Early-phase economic evaluations based on PKPD modelling

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Comparison of the costs relative to the benefits

Decision rule: new medicine is worthwhile if
- Marginal benefit > Marginal cost

Inform payer decisions on resource allocation (e.g. NICE, NHS)

Will underpin value-based pricing (from 2014)
- Price proportionate to benefit (weighted QALYs)
Early-phase economic evaluations

- Used increasingly to inform internal decisions on product development
  - Strategic R&D decision making
  - Pre-clinical preliminary market assessments
  - Go/no-go decisions, identification of potentially successful projects
  - Development of future trial design
  - Assessment of future reimbursement and pricing scenarios
  - Price determination
Methods of economic evaluation reliant on empirical models of treatment benefit

Pre phase III, there is a paucity of data on efficacy, safety
  ◦ Certainly nothing on comparative effectiveness

Price estimation
  ◦ UK pharmaceutical pricing is currently opaque, largely based on what the market can bear and not on the cost of the product’s development, nor linked to patient benefit
PKPDPE – a novel approach

**Disease model**
- Biology
  - Biomarker(s)/outcome relationship
  - Natural progression
- Placebo effect

**Drug model**
- Pharmacokinetics
- Pharmacodynamics
- Covariate effects

**Trial model**
- Patient population
  - Demographics
- Drop-out
- Adherence

**Economic model**
- Health state utilities
- Resource use
- Cost-effectiveness

Output of conventional population PKPD (and clinical trial simulation) models serve as the input to health economic models

Assign costs and utilities to different health states

£/QALY can thus be reached as an outcome measure

Trial design can be made, based on the actual end-criteria by which success will ultimately be judged

Amenable to Value of Information analysis
  ◦ Informing trial design, areas of research prioritisation
  ◦ Identification of subgroups etc
Case Study - Rituximab

- Rituximab is a monoclonal antibody used in the treatment of follicular lymphoma
- Separate evidence available for its PK, PD (progression-free survival) and cost-effectiveness
- Aim is to make use of these data to develop a PKPDPE model
  - Proof of concept exercise
  - Compare PKPDPE output with industry submission to NICE

Rituximab Model - overview

- **PK model** – Ng et al.
  - Two-compartment linear model
  - BSA and gender as significant covariates
  - Based on 102 patients with RA

- **PD model** – Ternant et al.

\[
C_m(t) = \frac{\int_{t_m}^{t} C(\tau) d\tau}{t - t_m}
\]

\[
PFS(t) = \exp \left( -\left( \lambda_{max} \left( 1 - \frac{C_m^\gamma}{C_{m50}^\gamma + C_m^\gamma} \right) \right) t \right)
\]
Overview:
- Replicate NICE STA economic model, but substitute trial-reported PFS with PFS derived from PKPD simulation

Clinical data:
- Overall survival data/parameters taken from EORTC 20981 trial
- Progression free survival simulated from PKPD model

Other parameters taken from the NICE STA submission:
- Incidences/costs of adverse events
- Other costs taken from NHS reference costs
- Health utility scores come from an Oxford Outcome Group study
PD Model – Ternant et al

Overall survival

Control group
Treatment group

Proportion

0 0.2 0.4 0.6 0.8 1.0

Time (years)

0 5 10 15 20 25 30

PFS

Time
Proportion
## Results

<table>
<thead>
<tr>
<th>Value</th>
<th>Simulation</th>
<th>Original</th>
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<tbody>
<tr>
<td>Median survival – Control</td>
<td>5.273</td>
<td>5.214</td>
</tr>
<tr>
<td>Median survival – Treatment</td>
<td>6.249</td>
<td>6.221</td>
</tr>
<tr>
<td>Mean life expectancy – Control</td>
<td>5.398</td>
<td>5.409</td>
</tr>
<tr>
<td>Mean life expectancy – Treatment</td>
<td>6.599</td>
<td>6.600</td>
</tr>
<tr>
<td>Total cost – Control</td>
<td>£17,355</td>
<td>£14,722</td>
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<tr>
<td>Total cost - Treatment</td>
<td>£22,728</td>
<td>£21,608</td>
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<tr>
<td>Incremental cost</td>
<td>£5,373</td>
<td>£6,886</td>
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<tr>
<td>Incremental life years</td>
<td>1.011</td>
<td>1.000</td>
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<tr>
<td>Incremental QALYs</td>
<td>0.592</td>
<td>0.892</td>
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<tr>
<td>Incremental cost per QALY</td>
<td>£9,076</td>
<td>£7,721</td>
</tr>
</tbody>
</table>
Probabilistic Sensitivity Analysis

Incremental QALYs gained vs Incremental cost
Cost-effectiveness Acceptability Curve

Simulated results
Trial-based results

Cost-effectiveness threshold (£/QALY)
Agreement of modelling approaches
Applications

- Estimation of price
  - Low price ensures market entry
  - High price risks reimbursement difficulties
  - Achieving £30k/QALY (VBP)

- Clinical trial design - simulations can help to inform protocol design:
  - Sample sizes, dosing regimens, important subgroups
  - Adaptive trial design
  - Extrapolation of data beyond the time limits of trials
  - Model protocol deviations (e.g. non-adherence)
  - Amenable to value of information analysis
  - Identify areas for future research prioritisation

- Inform stop/go decisions
  - If a product is not commercially viable