Pharmaceutical Phase III investments with uncertain reimbursement

Sebastian Jobjörnsson

Chalmers University of Technology

May 27, 2015

Overview

Joint work with Carl-Fredrik Burman[1], Martin Forster[2] and Paolo Pertile[3].

Outline of presentation:

1. Problem background
2. The model
3. Solving the model - General formulation
4. Solving the model - Logistic formulation
5. Application to a recent clinical trial
6. Possible extensions

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[1] Chalmers
[2] Uni. of York
[3] Uni. of Verona

Problem background - IDEAL project

IDEAL = Integrated Design and Analysis of small population group trials

- EU project on statistical methodology in small population groups.
- Consortium of researchers from European universities, research institutes and industry.
- Work divided into 11 Work Packages.
- WP9:
  - Consider the clinical trial process from different stakeholder perspectives, using decision theory.
  - For Health Technology Providers (HTPs), what are the optimal trial designs given certain regulatory rules?
  - For regulatory authorities and payers: what are the appropriate incentives for the development of new treatments for small population groups?

Problem background - Clinical trials from the perspective of an HTP

Real pharmaceutical development consists of several stages:

1. Pre-clinical research.
2. Phase I, Phase II and Phase III clinical trials.
3. Approval by a Regulatory Authority (RA).
4. Reimbursement decision by a Health Care Insurer (HCI).
5. Use by patients (upon recommendation by phycisians).

We will consider an HTP at the start of Phase III.

The model - Overview of decision process

- Stage 0
  1. The HTP chooses a sample size n. Trial cost = $l_0 + dn$.
  2. The trial results in an efficacy estimate $\bar{X} = \bar{x}$.[4]
  3. Based on n and $\bar{x}$, the RA accepts or rejects the new treatment.

- Stage 1 (only reached upon RA approval in Stage 0)
  1. The HTP suggests an incremental price c per patient.
  2. Based on c and $\bar{x}$, the HCI decides whether or not to pay.

[4] Realisations of RVs are denoted by small letters, so $\bar{x}$ denotes a particular realisation of $\bar{X}$.

The model - Statistical model for the trial data

- Given the true incremental efficacy μ, trial estimate is assumed normal:

$$\bar{X} \mid \mu \sim \mathrm{N}\left(\mu, \frac{\sigma^2}{n}\right).$$

- Before the trial, the HTP encodes its knowledge as a conjugate normal prior distribution:

$$\mu \sim \mathrm{N}\left(\mu_0, \sigma_0^2\right).$$

- It follows that the prior predictive distribution for $\bar{X}$ is

$$\bar{X} \sim \mathrm{N}\left(\mu_0, \sigma_0^2 + \frac{\sigma^2}{n}\right).$$

The model - Decision rule of the Regulatory Authority (Stage 0)

The RA is assumed to approve the new treatment if

1. There is a sufficient amount of evidence: $n \geq n_{\min}$.
2. Superiority to control can be shown at a certain one-sided level of statistical significance, α:

$$\bar{X} > h(n) \equiv \frac{z_\alpha \sigma}{\sqrt{n}}, \text{ where}$$
$$z_\alpha = \Phi^{-1}(1-\alpha).$$

Real world examples of RAs:

- In the EU, EMA, the European Medicines Agency.
- In the US, FDA, the Food and Drug Administration.

The model - Decision rule of the Health Care Insurer (Stage 1)

- The new treatment is reimbursed if and only if the Incremental Cost-Effectiveness Ratio (ICER) is below the HCI's Cost-Effectiveness Threshold (CET),

$$\text{ICER} = \frac{c}{\bar{x}} < \Lambda = \text{CET}.$$

- Assume that the distribution for the CET has the form

$$F_\Lambda(\lambda) = F\left(\frac{\lambda - \nu}{\omega}\right).$$

- Example: National Institute for Health and Care Excellence (NICE) in the UK.

The model - Assumptions on F

Letting

$$f \equiv F' \text{ be the density and}$$
$$r \equiv f/(1-F) \text{ the failure rate}$$

corresponding to F, it is assumed that

$$0 < F < 1,$$
$$F \in \mathcal{C}^{(2)},$$
$$|\mathbb{E}_F| < \infty,$$
$$r' > 0.$$

From the HTP's perspective, the probability P that a certain suggested price c will lead to reimbursement is then

$$P(c, \bar{x}, \nu, \omega) \equiv \mathbb{P}\left(\frac{c}{\bar{x}} < \Lambda\right) = 1 - F\left(\frac{c/\bar{x} - \nu}{\omega}\right).$$

Solving the model - Backward induction

The optimal policy for the HTP is constructed using backward induction.

1. For each potential $\bar{x} > h(n)$, find the optimal price c^* for Stage 1.
2. Find the optimal sample size n^* for Stage 0, under the assumption that, whatever the actual value $\bar{x}$ observed for $\bar{X}$, the choice in Stage 1 will be the optimal c^*.

Solving the model - Choice of optimal price in Stage 1

For a total patient population size k, the Stage 1 profit is

$$\begin{cases} k(c - c_p(k)) & \text{if the HCI accepts the price, and} \\ 0 & \text{if the HCI does not accept the price,} \end{cases}$$

where $c_p(k) \equiv I_1/k + b > 0$ is the production cost per patient.

The expected Stage 1 profit of the HTP is then

$$\Gamma_1(c, \bar{x}, \nu, \omega, k) \equiv k\,(c - c_p(k))\,P(c, \bar{x}, \nu, \omega),$$

and the optimisation problem becomes

$$\max_{c \geq 0} \Gamma_1 \iff \max_{c \geq 0} \{k\,(c - c_p(k))\,P(c, \bar{x}, \nu, \omega)\}\,.$$

Solving the model - Properties of the optimal price

From the assumptions placed on F, it may be shown that

1. there exists a unique solution, $c^*(\bar{x}, \nu, \omega, k)$ to $\max_{c \geq 0} k\left(c - c_p(k)\right) P$,
2. which also solves $P + \left(c - c_p(k)\right) \frac{\partial P}{\partial c} = 0$, satisfying
3. $c^* > c_p(k)$,
4. $c^* \in \mathcal{C}^{(1)}$,
5. $\frac{\partial c^*}{\partial \bar{x}} > 0$, $\frac{\partial c^*}{\partial \nu} > 0$ and $\frac{\partial c^*}{\partial k} < 0$.

Solving the model - Properties of the optimal Stage 1 profit

Letting

$$\Gamma_1^*(\bar{x}, \nu, \omega, k) = \Gamma_1\left(c^*(\bar{x}, \nu, \omega, k), \bar{x}, \nu, \omega, k\right),$$

the envelope theorem implies that

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

$$\frac{\partial \Gamma_1^*}{\partial \omega} \text{ is } \begin{cases} < 0 \text{ if } c^* < \bar{x}\nu, \\ = 0 \text{ if } c^* = \bar{x}\nu, \\ > 0 \text{ if } c^* > \bar{x}\nu. \end{cases}$$

Solving the model - Choice of optimal sample size

Let

$$\Gamma_0(n,\nu,\omega,k) = \mathbb{E}\left[\Gamma_1^*\left(\bar{X},\nu,\omega,k\right)\mathbb{I}\left(\bar{X} > h(n)\right)\right] - (l_0 + dn)$$
$$= \int_{h(n)}^{\infty} \Gamma_1^*\left(\bar{x},\nu,\omega,k\right)\pi_n(\bar{x})\,\mathrm{d}\bar{x} - (l_0 + dn)$$

be the expected utility of choosing a sample of size n and continue optimally in Stage 1.

The Stage 0 optimisation problem is then

$$\max_{n \geq n_{\min}} \Gamma_0(n,\nu,\omega,k).$$

The optimal sample size is denoted by n^*, with a corresponding optimal Stage 1 profit Γ_1^*.

A logistic model for P: Functional form (1)

Assume the logistic model:

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

Chosen for two reasons:

1. A logistic regression model for the CET used by NICE has recently been published by the CHE[5].
2. The logistic form allows for solving the Stage 1 FONC in terms of the Lambert W function. This function is defined implicitly so that $z = W(z)\exp(W(z))$.

[5] Centre for Health Economics, Uni. of York

A logistic model for P: Functional form (2)

Using the properties of W, it may be shown that

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

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

A logistic model for P: Dependence of c^* and Γ_1^* on ω

For constants $\beta_c \approx 5.87$ (found numerically) and $\beta_{\Gamma_1} = 2$:

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

Two qualitatively different cases may be distinguished:

1. $\bar{x}\nu \leq c_p(k)$: both c^* and Γ_1^* are strictly increasing in ω.
2. $\bar{x}\nu > c_p(k)$: both c^* and Γ_1^* are first decreasing and then increasing in ω. c^* has a strict global minimum at $\breve{\omega}_c$ and Γ_1^* has a strict global minimum at $\breve{\omega}_{\Gamma_1}$.

Application - Indication and treatment

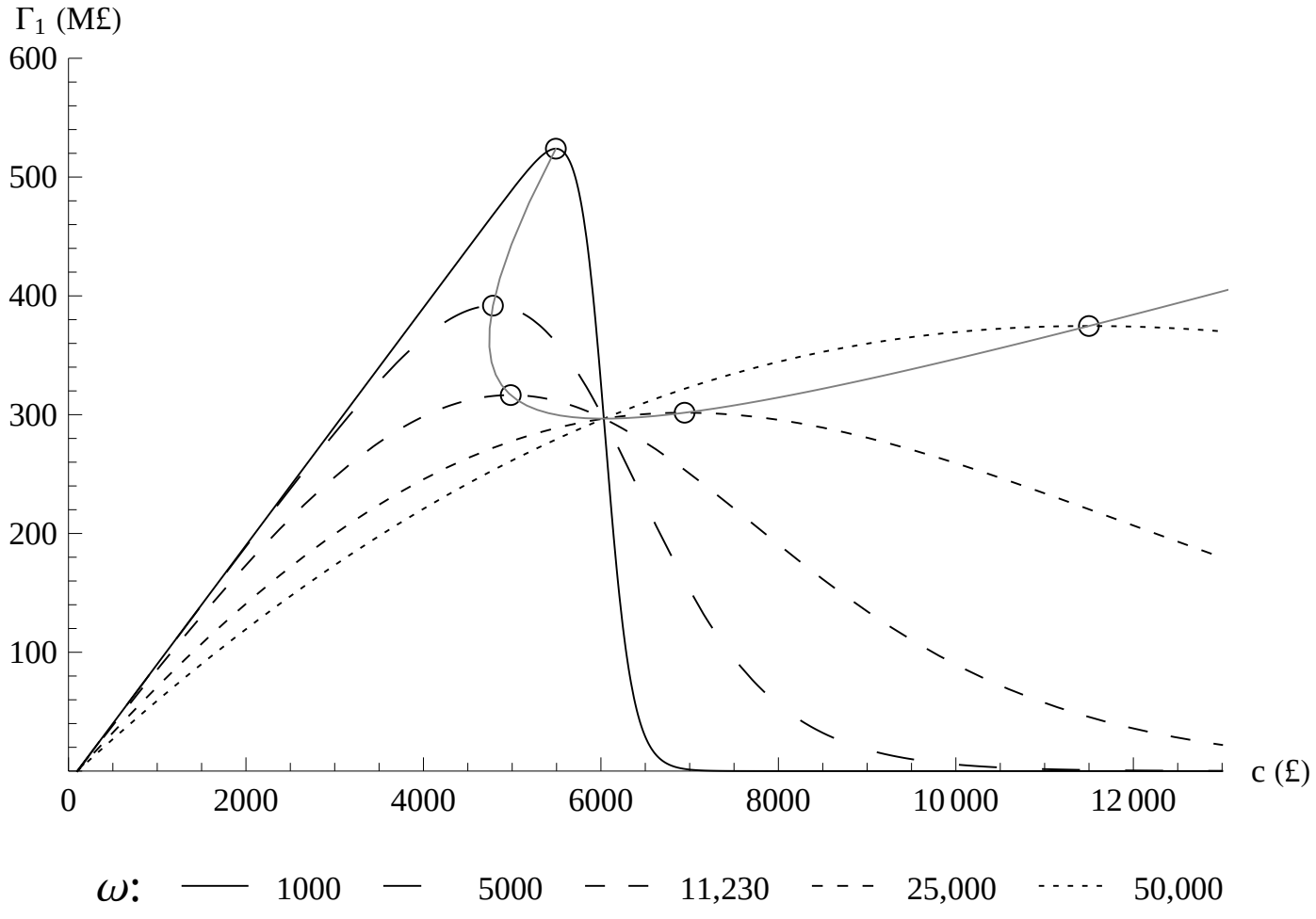
- HCI deciding on cost-effectiveness: NICE in the UK.
- Proposed new medication: mannitol dry powder (Bronchitol).
- Indication (disease): Cystic fibrosis, a genetic disorder that mostly affects the lungs.
- Estimated prevalence: 12.6 per 100,000 in Europe.

Application - Parameter values

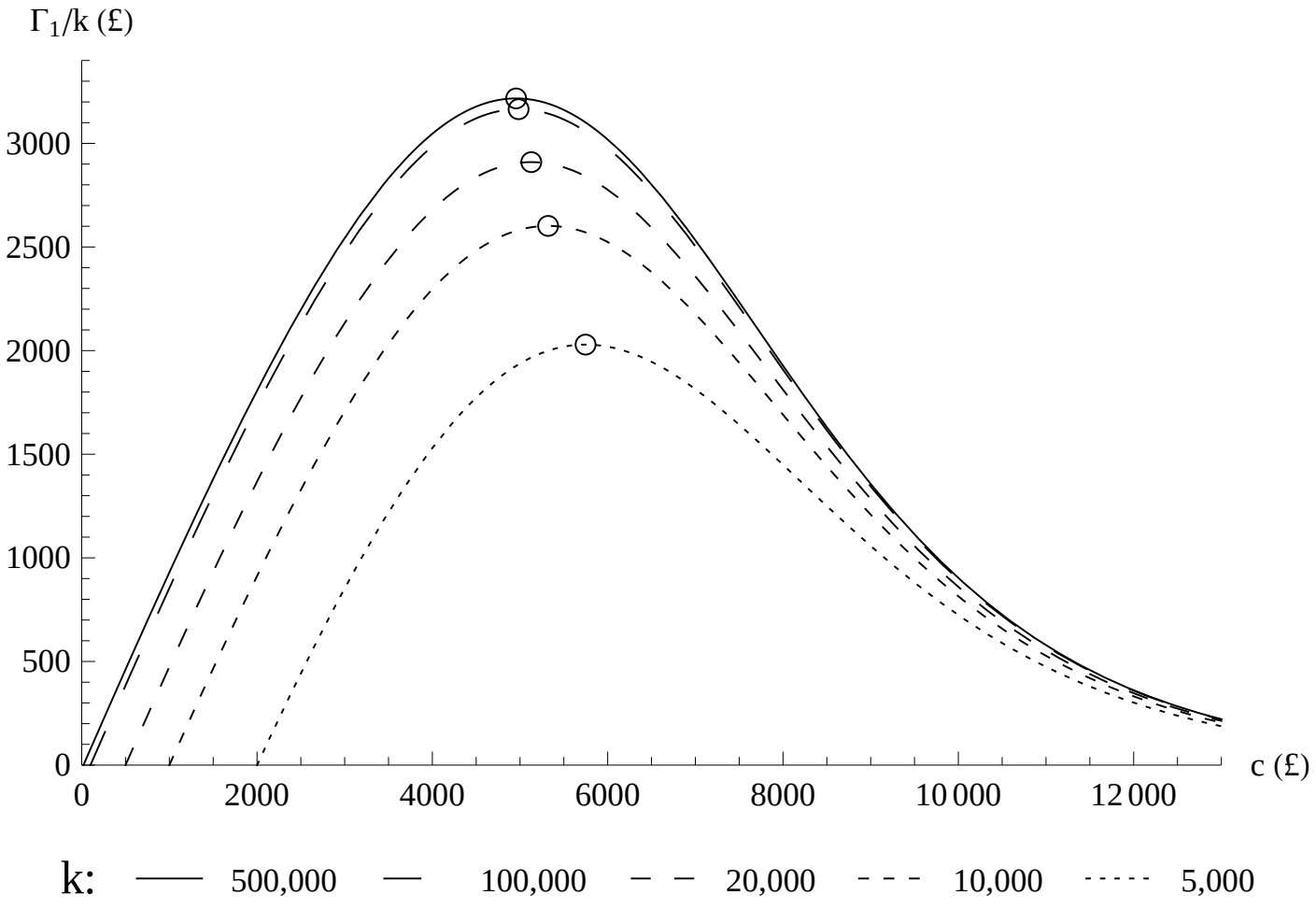
- The prior parameters μ_0, σ_0 and the population standard deviation σ were chosen to be consistent with a previous trial (Bilton et al., 2011).
- ν and ω estimated from a recent study (Dakin et al., 2014), giving $\nu =$ £39,417/QALY[6] and $\omega =$ £11,230/QALY.
- I_1, b, I_0 and d chosen as typical values for the pharma. industry.
- k was estimated as the product of the approximate prevalence in the UK (10,000) and the market exclusivity horizon (10 years in the EU), giving $k = 100{,}000$.

[6] Quality Adjusted Life-Year

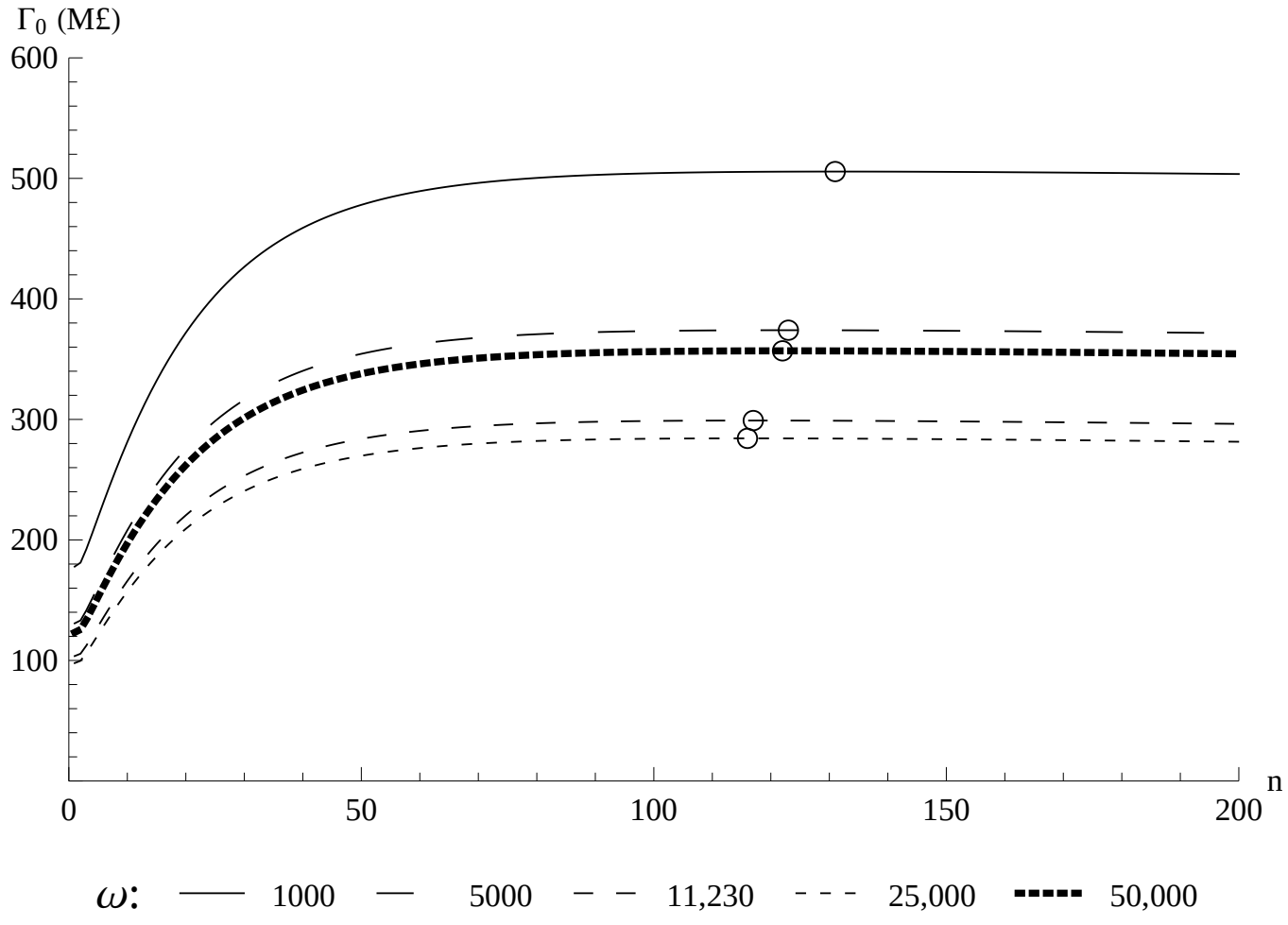
Application - Stage 1 expected profit as a function of c (different ω)



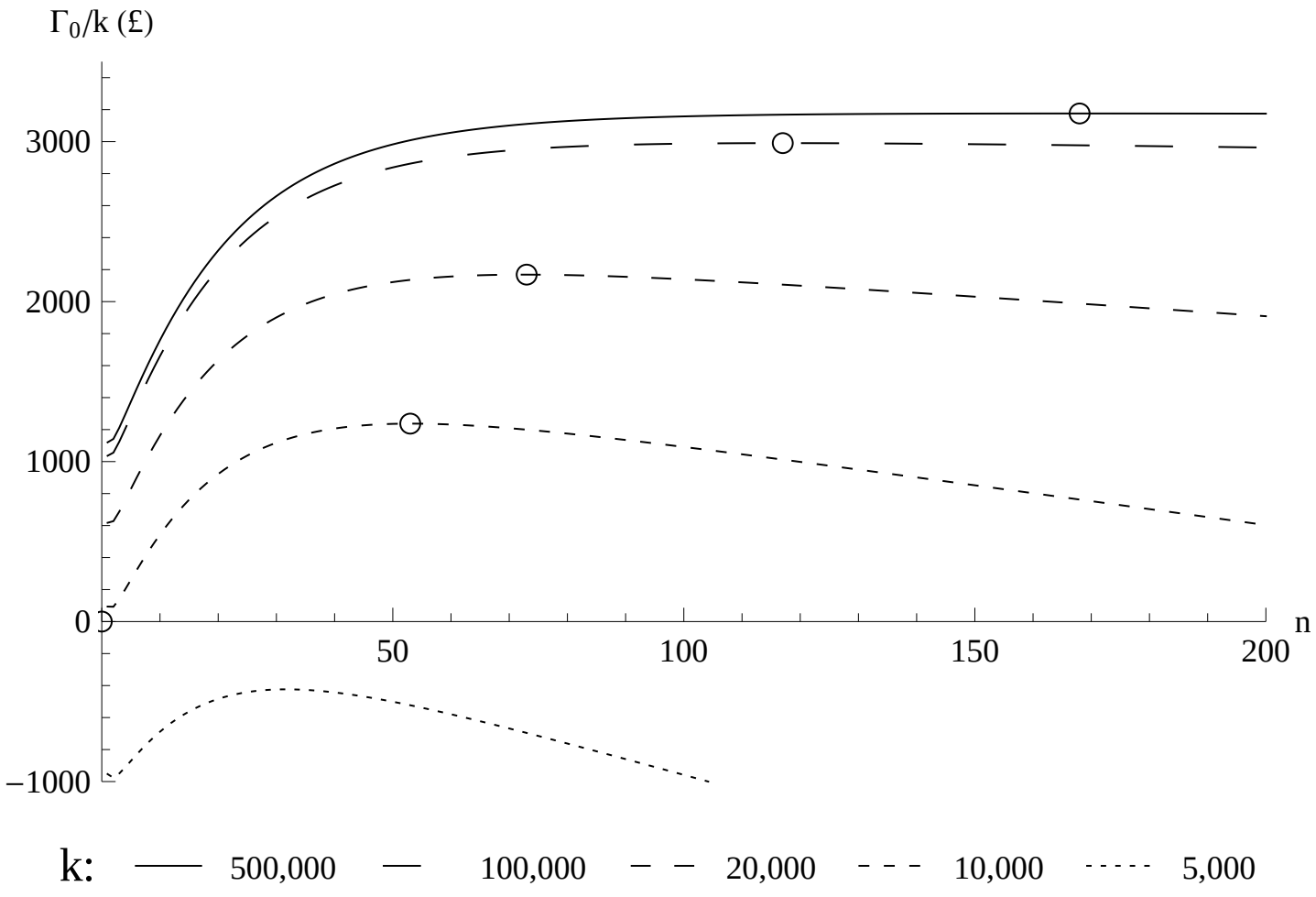
Application - Stage 1 expected profit (per patient-year) as a function of c (different k)



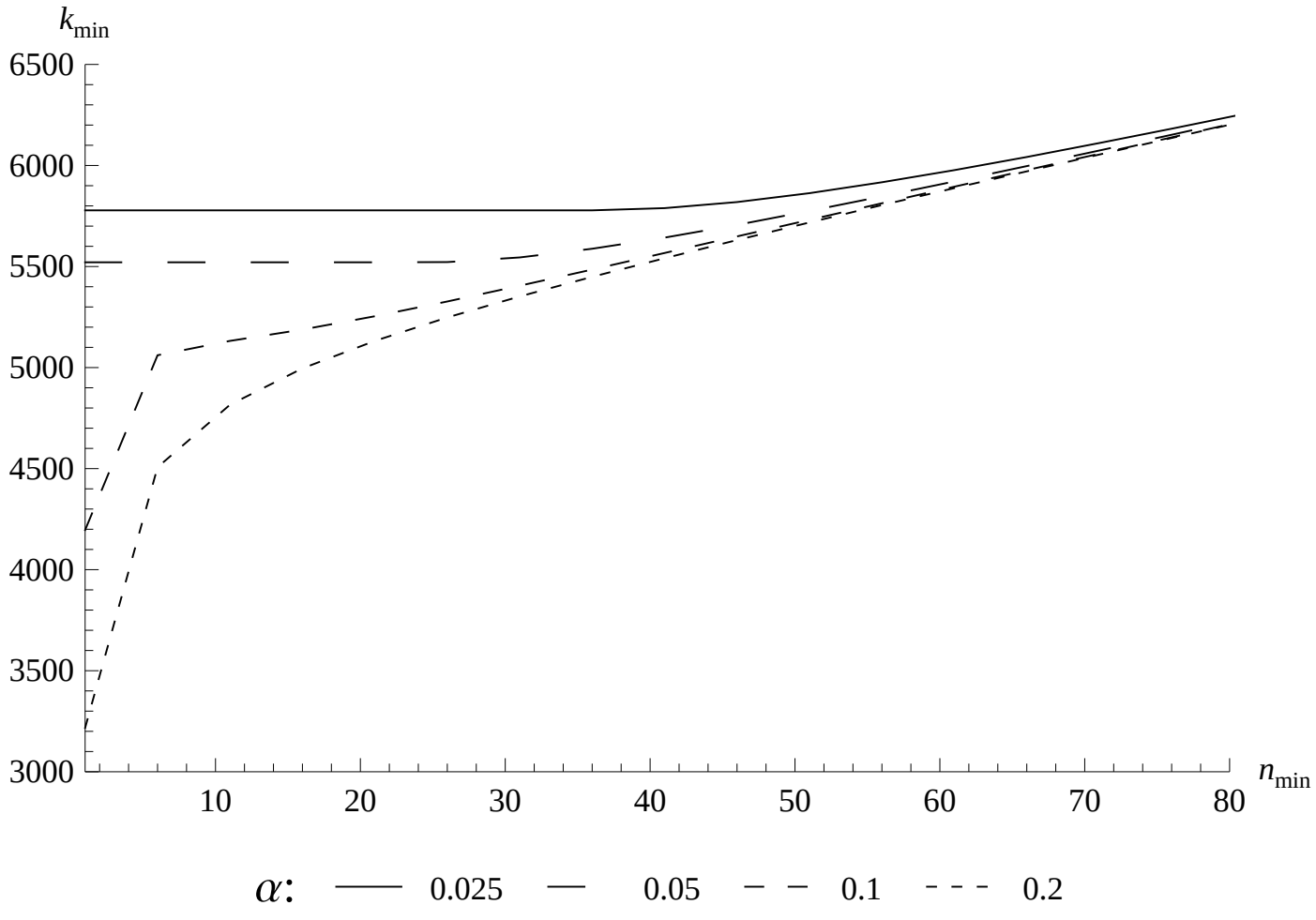
Application - Stage 0 expected profit as a function of n (different ω)



Application - Stage 0 expected profit (per patient-year) as a function of n (different k)



Application - $k_{\min}$ as a function of $n_{\min}$ for different α



Extensions

- Allow P to depend on n, k and disease area.
- Consider several HCIs when the price is set in Stage 1.
- Include bargaining process in Stage 1.
- Extend clinical trial model to also include Phase I and Phase II.
- Switch perspective to other stakeholders.
  - How can the parameters of this model be changed to increase willingness to invest in development for rare diseases?
  - Is a different regulatory structure needed?

Final slide

Thank you!