A decision-theoretic framework for the application of cost-effectiveness analysis in regulatory processes

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Outline of presentation

1. Health economic evaluations
2. Example: The market for statins
   - Cost-effectiveness analysis
   - Probabilistic sensitivity analysis & Expected Value of Information
3. Mixed strategy and non-optimal market configuration
   - Application to the market for statins
4. Conclusions
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Health economic evaluations

- **Objective**: Combine costs & benefits of a given intervention into a rational scheme for allocating resources
  - Recently, models have been built upon more advanced statistical foundations
  - This problem can be formalised within a statistical decision-theoretic approach. Rational decision-making is effected through the comparison of expected utilities
Health economic evaluations

- **Objective**: Combine costs & benefits of a given intervention into a rational scheme for allocating resources
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- Increasingly under a Bayesian framework, especially in the UK
    - Specific focus on Bayesian decision-theoretic development of cost-effectiveness analysis
  - Contributions by several scholars and research groups
    - Tony O’Hagan, Jeremy Oakley (University of Sheffield — Centre for Bayesian Statistics in Health Economics)
    - Karl Claxton, Mike Sculpher (University of York)
    - Giovanni Parmigiani (John Hopkins University), Gordon Hazen (Northwestern University)
    - Simon Thompson, Chris Jackson and Richard Nixon (MRC Cambridge)
Typically, we define a "health economic response" \((e, c)\), where for each intervention (treatment) \(t\):
- \(e\) represents a suitable measure of clinical benefits (e.g., QALYs)
- \(c\) are the costs associated with a given intervention
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The variables \((e, c)\) are usually defined as functions of a set of relevant parameters \(\theta^t\) which represent some population-level features of the underlying process:
- Probability of some clinical outcome
- Duration in treatment
- Reduction in the rate of occurrence of some event
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  Probability of some clinical outcome
  
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There are (at least) two sources of uncertainty
  
  **Sampling variability** is modelled using an intervention-specific distribution \(p(e, c \mid \theta^t)\)
  
  **Parametric uncertainty** is modelled using a (possibly subjective) prior distribution \(p(\theta^t \mid D)\), based on some background data \(D\)
  
  Sometimes, we can (should!) consider also structural uncertainty, i.e., about the modelling assumptions used
(Bayesian) Decision-making process

- In addition, we define a utility function to describe the quality of $t$
  - The function $u(e, c; t)$ describes the value associated with applying intervention $t$, in terms of the future (uncertain) outcomes
  - Uncertainty is expressed through $p(e, c, \theta) = p(e, c | \theta)p(\theta | D)$
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**NB**: typically, the utility function chosen is the monetary net benefit

$$u(e, c; t) := ke_t - c_t$$

- $k$ is the “willingness to pay”, i.e., the cost per extra unit of effectiveness gained.
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  - Computing for each intervention \( t \) the *expected utility*
  \[ U^t = E[u(e, c; t)] \]
  (computed with respect to both individual and population uncertainty)
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    U^t = E[u(e, c; t)]
    \]
    (computed with respect to both individual and population uncertainty)
  - Treating the entire homogeneous (sub)population with the most cost-effective treatment, ie that associated with the maximum expected utility
  - Performing sensitivity analysis (to parameter and/or structural uncertainty) to investigate the impact of underlying uncertainty on the decision process
Example: The market for statins

- Statins are a class of drug used to lower plasma cholesterol level by inhibiting an enzyme in the liver. This results in decreased cholesterol synthesis as well as increased clearance of low-density lipoprotein from the bloodstream.
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- Currently, there are 7 statins on the market, worldwide:
  - Atorvastatin (AS; synthetic, first marketed in 1997)
  - Fluvastatin (FS; synthetic, 1994)
  - Lovastatin (LS; fermentation-derived, 1976)
  - Pitavastatin (PtS; synthetic, 2003)
  - Pravastatin (PS; fermentation-derived, 1991)
  - Simvastatin (SS; synthetic derivate of fermentation process, 1988)
  - Rosuvastatin (RS; synthetic, 2003)
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- AS, RS and SS are market leaders, in Italy.

- Extensive data are available from controlled studies comparing the clinical effectiveness of several statins against placebo.

- We are interested in evaluating the efficiency of the market with respect to the fact that all the different statins are available for prescription and are all reimbursed by the Italian NHS (albeit under different conditions).
Statistical model

- Theoretical effectiveness
- Compliance
  - Reduction in effectiveness
  - Treatment costs
  - Hospitalisation costs
  - $e$
  - $c$
The model is based on the combination of evidence from RCTs and observational data available for Italy.

Statin $s$ is evaluated against statin $t$ using the monetary net benefit as utility measure, and by means of the **Expected Incremental Benefit**

$$EIB(s, t) = Expected \text{ utility}(s) - Expected \text{ utility}(t) = U^s - U^t$$

**Decision rule:**
If $EIB(s, t) > 0$ then $s$ is more cost-effective (C/E) than $t$
Based on published data on RCTs comparing statins to placebo

Define $y_{sj}$ and $n_{sj}$ as the number of Non Fatal Myocardial Infarction (NFMI) cases and of individual observed in the $j$-th study on statin $s$.
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Then for $s = 1, \ldots, S = 6$ statins and $j = 1, \ldots, N_s$ studies, we model

$$y_{sj} \sim \text{Binomial}(p_{sj}, n_{sj})$$

$$\text{logit}(p_{sj}) \sim \text{Normal}(\gamma_s, \tau_s)$$
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The parameter $\gamma_s$ represent a “pooled estimate” of the theoretical effectiveness for statin $s$
We use observational data on clinical practice to model the decrease in effectiveness due to $G = 4$ levels of non-compliance.
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We define $\mu_g$ and $\sigma^2$ to encode information from the literature and model

$$
\xi_g := \log \rho_g \sim \text{Normal}(\mu_g, \sigma^2) \quad g = 2, 3, 4
$$

$$
\rho_1 = \frac{1}{\exp(\xi_4)}, \quad \rho_2 = \frac{\exp(\xi_2)}{\exp(\xi_4)},
$$

$$
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<table>
<thead>
<tr>
<th>Compliance group</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low users</td>
<td>1 —</td>
</tr>
<tr>
<td>Low users</td>
<td>0.85 [0.73 – 0.98]</td>
</tr>
<tr>
<td>Intermediate users</td>
<td>0.82 [0.71 – 0.95]</td>
</tr>
<tr>
<td>High users</td>
<td>0.80 [0.70 – 0.93]</td>
</tr>
</tbody>
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$\Rightarrow \mu = \begin{bmatrix} -0.1625 \\ -0.1985 \\ -0.2231 \end{bmatrix}, \quad \sigma^2 = 0.0049$
Statistical model

- Compliance levels, treatment and hospitalisation costs are also estimated using observational data.
- All the relevant parameters are then combined to define:
  - $e$ = a weighted effectiveness in terms of chance of (non) experiencing NFMI, based on RCT data and compliance.
  - $c$ = a total cost of the treatment, accounting for the level of compliance and the risk of experiencing hospitalisations for NFMI.
Statistical model

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  - \( e = a \) weighted effectiveness in terms of chance of (non) experiencing NFMI, based on RCT data and compliance
  - \( c = a \) total cost of the treatment, accounting for the level of compliance and the risk of experiencing hospitalisations for NFMI
- These are then combined to define
  - The incremental effectiveness: \( \Delta e = E[e | s, \theta] − E[e | t, \theta] \)
  - The incremental costs: \( \Delta c = E[c | s, \theta] − E[c | t, \theta] \)
  - The expected incremental benefit: \( EIB = kE[\Delta e] − E[\Delta c] = U^s − U^t \)
- The economic analysis can be then performed to estimate which statin is the most “cost-effective”
We (arbitrarily) use AS as the reference intervention and compare it to all the other statins.

If EIB > 0 then AS is more cost-effective than the comparator.

First, compare AS against PS: for all $k \geq 0$, AS is more C/E as the black line is always above 0.

Thus, PS is irrelevant, as it is dominated by AS.
Then, include LS: for all $k \leq €415$, LS has a higher expected utility compared to AS (the red line is negative)

Thus LS is more C/E than AS for $k \leq €415$, while AS is more C/E for $k > €415$
Cost-effectiveness analysis

- **However**, for all $k \leq €2,760$, FS has an even higher expected utility (the blue line is negative and lower than the red one).
- Consequently, LS is irrelevant too: it is dominated by FS for $k \leq €2,760$ and by AS for $k > €2,760$.
• **However**, for all $k \leq €3 \, 890$, RS has an even higher expected utility (the magenta line is negative and lower than both the red and the blue ones).

• Consequently, FS is irrelevant too: it is dominated by RS for $k \leq €3 \, 890$ and by AS for $k > €3 \, 890$. 

\[ k = €3 \, 890 \]
- **However**, when $k \leq €16\,000$, SS has an even higher expected utility (the green line is negative and the lowest in that range).

- Consequently, RS is irrelevant too: it is dominated by SS for $k \leq €16\,000$ and by AS for $k > €16\,000$.

- The decision problem is then solved with the outcome: choose SS for $k \leq €16\,000$, and choose AS when $k > €16\,000$. 

Expected Incremental Benefit

- **Atorvastatin vs Pravastatin**
- **Atorvastatin vs Lovastatin**
- **Atorvastatin vs Fluvastatin**
- **Atorvastatin vs Rosuvastatin**
- **Atorvastatin vs Simvastatin**
The quality of the current evidence is often limited

- During the pre-market authorisation phase, the regulator should decide whether to grant reimbursement to a new product — and in some countries also set the price — on the basis of uncertain evidence, regarding both clinical and economic outcomes.

- Although it is possible to answer some unresolved questions after market authorisation, relevant decisions such as that on reimbursement (which determines the overall access to the new treatment) have already been taken.
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- Although it is possible to answer some unresolved questions after market authorisation, relevant decisions such as that on reimbursement (which determines the overall access to the new treatment) have already been taken.

This leads to the necessity of performing (probabilistic) sensitivity analysis (PSA)

- Formal quantification of the impact of uncertainty in the parameters on the results of the economic model.
- Standard requirement in many health systems (e.g. for NICE in the UK), but still not universally applied.
PSA to parameter uncertainty

Parameters

- Theoretical effectiveness
- Reduction in effectiveness
- Compliance
- Costs

Model structure

Statin $s$

- Theoretical effectiveness
- Compliance
- Reduction in effectiveness
- Hospitalisation costs
- Treatment costs

Statin $t$

- Theoretical effectiveness
- Compliance
- Reduction in effectiveness
- Hospitalisation costs
- Treatment costs

Decision analysis

<table>
<thead>
<tr>
<th>Statin $s$</th>
<th>Benefits</th>
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PSA to parameter uncertainty

Parameters

Model structure

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Theoretical effectiveness

Reduction in effectiveness

Compliance

Treatment costs

Hospitalisation costs

Statin t

Theoretical effectiveness

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Compliance

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Hospitalisation costs

Decision analysis

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<tbody>
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<td>1</td>
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<tr>
<td>1</td>
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<td>0</td>
<td>5 000</td>
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<tr>
<td>2</td>
<td>30 000</td>
</tr>
<tr>
<td>3</td>
<td>20 000</td>
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ICER = 20 000 1QALY

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EVI in regulatory contexts
Bayes 2012, 10 May 2012
Parameters

- Theoretical effectiveness
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- Compliance
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Model structure

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<tr>
<td>2</td>
<td>15 000</td>
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<td></td>
<td></td>
<td>2.55</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 000</td>
</tr>
</tbody>
</table>

ICER = \( \frac{20 000}{1.25} = 16 004 \)
Cost-effectiveness analysis

Cost effectiveness plane
Atorvastatin vs Simvastatin

Effectiveness differential vs Cost differential

ICER = 16003.59

k = 25000

Gianluca Baio (UCL)
EVI in regulatory contexts
Bayes 2012, 10 May 2012
Cost Effectiveness Acceptability Curve

- Atorvastatin vs Fluvastatin
- Atorvastatin vs Lovastatin
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- Atorvastatin vs Rosuvastatin
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Cost Effectiveness Acceptability Curve

- Use net benefit utility $u(e, c, s) = ke_s - c_s$, but consider varying $k$.
- CEAC represents $\Pr(k\Delta_e - \Delta_c > 0 \mid \text{Data})$ as a function of $k$.
- Suggested as the standard tool for PSA by NICE.
Cost Effectiveness Acceptability Curve

- Use net benefit utility \( u(e, c, s) = ke_s - c_s \), but consider varying \( k \).
- CEAC represents \( \Pr(k\Delta_e - \Delta_c > 0 \mid \text{Data}) \) as a function of \( k \).
- Suggested as the standard tool for PSA by NICE.
- Summarises the probability of cost effectiveness, as it depends on the willingness to pay parameter \( k \).
- Meaningful only if the parameters are considered random, i.e. within the Bayesian framework.
Expected value of (perfect) information

Expected Value of Information

SS most C/E ← AS most C/E

Willingness to pay

EVPI
Expected value of (perfect) information

- Compares the ideal decision process (ie if the uncertainty on the parameters were resolved to the simulated values) with the actual one (ie when uncertainty is averaged out in the expected utility)
- Describes the maximum amount the decision maker should be willing to pay to resolve the uncertainty in the parameters
Expected value of (perfect) information

- Compares the ideal decision process (i.e., if the uncertainty on the parameters were resolved to the simulated values) with the actual one (i.e., when uncertainty is averaged out in the expected utility).
- Describes the maximum amount the decision maker should be willing to pay to resolve the uncertainty in the parameters.
- By construction, combines:
  1. how much we are likely to lose if we take the “wrong” decision
  2. how likely it is that we take it
- Drives the process of gathering additional evidence.
Cost-effectiveness analysis summary

Reference intervention: Atorvastatin
Comparator intervention(s): Fluvastatin
: Lovastatin
: Pravastatin
: Rosuvastatin
: Simvastatin

Optimal decision: choose Simvastatin for $k<16000$ and Atorvastatin for $k>=16000$

Analysis for willingness to pay parameter $k = 25000$

Expected utility
Atorvastatin 22770
Fluvastatin 22336
Lovastatin 21002
Pravastatin 21579
Rosuvastatin 22415
Simvastatin 22628

<table>
<thead>
<tr>
<th></th>
<th>EIB</th>
<th>CEAC</th>
<th>ICER</th>
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<tbody>
<tr>
<td>Atorvastatin vs Fluvastatin</td>
<td>434.63</td>
<td>0.786</td>
<td>2759.65</td>
</tr>
<tr>
<td>Atorvastatin vs Lovastatin</td>
<td>1768.49</td>
<td>0.869</td>
<td>414.67</td>
</tr>
<tr>
<td>Atorvastatin vs Pravastatin</td>
<td>1191.01</td>
<td>0.973</td>
<td>-228.97</td>
</tr>
<tr>
<td>Atorvastatin vs Rosuvastatin</td>
<td>355.24</td>
<td>0.755</td>
<td>3989.22</td>
</tr>
<tr>
<td>Atorvastatin vs Simvastatin</td>
<td>142.44</td>
<td>0.636</td>
<td>16003.59</td>
</tr>
</tbody>
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Optimal intervention (max expected utility) for $k=25000$: Atorvastatin

EVPI 175.25
Mixed strategies

- Clinical practice and the regulator’s decisions in particular are generally not able to move towards a rapid substitution of the available therapeutic options with a new one that is more cost-effective
  - Only rarely a new treatment proves to be cost-effective over the entire population
  - Irreversibility risks associated with implementing an intervention (ie the decision maker might want to temporize, in order to have more reliable evidence on which to base the final decision)
  - The market usually takes some time to “adjust” to the new configuration generated by the innovative drug just introduced
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- Consequently, non-optimal interventions tend to remain active on the market
  - The regulator is faced with the problem of balancing the optimal decision (i.e., implementing the most cost-effective treatment) under the constraints that the market shares of the other molecules already present on the market can not be all set to zero
Since many interventions are kept on the market, in this case, the overall expected utility in the population is

$$\bar{U} = \sum_{s=1}^{S} q_s U^s,$$

where

- $q_s$ represents the market share for statin $s$
- $U^s$ is the expected utility for statin $s$
Mixed strategies (cont’d)

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where
- \( q_s \) represents the market share for statin \( s \)
- \( U^s \) is the expected utility for statin \( s \)

- The impact of uncertainty in the decision process, when the mixed strategy is actually chosen by the decision maker (ie when all the options \( s \) are on the market, with shares \( q_1, q_2, \ldots, q_S \), respectively) can be measured extending the analysis of the EVPI
Analysis of the Mixed strategy

Expected Value of Information

- **Optimal strategy**
- **Mixed strategy:**
  - Atorvastatin = 31.07%
  - Fluvastatin = 4.20%
  - Lovastatin = 4.35%
  - Pravastatin = 6.84%
  - Rosuvastatin = 19.37%
  - Simvastatin = 34.18%

**Willingness to pay**

- EVPI
- EVI in regulatory contexts
Analysis of the Mixed strategy

Expected Value of Information

- For each $k$, the impact of the mixed strategy is an increase in the EVPI with respect to the optimal scenario. The loss in expected value of information reaches €690 for $k = €50,000$

- This depends on
  
  a) The company that market a non-C/E alternative
  b) The regulator that does not disinvest from a non-C/E treatment
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The value of the extra uncertainty can be used to

- a) Establish the amount of investment for research that would be cost-effective to reduce the uncertainty about optimal decision
- b) Determine/modify the reimbursed retail price
- c) Represent the payback value from the company to the regional provider
Conclusions

- PSA to parameter uncertainty is a fundamental part of each health economic evaluation, and it should complement the standard decision analysis.
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- Therefore, it drives research prioritisation: if the value of acquiring further information to reduce uncertainty is too high, then the decision-maker should choose the optimal treatment based on the current evidence.
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**NB:** The R package BCEA (soon available on CRAN and for the moment downloadable at [www.statistica.it/gianluca/BCEA](http://www.statistica.it/gianluca/BCEA)) allows to produce a systematic economic analysis based on the results of a suitable Bayesian model, including the mixed strategy analysis.
Spiegelhalter D., Abrams K., Myles J. (2004). *Bayesian Approaches to Clinical Trials and Health-Care Evaluation*. John Wiley and Sons, Chichester, UK.


Thank you!