Pharmaceutical Phase III investments with uncertain reimbursement

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Overview

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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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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 physicians).

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 = \( I_0 + dn \).
2. The trial results in an efficacy estimate \( \bar{X} = \bar{x} \).
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.

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\(^4\) Realisations of RVs are denoted by small letters, so \( \bar{x} \) denotes a particular realisation of \( \bar{X} \).
Given the true incremental efficacy $\mu$, trial estimate is assumed normal:

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

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

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

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

$$\bar{X} \sim N \left(\mu_0, \sigma_0^2 + \frac{\sigma^2}{n}\right).$$
The RA is assumed to approve the new treatment if

1. There is a sufficient amount of evidence: \( n \geq n_{\text{min}} \).

2. Superiority to control can be shown at a certain one-sided level of statistical significance, \( \alpha \):

\[
\bar{X} > h(n) \equiv \frac{z_{\alpha} \sigma}{\sqrt{n}}, \text{ where}
\]

\[
z_{\alpha} = \Phi^{-1}(1 - \alpha).
\]

Real world examples of RAs:

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

\[ f \equiv F' \] be the density and
\[ r \equiv f/(1 - F) \] the failure rate corresponding to $F$, it is assumed that

\[ 0 < F < 1, \]
\[ F \in C^{(2)}, \]
\[ |E_F| < \infty, \]
\[ r' > 0. \]

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

\[ P(c, \bar{x}, \nu, \omega) \equiv \mathbb{P}\left( \frac{c}{\bar{x}} < \Lambda \right) = 1 - F\left( \frac{c/\bar{x} - \nu}{\omega} \right). \]
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 \( c^* \).
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 $c_p(k) \equiv l_1/k + b > 0$ 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

$$\max_{c \geq 0} \Gamma_1 \iff \max_{c \geq 0} \{ k(c - c_p(k)) P(c, \bar{x}, \nu, \omega) \}.$$
From the assumptions placed on $F$, it may be shown that

1. there exists a unique solution, $c^*(\bar{x}, \nu, \omega, k)$ to
   \[ \max_{c \geq 0} k (c - c_p(k)) P, \]

2. which also solves $P + (c - c_p(k)) \frac{\partial P}{\partial c} = 0$, satisfying

3. $c^* > c_p(k)$,

4. $c^* \in C^{(1)}$,

5. $\frac{\partial c^*}{\partial x} > 0, \frac{\partial c^*}{\partial \nu} > 0$ and $\frac{\partial c^*}{\partial k} < 0$. 
Letting

$$\Gamma^*_1(\bar{x}, \nu, \omega, k) = \Gamma_1(\mathbf{c}^*(\bar{x}, \nu, \omega, k), \bar{x}, \nu, \omega, k),$$

the envelope theorem implies that

$$\frac{\partial \Gamma^*_1}{\partial \bar{x}} > 0, \quad \frac{\partial \Gamma^*_1}{\partial \nu} > 0, \quad \frac{\partial \Gamma^*_1}{\partial k} > 0,$$

$$\frac{\partial \Gamma^*_1}{\partial \omega} \begin{cases} < 0 & \text{if } \mathbf{c}^* < \bar{x} \nu, \\ = 0 & \text{if } \mathbf{c}^* = \bar{x} \nu, \\ > 0 & \text{if } \mathbf{c}^* > \bar{x} \nu. \end{cases}$$
Solving the model - Choice of optimal sample size

Let

$$\Gamma_0(n, \nu, \omega, k) = \mathbb{E} \left[ \Gamma_1^* (\bar{X}, \nu, \omega, k) \mathbb{I} (\bar{X} > h(n)) \right] - (l_0 + d_n)$$

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 $\Gamma_1^*$. 
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\textsuperscript{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 $z = W(z) \exp(W(z))$.

\textsuperscript{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 $\Gamma_1^*$ on $\omega$

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

\[
\frac{\partial c^*}{\partial \omega} < 0 \text{ if } \omega < \tilde{\omega}_c, \quad \frac{\partial \Gamma_1^*}{\partial \omega} < 0 \text{ if } \omega < \tilde{\omega}_{\Gamma_1},
\]

\[
\frac{\partial c^*}{\partial \omega} = 0 \text{ if } \omega = \tilde{\omega}_c, \quad \frac{\partial \Gamma_1^*}{\partial \omega} = 0 \text{ if } \omega = \tilde{\omega}_{\Gamma_1},
\]

\[
\frac{\partial c^*}{\partial \omega} > 0 \text{ if } \omega > \tilde{\omega}_c, \quad \frac{\partial \Gamma_1^*}{\partial \omega} > 0 \text{ if } \omega > \tilde{\omega}_{\Gamma_1},
\]

where: $\tilde{\omega}_c = \frac{\nu - c_p(k)/\bar{x}}{\beta_c}$, $\tilde{\omega}_{\Gamma_1} = \frac{\nu - c_p(k)/\bar{x}}{\beta_{\Gamma_1}}$.

Two qualitatively different cases may be distinguished:

1. $\bar{x}\nu \leq c_p(k)$: both $c^*$ and $\Gamma_1^*$ are strictly increasing in $\omega$.

2. $\bar{x}\nu > c_p(k)$: both $c^*$ and $\Gamma_1^*$ are first decreasing and then increasing in $\omega$. $c^*$ has a strict global minimum at $\tilde{\omega}_c$ and $\Gamma_1^*$ has a strict global minimum at $\tilde{\omega}_{\Gamma_1}$. 
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.
The prior parameters $\mu_0$, $\sigma_0$ and the population standard deviation $\sigma$ were chosen to be consistent with a previous trial (Bilton et al., 2011).

$\nu$ and $\omega$ estimated from a recent study (Dakin et al., 2014), giving $\nu = £39,417/QALY^6$ and $\omega = £11,230/QALY$.

$l_1$, $b$, $l_0$ 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 $k = 100,000$.

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6Quality Adjusted Life-Year
Application - Stage 1 expected profit as a function of $c$ (different $\omega$)
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 $\omega$)

![Graph showing Stage 0 expected profit as a function of $n$ with different values of $\omega$. The x-axis represents $n$ ranging from 0 to 200, and the y-axis represents the profit in £M. The graph includes lines for different values of $\omega$ (1000, 5000, 11,230, 25,000, 50,000).]
Application - Stage 0 expected profit (per patient-year) as a function of $n$ (different $k$)
Application - $k_{\text{min}}$ as a function of $n_{\text{min}}$ for different $\alpha$
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?
Thank you!