

609 Our main results relate to how the degree of uncertainty surrounding the true value of the  
610 health care insurer's maximum willingness to pay for one unit of effectiveness impacts optimal  
611 profit, price and sample size. In particular, it is shown that, for reasonable functional forms  
612 describing the uncertainty surrounding the true value of the insurer's willingness to pay, optimal  
613 profit, price and sample size are U-shaped functions of the uncertainty parameter. This allows us  
614 to identify three regions – 'low uncertainty', 'intermediate uncertainty' and 'high uncertainty' –  
615 within which changes in the uncertainty parameter have different qualitative effects. Although  
616 a full welfare analysis is beyond the scope of our paper and we cannot characterize the optimal  
617 degree of uncertainty either from the societal or the HCI's perspective, the regions provide clear  
618 insights on who gains and who loses from changes in the degree of uncertainty. In the 'low  
619 uncertainty' region, an increase in uncertainty leads to lower prices, lower expected profits, and  
620 smaller sample size. Overall, the policy implication is that, in the 'low uncertainty' region,  
621 an increase in uncertainty benefits the insurer via a reduced impact of the new product on the  
622 budget, but it also reduces expected returns for the industry and hence incentives to invest in  
623 R&D. Even if development is undertaken, sample sizes of Phase III trials will be smaller. In  
624 contrast, in the 'high uncertainty' region, the impact of an increase in uncertainty leads to a  
625 higher price, higher expected profit, a larger impact on health budgets, and a larger sample size.  
626 A particularly interesting case is that of 'intermediate uncertainty': in this region, by reducing  
627 uncertainty, insurers would be better off due to the lower prices and the more precise estimate  
628 of effectiveness provided by trials with larger samples; the industry would benefit from larger  
629 expected profits; this in turn will benefit patients, especially those with diseases in areas that are  
630 of limited interest for the industry, such as orphan diseases, by making the decision to invest in  
631 R&D more likely. This final case is of particular interest given the results of the application,  
632 which show that the calibrated value for the uncertainty parameter lies within the intermediate  
633 region.

634 A question that naturally follows from this result is how, in practice, an insurer could change  
635 the degree of uncertainty around its maximum WTP for one unit of effectiveness. While many  
636 insurers include cost-effectiveness among criteria on which their adoption decisions are based,  
637 few of them explicitly state a specific threshold or a range for the maximum value of the ICER.  
638 Those that already refer to a specific range could reduce uncertainty by either narrowing the  
639 range, or by defining, and making public, rules that affect the adoption decision within that  
640 range. For example, a price premium could be explicitly defined as a function of the size of the  
641 population to treat, if favouring orphan drugs is an objective, or it could be stated that the upper  
642 limit of a range is the relevant cost-effectiveness threshold for drugs targeted to life-threatening  
643 conditions.

644 Concerning incentives that can be provided at the development stage, it has been suggested  
645 that this opportunity for regulators might have been under-explored so far (Clarke et al., 2014).  
646 Our model provides a framework to investigate this and, in principle, to study the substitutability  
647 of incentives at the commercialisation and the development stage. Our application includes a  
648 tentative estimate of the impact of a change in the significance level ( $\alpha$ ) of the statistical test, used  
649 by the RA to approve a new drug, on the minimum size of the market that ensures non negative  
650 expected profit from an investment in R&D. There is a strong convention within RAs that the  
651 type I error rate should be controlled at 5% 2-sided, that is, that the one-sided level,  $\alpha$ , should



652 be 0.025. However, the FDA has stressed that this rule is not written in stone and actual FDA  
653 decisions for rare diseases confirm this (Sasinowski, 2012). Our results on the consequences of  
654 different choices of  $\alpha$  are therefore practically relevant.

655 We conclude with a discussion of a number of limitations of the model and opportunities for  
656 future research. It is assumed that there is only one authority which controls access to the market  
657 – the RA – and one which decides on reimbursement – the HCI. Although key decisions tend to  
658 be concentrated in a limited number of RAs in the real world (e.g. the FDA in the US and the  
659 EMA in Europe), this is not the case for insurers. In addition, it is assumed that the regulatory  
660 hurdles are set exogenously, and we study the optimal behaviour of the HCI in the presence  
661 of these hurdles. A natural next step would be to consider the regulatory process itself as an  
662 optimisation problem, and to model the optimal behaviour of both HCI and regulatory agencies.

663 Regarding reimbursement decisions, our model is based on a ‘cost per unit of effectiveness’  
664 criterion. However, not all insurers use such an approach. For example, multiple HCIs are active  
665 in the US, and US legislation bans the formal use of cost per QALY for insurance decisions.  
666 Both the concept of quality-adjustment of life, and of setting a price on the value of a life (year)  
667 are far from uncontroversial. Our model could potentially be extended to allow the sponsor gain  
668 to be dependent on decisions from a multitude of RAs and HCIs. Moreover, decisions made  
669 in different countries may not be independent, such as when reference pricing mechanisms are  
670 adopted. Taking this into account would raise a number of interesting and challenging questions  
671 related to strategic interactions and a provider’s optimal sequence of reimbursement decisions.  
672 Another valuable extension would be the formal modelling of price negotiations at Stage 1.

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

678 Although exogenous in our model, the HTP’s beliefs about the HCI’s maximum WTP could  
679 be modelled as endogenous, so that the HTP learns about the true value of the maximum WTP  
680 by observing the HCI’s decisions and updating beliefs.

681 Although it is acknowledged that the drug discovery and development process extends well  
682 beyond the remit of this paper (Pennings and Sereno, 2011), the part of the process that we  
683 consider is crucial because of the size of its costs, which are estimated to be around 50% of  
684 the total cost of clinical development (Pharmaceutical Research and Manufacturers of America,  
685 2014), and the high probability of failure (estimated to be around 50% in Phase III). Neverthe-  
686 less, the recursive nature of the solution to the model could permit earlier stages in the drug  
687 development process to be added.

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

695 drug development. A further extension could consider use of the product for multiple conditions.

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 errors remain our own.



703

## 704 A Proofs

### 705 A.1 Stage 1

706 *Proofs of comparative static results (Eqs. (9a) and (9b)):*

- 707 • *Results for  $\Gamma_1^*$ :* Since  $v^*(m, s) > 0$  and  $0 < F_W < 1$ , that  $\frac{\partial \Gamma_1^*}{\partial N}$  and  $\frac{\partial \Gamma_1^*}{\partial x}$  are positive is  
 708 immediate from Eq. (8b). By the Envelope Theorem,

$$\frac{\partial \Gamma_1^*}{\partial m} = \frac{\partial \Gamma_1}{\partial m} \Big|_{p=p^*} = N p^* \left( \frac{1}{s} \right) f_T \left( \frac{p^*/x - m}{s} \right) > 0.$$

- 709 • *Results for  $p^*$ :* Partial differentiation of Eq. (8a) immediately gives  $\frac{\partial p^*}{\partial N} = 0$  and  $\frac{\partial p^*}{\partial x} =$   
 710  $v^*(m, s) > 0$ . Since  $v^*$  satisfies the first order condition, differentiation of Eq. (7) gives

$$\begin{aligned} \frac{\partial v^*}{\partial m} r_W(v^*; m, s) + v^* \left( \frac{\partial r_W}{\partial v}(v^*; m, s) \frac{\partial v^*}{\partial m} + \frac{\partial r_W}{\partial m}(v^*; m, s) \right) &= 0 \iff \\ \frac{\partial v^*}{\partial m} &= - \frac{v^* \frac{\partial r_W}{\partial m}(v^*; m, s)}{r_W(v^*; m, s) + v^* \frac{\partial r_W}{\partial v}(v^*; m, s)}. \end{aligned}$$

- 711 By Assumption A2,  $\frac{\partial r_W}{\partial v} \geq 0$ . Since  $v^* > 0$  and  $r_W > 0$  always hold, the denominator of  
 712 the fraction above is positive and the sign of  $\frac{\partial v^*}{\partial m}$  equals the sign of  $-\frac{\partial r_W}{\partial m}$ . But  $\frac{\partial r_W}{\partial m} \leq 0$ ,  
 713 so that  $\frac{\partial v^*}{\partial m} \geq 0$  and  $\frac{\partial p^*}{\partial m} \geq 0$ .

714

□

715 *Proof of Proposition 1:*

716 Let  $g(v; m, s) = vr_W(v; m, s)$ . Assumption **A2** can be used to show that  $g$  is strictly increas-  
717 ing in  $v$ :

$$\frac{\partial g(v; m, s)}{\partial v} = r_W(\cdot) + v \frac{\partial r_W(\cdot)}{\partial v} > 0. \quad (19)$$

718 Note that the hazard function for  $W$  is  $r_W(w) = r_T\left(\frac{w-m}{s}\right)/s$ .<sup>5</sup> As can be seen by rearranging  
719 Eq. (6),  $g(v^*(m, s); m, s) = 1$ . Combining this result with Eq. (19) implies that, for any  $v$ ,  
720  $v \lesseqgtr v^*(m, s)$  if and only if  $g(v; m, s) \gtrless 1$ . In particular, for  $v = m$ ,

$$m \lesseqgtr v^*(m, s) \iff mr_W(m; m, s) \lesseqgtr 1 \iff mr_T(0)/s \lesseqgtr 1 \iff mr_T(0) \lesseqgtr s.$$

721 Hence, for any fixed  $m > 0$ , there exists a value of the scale parameter,  $\hat{s} = mr_T(0)$ , such that  
722 the optimal ICER,  $v^*(\cdot)$ , is greater than  $m$  if and only if  $s > \hat{s}$ . This observation may be used  
723 to characterise the response of  $\Gamma_1^*$  to changes in  $s$ . For, by the Envelope Theorem applied to Eq.  
724 (8b) and the rotation result for  $F_W$  in Eq. (4) (and shown in Figure 1):

$$\frac{\partial \Gamma_1^*}{\partial s} = \frac{\partial \Gamma_1}{\partial s} \Big|_{p=p^*} = -N_x v^* \frac{\partial F_W}{\partial s}(v^*; m, s) \gtrless 0 \iff v^* \gtrless m \iff s \gtrless \hat{s}.$$

725

□

726 *Proof of Proposition 2:*

727 By making use of the substitution  $v = m + st$ , we see that solving the first order necessary  
728 condition in Eq. (7) for  $v > 0$  is equivalent to solving the following transformed problem for  
729  $t > -m/s$ ,

$$(m + st)r_T(t)/s = 1 \iff -m/s = t - 1/r_T(t) \iff \psi(t) = -m/s,$$

730 where  $\psi(t) \equiv t - 1/r_T(t)$ . By Assumption **A2**,  $\psi(t)$  is strictly increasing. This implies that  
731 its inverse  $\psi^{-1}$  is well-defined and that the solution to the equation above may be written as  
732  $t^* = \psi^{-1}(-m/s)$ . The corresponding solution for the original problem is then  $v^* = m +$   
733  $s\psi^{-1}(-m/s)$ . Fixing  $m$ , differentiation with respect to  $s$  yields

$$\frac{\partial v^*}{\partial s}(s) = \psi^{-1}(-m/s) + \frac{m/s}{\psi'(\psi^{-1}(-m/s))}.$$

734 Now, since the change of variable  $\theta = \psi^{-1}(-m/s) \iff \psi(\theta) = -m/s$  defines a strictly  
735 increasing mapping of  $s \in (0, \infty)$  on to  $\theta \in (-\infty, \psi^{-1}(0))$ ,  $\frac{\partial v^*}{\partial s}(s)$  is strictly increasing if and  
736 only if  $\theta \mapsto \theta - \frac{\psi(\theta)}{\psi'(\theta)}$  is strictly increasing. Differentiation with respect to  $\theta$  results in the sufficient  
737 condition

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

<sup>5</sup>The probability density function of  $W$  may be written as  $f_W(w) = F_T'(\frac{w-m}{s}) = f_T(\frac{w-m}{s})/s$ . The hazard function for  $W$  is therefore:  $r_W(w) = [f_T(\frac{w-m}{s})/s] / [1 - F_T(\frac{w-m}{s})] = r_T(\frac{w-m}{s})/s$ .

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

740 This concludes the proof that  $M'' > 0$  implies that  $\frac{\partial v^*}{\partial s}(s)$  is strictly increasing. By combining  
 741 this result with the result from Proposition 1 that  $m \leq v^*(m, s) \iff \hat{s} \leq s$ , it is straightforward  
 742 to show that  $\lim_{s \rightarrow 0} v^*(m, s) = m$ . This in turn implies that, as  $s$  increases,  $v^*$  is first strictly  
 743 decreasing and then strictly increasing, attaining a minimum value at some  $\tilde{s}$  which must satisfy  
 744  $0 < \tilde{s} < \hat{s}$ .

745

□

746 *Position of  $\tilde{s}$  relative to  $\hat{s}$ :*

747 Proposition 1 defines  $\hat{s} = mr_T(0)$ . There is no closed form solution for the value of  $\tilde{s}$ . However,  
 748 from the proof of Proposition 2, it may be shown that  $\tilde{s}/m = 1/|\psi(\tilde{\theta})|$ , where  $\psi(t) = t - 1/r_T(t)$   
 749 and  $\tilde{\theta} = \operatorname{argmax}_{\theta < 0} |\theta| r_T(\theta)$ . As a result, the ratio  $\hat{s}/\tilde{s}$  may be written as  $r_T(0)|\psi(\tilde{\theta})|$  and is  
 750 entirely determined by the choice of the standardised distribution for the uncertainty concerning  
 751 the HTP's maximum WTP. Numerical computations show that  $\hat{s}/\tilde{s} = 2.935$  for the standard  
 752 logistic distribution and  $\hat{s}/\tilde{s} = 2.946$  for the standard normal distribution.

## 753 A.2 Stage 0

754 *Proof of Proposition 3:*

755 Let  $\zeta(n) = \mathbb{E} \left[ X \mid X > x_{\text{crit}}(n) \right] \mathcal{P}(X > x_{\text{crit}}(n))$ , so that  $\Gamma_0 = N \rho^*(m, s) \zeta(n) - (I_0 + dn)$ .

756 By the Envelope Theorem,

$$\frac{\partial \Gamma_0^*}{\partial s} = \frac{\partial \Gamma_0}{\partial s} \Big|_{n=n^*} = \zeta(n^*) N \frac{\partial \rho^*(m, s)}{\partial s}. \quad (20)$$

757 Since  $\zeta(n^*)$  is always positive and the sign of  $\partial \rho^*/\partial s$  equals the sign of  $\partial \Gamma_1^*/\partial s$  (for any fixed,  
 758 but arbitrary,  $x$ ), part (a) follows from Proposition 1.

759 By the implicit function theorem,

$$\frac{\partial n^*}{\partial s} = - \left( \frac{\partial^2 \Gamma_0}{\partial n^2} \right)^{-1} \frac{\partial^2 \Gamma_0}{\partial s \partial n} \Big|_{n=n^*}. \quad (21)$$

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

$$\frac{\partial^2 \Gamma_0}{\partial s \partial n} \Big|_{n=n^*} = \frac{\partial^2}{\partial s \partial n} (N \rho^* \zeta - (I_0 + dn)) \Big|_{n=n^*} = N \frac{\partial \rho^*(m, s)}{\partial s} \frac{\partial \zeta(n^*)}{\partial n}. \quad (22)$$

761 By definition,  $n^*$  solves the first order necessary condition, implying  
 762  $\partial \zeta(n^*) / \partial n = d / (N \rho^*(m, s)) > 0$ . Therefore, the sign of  $\partial n^* / \partial s$  equals the sign of  $\partial \rho^* / \partial s$ ,  
 763 and part (b) follows from Proposition 1.

764

□

## 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 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 was 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.

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  $x$  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  $\mu_0 = 85.03\text{mL}$  for the start of the second Phase III trial (Aitken et al., 2013).

805 The 95% confidence interval reported by Bilton et al. is used to obtain an estimate of  $\sigma$ , the  
 806 standard deviation of the difference between effects in the treatment and control arms. Assume  
 807 that the standard deviations in the two trial arms are equal, with a common value,  $\sigma/\sqrt{2}$ . Then,  
 808 referencing Table 1 of Bilton et al. (2011), the sample sizes of  $n_t = 177$  (number of subjects in  
 809 treatment arm) and  $n_c = 118$  (number of subjects in control arm), an estimate of  $\sigma/\sqrt{2}$  may be  
 810 obtained by rearranging the standard error formula for two independent means when the variance  
 811 is known:

$$\hat{\sigma}/\sqrt{2} = \text{SE}(X) \left( \sqrt{1/n_t + 1/n_c} \right)^{-1}, \quad (23)$$

812 where  $\text{SE}(X) = (116.6 - 85.03)/1.96 = 16.10$ , obtained from the 95% confidence interval.  
 813 Solving Eq. (23) yields  $\hat{\sigma} = \sqrt{2} * 135.5 = 191.63$ . Alternatively, we may assume a sample  
 814 size equivalent to approximately  $n = 140$  pairwise allocations and estimate  $\sigma$  directly as  $\hat{\sigma} =$   
 815  $\text{SE}(X)\sqrt{n} = 16.10 \times \sqrt{140} = 190.5$ . The standard deviation for the prior is simply taken to be  
 816 the standard error,  $\sigma_0 = \text{SE}(X) = 16.10$ .

817 The calibration of the values for  $m$  and  $s$  of the logistic function merit some discussion.  
 818 The values in units of £/QALY are taken from Dakin et al. (2014), who estimate a number of  
 819 different regression models for past NICE appraisal decisions and find that the reported ICER  
 820 was the major factor influencing the probability of acceptance (no other factor, other than the  
 821 type of condition, was found to have a statistically significant effect on NICE's decision). For  
 822 the model with the highest prediction accuracy, Dakin et al. (2014) report that the ICER values  
 823 corresponding to probabilities of NICE recommendations of 0.25, 0.50 and 0.75 were £51,754,  
 824 £39,417 and £27,047 per QALY, respectively (Table III, model 4 in Dakin et al. (2014)). The  
 825 pairs (0.5, 39,417) and (0.75, 51,754), when inserted into the logistic function, give two equations  
 826 for  $m$  and  $s$  which can be solved to yield the following estimates:  $m = \text{£}39,417/\text{QALY}$  and  
 827  $s = \text{£}11,230/\text{QALY}$ . Now, the unit of the incremental efficacy  $x$  is not measured in QALYs,  
 828 but as FEV1 mL. Hence, when performing computations within the model, it is first necessary  
 829 to convert incremental efficacy into the corresponding number of QALYs. Calibration gives a  
 830 conversion factor of 0.0018 QALY/mL.

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

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