Early health economic modeling to inform medical product development and market access

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Some thoughts...

- Early models are not useful if not properly explained. Align with target audience before you start and make clear which decision has to be made, and by whom.
- Commercial, R&D and health economic models are typically used in isolation from each other and most people only refer to one specific type of models if asked about early modeling.
- Too often, early models are referred to as models that precede the decision they inform. Yet, they are not necessarily started early.
- It may be useful to use health economic evidence in earlier stages of R&D.
What is early modeling?

- Emphasis on efficient use of resources in medical product development and market access
  - Determine health economic value early on to either continue or discontinue further development (in particular SME’s)
- Different initiatives
  - Inno-HTA, MaRS Excite, MATCH, OncoTyrol, CTMM, LITHE
  - Taskforce initiative ISPOR
- But also different meanings:
  - Early modeling/horizon scanning for (research) priority setting
    - From a societal perspective – i.e. allocative efficiency
  - Early stage modeling for R&D and commercial decisions
    - From an industry perspective – i.e. business opportunities

Early modeling in the view of...

- Society
  - Maximize health benefits given scarce resources
    - Use of early models to justify research funding (PPP)
    - Use of early models to determine health economic value
- Engineer/scientist
  - Ground-breaking new concepts aimed at improving health outcomes for (groups of) individuals
    - Use of models to determine development targets and competitor performance
- Business
  - Early identification of the commercial value of a product
    - Use of models to estimate discounted cash flow and NPV
Technology use by patients

Basic research
Translational research
Clinical research
Access & pricing

Very early HTA
Early HTA
Main stream HTA (+horizon scanning)

Decision uncertainty

Market Access

Ijzerman & Steuten, Appl. Health Econ & Health Pol. 2011
Early modeling to inform health policy

<table>
<thead>
<tr>
<th>Stage</th>
<th>Typical level of diffusion</th>
<th>Dominant clinical research strategy</th>
<th>Types of economic analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>I: Early developmental</td>
<td>Small number of innovators</td>
<td>Small, uncontrolled case series</td>
<td>Systematic review of evidence relating to cost and effectiveness of existing practice; use of informal clinical opinion to assess the potential value of the new technology</td>
</tr>
<tr>
<td>II: Maturing innovation</td>
<td>A few specialist centres</td>
<td>Case series and small RCTs</td>
<td>Modelling studies using data from existing clinical studies; pilot studies of economic data collection alongside controlled trials</td>
</tr>
<tr>
<td>III: Close to widespread diffusion</td>
<td>A larger number of centres (specialist and other)</td>
<td>Large RCTs</td>
<td>Economic data collection alongside RCTs; refined modelling studies using systematic overviews of clinical data</td>
</tr>
<tr>
<td>IV: Moving into practice</td>
<td>Generalised adoption</td>
<td>Pragmatically designed controlled trials; observational studies of the technology in normal use</td>
<td>Economic data collection alongside pragmatic trials; modelling studies to generalise results to other settings, or to extrapolate to the long term</td>
</tr>
</tbody>
</table>

A preliminary economic evaluation of percutaneous neuromuscular electrical stimulation in the treatment of hemiplegic shoulder pain

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Abstract
Objective. The objective of this study was to compare the cost-effectiveness of various treatment modalities for hemiplegic shoulder pain.

Design. A stage II economic evaluation.

Main outcome measures. Incremental cost effectiveness ratio of P-NMES, compared to slings and anti-inflammmatory injections.

Results. The incremental cost effectiveness ratio (ICER) of P-NMES, compared to anti-inflammatory injections is €6,061 (± 3,285). The incremental cost of the first quality-adjusted life year after implantation of the P-NMES device compared to anti-inflammatory injections is €33,007 (± 5,434). This decreases to €7,000 after 5 years, and to €5,000 after 10 survival years.

Conclusion. In this early evaluation, P-NMES seems to be cost-effective according to known guidelines. Treatment with P-NMES is recommended for patients with chronic HSP.

Keywords: Electrical stimulation, hemiplegic shoulder pain, stroke, economic evaluation
Utility estimates from phase I, uncontrolled trial

Simulated Incremental Cost-Effectiveness Ratio (1 year)
Early modeling for R&D and commercial decisions

Table 1. Similarities and Differences between Classical HTA and Early HTA

<table>
<thead>
<tr>
<th></th>
<th>Classical HTA</th>
<th>Early HTA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aim</strong></td>
<td>Assess safety, effectiveness, and cost-effectiveness profiles of a new technology</td>
<td>Assess (likely) safety, effectiveness, and cost-effectiveness profiles of a new technology</td>
</tr>
<tr>
<td><strong>Decision support</strong></td>
<td>Decision support for regulators, payers, and patients about market clearance, payment, and usage of a technology</td>
<td>Decision-support for manufacturers and investors about design and management of a technology, as well as regulatory and reimbursement strategy</td>
</tr>
<tr>
<td><strong>Available evidence</strong></td>
<td>Usually evidence from clinical studies performed with the new technology</td>
<td>Evidence from early bench and animal testing, early clinical experience, and from previous generations of the technology</td>
</tr>
<tr>
<td><strong>Influence on technology performance</strong></td>
<td>Limited or no influence on clinical performance of a new technology</td>
<td>Potentially significant influence on (future) clinical performance of a new technology</td>
</tr>
</tbody>
</table>
Scoping review on methods in early assessment

- Which methods are used to determine value in early development stages?

- Databases: Pubmed, Scopus, Science Direct and cochrane databases

- Key-words:
  - Generic: early HTA, device, innovation, technology assessment, decision model, industrial engineering, healthcare
  - Methods: horizon scanning, clinical trial simulation, conjoint analysis, multi-criteria decision analysis, health impact model

Figure 2. Flow chart: selection of the literature.
Early Health Economic Modeling: A simple starting point

Key questions in this example:

→ What is the incidence ($X, \sigma$) of failure in real life?
→ What is the QALY loss ($X, \sigma$) of failure/disease?
→ How is failure managed in real life?
→ What is the cost ($X, \sigma$) of failure?

Anticipated in TPP (target product profile)
Early health economic models

- Deterministic sensitivity analysis
  - What effect size would be needed to demonstrate value
  - What range of prices is acceptable
  - What model parameters drive value
  - What priorities for evidence generation

- Uncertainty in early models
  - Parameter uncertainty, possible to quantify using VOI
  - Decision maker uncertainty, i.e. probability of approval
    - What criteria are used for decision making?
  - Market uncertainty: expected volume / share

- Some uncertainty can be solved if comparator is known, yet this is difficult to determine early stage

Early Health Economic Modeling
Bayesian model of Lab-on-Chip potassium monitoring

- State transition model
- Transition probabilities obtained from literature
- Costs of each health state obtained from literature
- Estimated benefit of monitoring in terms of change in transition probability
- 20,000 simulations

Wetering et al, Techn Forec Soc Change, 2011
Cost-effectiveness gap analysis

- Headroom for improvement, given expected benefits
- Requires
  - Willingness to pay for a QALY (e.g. 30K€/QALY)
  - Incremental QALY gain (estimated)
  - Expected duration of the QALY gain
- If ICER = $C / \Delta U$ then, $\Delta C = \text{ICER} \times \Delta U$ or $\Delta C = \text{WTP} \times \Delta U$
- Case: POCT for potassium monitoring (vd Wetering, 2011)
  - Cost of severe potassium imbalance: 752 €
  - Utility decrement of potassium imbalance: 0.04/year (low probability)
  - CE-gap: $30,000 \times 5 \times 0.04 + 752 = 6752€$
  - Offers good prospects: unit cost of POCT not likely to exceed 6752€

Deterministic sensitivity analysis to estimate model sensitivity for uncertain priors (e.g. pricing)

Value of information to determine value of additional research to reduce decision uncertainty
EVPI: 432 Meuro (threshold 25K€uro/QALY)
### Uncertainty in (early) models

<table>
<thead>
<tr>
<th>Structural Uncertainty (model simplifications)</th>
<th>IN THE MODEL DESIGN</th>
<th>IN THE MODEL ANALYSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Scenario drafting</td>
<td></td>
<td>---</td>
</tr>
<tr>
<td>• Focus groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• MCDA methods</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Methodological Uncertainty</th>
<th>Modeling guidelines (eg. Gold and Ramsey)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parameter uncertainty</strong></td>
<td></td>
</tr>
<tr>
<td>• Clinical trials</td>
<td></td>
</tr>
<tr>
<td>• Meta analysis</td>
<td></td>
</tr>
<tr>
<td>• Indirect treatment comparison (ITC)</td>
<td></td>
</tr>
<tr>
<td>• Expert elicitation techniques for estimating priors</td>
<td></td>
</tr>
<tr>
<td>• Deterministic Sensitivity Analysis</td>
<td></td>
</tr>
<tr>
<td>• Probabilistic Sensitivity Analysis</td>
<td></td>
</tr>
<tr>
<td>• Value of Information analysis</td>
<td></td>
</tr>
</tbody>
</table>

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**Diagram:**

- **Market Access**
  - First clinical use
  - Coverage and adoption
- **Technology use by patients**
  - R&D decisions
  - Basic research
  - Targeting for specific product
  - Proof of principle
  - Prototype development
  - Translational research
  - Clinical research
  - Access & pricing
  - Main stream HTA (+horizon scanning)

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IJzerman & Steuten, Appl. Health Econ & Health Pol 2011
Developments in medical imaging for breast cancer
A portfolio approach to determine implementation sites
(case: 24-hours EEG monitoring at home in epilepsy)

![Diagram](image)

Figure 4: Implementation possibilities of HBM.

Breteler, Roorda, van Putten, Ijzerman, 2013
Technical requirements and uncertainty

<table>
<thead>
<tr>
<th>Uncertainties:</th>
<th>Estimated probability of success</th>
<th>Scenario 1</th>
<th>Scenario 2</th>
<th>Scenario 3</th>
<th>Scenario 4</th>
<th>Scenario 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very high diagnostic value</td>
<td>29%</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High diagnostic value</td>
<td>50%</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Implementation of HBM at other positions</td>
<td>42%</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detection algorithm</td>
<td>85%</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acceptation among patients</td>
<td>82%</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Technical uncertainties</td>
<td>98%</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability per scenario:</td>
<td></td>
<td>8.40%</td>
<td>11.40%</td>
<td>14.30%</td>
<td>6.00%</td>
<td>0.80%</td>
</tr>
<tr>
<td>Contribution to option value:</td>
<td></td>
<td>38640</td>
<td>44574</td>
<td>19891.3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Option value:</td>
<td></td>
<td>103105.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Breteler, Roorda, van Putten, Ijzerman, 2013

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