The challenges of preparing evidence for decision modelling

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MRC biostats
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Overview

• Context
  Overview of decision modelling
  Overview of decision uncertainty and value of further research
• Challenges of preparing input data
• Case study 1
• Case study 2
Context
Cost-effectiveness is often used in health care to inform policy decisions about which strategy to use within a health system (societal level decision) not treatment decisions for an individual patient.

NHS is collectively funded
- Primary purpose is to improve health (of all)
Optimal strategies are those that confer the most:

- **Health** (benefits minus harms), if budget is assumed **unlimited**

- **Net health**, if budget is assumed **limited** (e.g. UK)

  The decision to commit to funding a technology implies other patients may lose health (by displacement of current NHS activities from the funds committed by approval of the new technology).

  How much health likely to be forgone – the NICE threshold in the UK

  $$\text{INH} = \Delta E - \Delta C^* \lambda \text{ (health units) or } \Delta E / \lambda - \Delta C \text{ (monetary units)}$$

  decision rule: if $\text{INH} > 0$ the new technology should be adopted
Decision modelling

- Uncertainty in knowledge
  - Evidence, judgements, others

- Intervention A
- Intervention B
- Efficacy, safety, unit costs, HRQOL, etc

- Decision model

- LYs, QALY
  - Costs

- Expected effectiveness, or cost effectiveness

- Decision uncertainty
  - Consequences of an incorrect decision
  - Value of information

- Adoption decision: A or B?
Modelling in cost effectiveness

What is a decision model?

- Mechanistic model of disease progression or other events relevant to the appraisal that allows analysing alternative policy options e.g. whether to treat or not

- Uses mathematical relationships to define a set of possible consequences that would flow from each alternative treatment being evaluated in a way that is relevant to estimating health/net health outputs = f(inputs)
  e.g. INB = f(baseline risk, relative effectiveness, costs, utility)
Models often use health states between which patients can transit. A very simple example, sometimes used in cancer:

![Diagram showing health states and transitions](image)

### Parameter Details and Hypothetical Value Assumed

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Detail</th>
<th>Hypothetical value assumed</th>
</tr>
</thead>
<tbody>
<tr>
<td>P_dead</td>
<td>Probability of patients dying in each cycle (no treatment)</td>
<td>0.5</td>
</tr>
<tr>
<td>Costs_treat</td>
<td>Costs of treatment (one-off costs)</td>
<td>€2000</td>
</tr>
<tr>
<td>Costs_alive</td>
<td>Yearly costs of patients alive</td>
<td>€500</td>
</tr>
<tr>
<td>HRQL_alive</td>
<td>Health Related Quality of Life score of patients</td>
<td>0.8</td>
</tr>
<tr>
<td>Relative effect</td>
<td>Relative treatment effect on death (relative risk)</td>
<td>0.8</td>
</tr>
</tbody>
</table>
The information is used to evaluate a profile of costs and QALY:

### no treatment

<table>
<thead>
<tr>
<th>time</th>
<th>Alive</th>
<th>dead</th>
<th>Costs</th>
<th>QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0-1</td>
<td>0.5</td>
<td>0.5</td>
<td>250</td>
<td>0.40</td>
</tr>
<tr>
<td>1-2</td>
<td>0.25</td>
<td>0.75</td>
<td>125</td>
<td>0.20</td>
</tr>
<tr>
<td>2-3</td>
<td>0.125</td>
<td>0.875</td>
<td>63</td>
<td>0.10</td>
</tr>
<tr>
<td>3-4</td>
<td>0.0625</td>
<td>0.9375</td>
<td>31</td>
<td>0.05</td>
</tr>
<tr>
<td>4-5</td>
<td>0.03125</td>
<td>0.96875</td>
<td>16</td>
<td>0.03</td>
</tr>
<tr>
<td>total</td>
<td>0.97</td>
<td></td>
<td>484</td>
<td>0.78</td>
</tr>
</tbody>
</table>

### treatment

<table>
<thead>
<tr>
<th>time</th>
<th>Alive</th>
<th>dead</th>
<th>Costs</th>
<th>QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2000</td>
<td>0</td>
</tr>
<tr>
<td>0-1</td>
<td>0.6</td>
<td>0.4</td>
<td>300</td>
<td>0.48</td>
</tr>
<tr>
<td>1-2</td>
<td>0.36</td>
<td>0.64</td>
<td>180</td>
<td>0.29</td>
</tr>
<tr>
<td>2-3</td>
<td>0.216</td>
<td>0.784</td>
<td>108</td>
<td>0.17</td>
</tr>
<tr>
<td>3-4</td>
<td>0.1296</td>
<td>0.8704</td>
<td>65</td>
<td>0.10</td>
</tr>
<tr>
<td>4-5</td>
<td>0.07776</td>
<td>0.92224</td>
<td>39</td>
<td>0.06</td>
</tr>
<tr>
<td>total</td>
<td>1.38</td>
<td></td>
<td>2692</td>
<td>1.11</td>
</tr>
</tbody>
</table>

#### Evaluating cost effectiveness

**Incremental (expected) costs** = £2692 - £484 = £2207

**Incremental (expected) QALYs** = 0.332

**Incremental cost effectiveness ratio (ICER)** = £6655/QALY gained
Modeling in cost effectiveness

A slightly more complex model may be

![Diagram showing transitions between states: Stable disease, Progressed disease, and Dead.]

Time to event analysis on
  time to progression or death, and
time to death
are often used to inform transitions between states

Example: [http://www.hta.ac.uk/fullmono/mon1714.pdf](http://www.hta.ac.uk/fullmono/mon1714.pdf)
Modeling in cost effectiveness

An even more complex model …
Example of decision models

Acute coronary syndromes

The cost-effectiveness of an early interventional strategy in non-ST-elevation acute coronary syndrome based on the RITA 3 trial; Henriksson et al, Heart 2008
Instead of modelling, one could use data on costs and effects collected directly from patients in RCTs to establish cost effectiveness.

So why modeling?
Single studies often do not provide all of the information necessary to inform decisions about the adoption of health technologies, particularly those regarding cost-effectiveness.

Modelling allows:
1. Using evidence from multiple sources
2. Appropriate time horizon
3. Generalisability
4. Explicit characterisation of uncertainty, its consequences and sources...
Why modeling for societal decision making?

1. **Using evidence from multiple sources** consistent with evidence-based medicine

   - Different sources may appropriately inform different parameters
     Whilst RCTs provide the strongest evidence of the efficacy of interventions
     Baseline parameters, costs and HRQoL scores may be better derived from observational studies

   - There may be multiple studies providing relevant evidence on one aspect of the appraisal
     Meta-analyses and network meta-analyses
     Multiple comparators

   - Linking intermediate to final outcomes
Decision modelling allows

** Explicit characterisation of uncertainty, its consequences and sources

- Allows explicit partitioning of the problem into its relevant components (parameterisation)
  Thus uncertainty over each parameter/source can be made explicit.

- Other sources of uncertainty can also be made explicit
  - **Structural**: uncertainty generated by the use of scientific judgments made when constructing a model (Bojke 2009)
  - **Other**: for example, uncertainty due to poor representativeness of the evidence.
Uncertainty is ubiquitous, and decisions are often uncertain.

This means decisions made today may be wrong, other courses of action could potentially have been better, in which case health would be lost.

Further research decreases uncertainty over decisions made today.

The value of research = value of avoiding the losses due to uncertainty.
Value of further research

Consequences of uncertainty = value of further research
  . arise from the possibility of a decision based on current evidence being wrong,
  . in which case another treatment alternative could have conferred higher health gains
  . and thus we may be loosing health
Evaluating decision uncertainty

Asymptomatic $P_{A-P}$

Progressive $P_{P-D}$

Dead

1. incr costs: £10,400
   incr effects: 5
   incr NHB: 3.96

2. incr costs: £24,745
   incr effects: 5.38
   incr NHB: 2.9

3. incr costs: £21,364
   incr effects: 1.1
   incr NHB: -1.03

Costs vs. Quality of Life (hrqol)
Uncertainty
Incremental (net) health, 2 alternatives

Uncertainty over benefits

Expected value of the technology = 2 health units
ADOPT
Uncertainty

Uncertainty over benefits
Decision uncertainty = 0.2

Probability of error = 0.20
Probability of being E/CE = 0.80

(net) health
Uncertainty, EVPI

Expected value of perfect information, loss function

Probability of error = 0.20
Expected losses = 0.3 health units

(net) health

(net) health
Is further evidence worth collecting? (EVPI)

<table>
<thead>
<tr>
<th>How things could turn out</th>
<th>(Net) Health Benefit</th>
<th>Best we could do if we knew</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment A</td>
<td>Treatment B</td>
</tr>
<tr>
<td>θ1</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>θ2</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>θ3</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>θ4</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>θ5</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>Average</td>
<td>11</td>
<td>12</td>
</tr>
</tbody>
</table>

What’s the best we can do now?
Choose B
Expect 12 QALYs, gain 1 QALY
But uncertain
Wrong decision 2/5 times (error probability = 0.4)

Could we do better?
If we knew
Expect 14 QALYs

EVPI = $E_\theta \max_j \text{NB}(j, \theta) - \max_j E_\theta \text{NB}(j, \theta) = 2$ QALYs per patient
Is further evidence worth collecting? (EVPI)

- EVPI for an individual
  - Information is a public good
  - EVPI for current and future patients

- EVPI for a population:
  \[ \text{EVPI}^* \sum_{t=1}^{T} \frac{\text{Pop}_t}{(1+r)^t} \]
  where:
  \[ \text{Pop}_t = \text{incidence and/or prevalence at time } t \ (t = 1, \ldots, T), \]
  \[ r = \text{discount rate}, \]
  \[ T = \text{effective lifetime of the evidence} \]

- Implications
  - Finite value of information
  - Finite patient horizon if \( r > 0 \)
  - \( T \) is a proxy for complex and uncertain changes
Uncertainty

Expected value of further research

Probability of error = 0.20
Expected losses = 0.3 health units = $3000
Uncertainty

Expected value of further research

Probability of error = 0.20
Expected losses = $3000

<table>
<thead>
<tr>
<th>Probability of error = 0.20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expected losses = $6000</td>
</tr>
</tbody>
</table>

(net) health

$
What type of evidence? (EVPI for parameters)

\[
\text{EVPI}_{\theta_1} = E_{\theta_1} \max_j E_{\theta_2|\theta_1} \text{NB}(j, \theta_1, \theta_2) - \max_j E_{\theta} \text{NB}(j, \theta)
\]

\[\begin{align*}
\theta & \\
\theta_1 & = \text{parameter of interest} \\
\theta_2 & = \text{other uncertainties}
\end{align*}\]

- Value of eliminating uncertainty in a subset of input parameters
- Useful to identify which parameters responsible for decision uncertainty
- Helps target research designs
Identifying research priorities

• EVPPI
  – Maximum return to research (endpoint)
  – Considering the costs of research

• What type of research?
  – Is an RCT required
  – Should there be longer follow-up
  – Head to head comparisons
  – Observational and epidemiological research
  – Portfolio of research
Expected value of sample information

Benefit of sample information is the reduction in the expected cost of uncertainty (EVSI)

$$EVSI = E_{\phi} E_{D|\phi} \max_j E_{\psi,(\phi|D)} NB(j,\phi,\psi) - \max_j E_\theta NB(j, \theta)$$

$EVSI$ – cost of sampling = societal payoff from proposed research  
($ENBS = EVSI – \text{cost of research}$)

The issues:

- Research is efficient if $ENBS > 0$
- Optimal sample size which maximises $ENBS$
- Efficient allocation of patients to arms of the trial
- Which endpoints should be included?
- Optimal follow-up which maximises $ENBS$
Technically efficient research design

- Benefit of sample information is the reduction in the expected cost of uncertainty (EVSI)

- EVSI - cost of sampling is the societal payoff from proposed research (ENBS = EVSI – cost of research)

- The issues:
  - Research is efficient if ENBS>0
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Technically efficient research design

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• The issues:
  – Research is efficient if ENBS>0
  – Optimal sample size which maximises ENBS
  – Efficient allocation of patients to arms of the trial
  – Which endpoints should be included?
  – Optimal follow-up which maximises ENBS
Challenges in preparing evidence for decision modelling
Preparing evidence for decision modelling

Matching parameter and evidence space
Most comprehensive evidence-base
Preparing evidence for decision modelling

Considerations when informing mechanistic models

Parameter space
- Types of parameters
- Judgements

Evidence space
- Study design
- Multiple sources
- Format of evidence
- Non-data
- Direct info on inputs
- Mechanistic relations
- Imperfect or sparse data

Breadth of evidence
- Quality
- Indirect evidence
- Inconsistent evidence
Preparing evidence for decision modelling

Considerations when informing mechanistic models

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- Inconsistent evidence
Preparing evidence for decision modelling

Considerations relating to parameter space

Typical parameter space for multi state decision models

<table>
<thead>
<tr>
<th>Types of parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transition probabilities</td>
</tr>
<tr>
<td>Relative effectiveness parameters</td>
</tr>
<tr>
<td>Costs for each health state</td>
</tr>
<tr>
<td>Utilities for each health state</td>
</tr>
<tr>
<td>Parameterised structural uncertainties</td>
</tr>
<tr>
<td>Non-parameterised structural uncertainties</td>
</tr>
<tr>
<td>Judgements</td>
</tr>
</tbody>
</table>

Judgements

Diagram:
- Asymptomatic
- Progressive
- Dead

Asymptomatic -> Progressive
Progressive -> Dead
Dead -> Asymptomatic
Preparing evidence for decision modelling

Considerations relating to parameter space

Example: relative treatment effects

Price, Stats in Med, 2010
Preparing evidence for decision modelling

Considerations relating to parameter space

Example: relative treatment effects, challenge of dealing with structural uncertainties

Price, Stats in Med, 2010
Preparing evidence for decision modelling

Structural uncertainties

- Define global model with parameters defining structures, and seek for evidence
- In the absence of evidence, is there sufficient expert belief about the parameter?
- If yes, obtain distribution from expert elicitation
- If no, separate scenarios defined by plausible parameter values
- Model averaging if no clear best fitting model and results differ

Jackson et al, MDM, 2011
Preparing evidence for decision modelling

Considerations when informing mechanistic models

Parameter space
- Types of parameters
- Judgements

Evidence space
- Study design
- Multiple sources
- Format of evidence
- Other sources of evidence
- Direct info on inputs
- Mechanistic relations

Breadth of evidence
- Quality
- Indirect evidence
- Inconsistent evidence
Preparing evidence for decision modelling

Exploring which pieces of evidence can inform each parameter (‘’

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Study 1</th>
<th>Study 2</th>
<th>Study 3</th>
<th>Study 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transition probabilities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative effectiveness parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Costs for each health state</td>
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<td></td>
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<tr>
<td>Parameterised structural uncertainties</td>
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<tr>
<td>Non-parameterised structural uncertainties</td>
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</tr>
<tr>
<td>Judgements</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Evidence on mechanistic relations
Preparing evidence for decision modelling

Considerations relating to the evidence space

Typical evidence space for multi-state decision models

- Observational study
- Observational study
- Judgements
- Evidence on mechanistic relations
- RCT
- RCT

Options:
- Multiple sources
- Format of evidence
- Non-data
- Direct info on inputs
- Mechanistic relations
Preparing evidence for decision modelling

Considerations relating to the evidence space

Example:

<table>
<thead>
<tr>
<th>Transition probabilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative effectiveness parameters</td>
</tr>
<tr>
<td>Costs for each health state</td>
</tr>
<tr>
<td>Utilities for each health state</td>
</tr>
<tr>
<td>Parameterised structural uncertainties</td>
</tr>
<tr>
<td>Non-parameterised structural uncertainties</td>
</tr>
<tr>
<td>Judgements</td>
</tr>
</tbody>
</table>

Study design

Observational study

Observational study

judgements

Evidence on mechanistic relations

RCT

RCT
Preparing evidence for decision modelling

Considerations relating to the evidence space

Example challenge: using observational evidence to infer over relative treatment effects
[Faria et al. TSD NICE DSU forthcoming]

METHODS ASSUMING SELECTION ON OBSERVABLES
• E.g. Regression adjustment, Inverse probability weighting or Matching procedures

METHODS FOR SELECTION ON UNOBSERVABLES
• Instrumental variable methods, structural models and panel data models

NATURAL EXPERIMENT APPROACHES
• Difference in differences, and regression discontinuity design
Preparing evidence for decision modelling

Considerations relating to the evidence space

Example:

- Transition probabilities
- Relative effectiveness parameters
- Costs for each health state
- Utilities for each health state
- Parameterised structural uncertainties
- Non-parameterised structural uncertainties
- Judgements

Format of evidence:
- Observational study
- Observational study
- Direct info on inputs
- RCT
- RCT
- Evidence on mechanistic relations
- Judgements
## Preparing evidence for decision modelling

### Considerations relating to the evidence space

### Sources and format of evidence

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Source of evidence</th>
<th>Format of data</th>
<th>Parameter</th>
<th>Methods*</th>
<th>Relevant references</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>Single</td>
<td>AD</td>
<td>Single</td>
<td>Direct inclusion of reported estimate (or transformation of it) in the model</td>
<td>–</td>
</tr>
<tr>
<td>B1</td>
<td>Single</td>
<td>AD</td>
<td>Multiple</td>
<td>Direct inclusion of estimates or transformations of them in the model—correlation should be included if reported</td>
<td>[22–24]</td>
</tr>
<tr>
<td>C1</td>
<td>Single</td>
<td>IPD</td>
<td>Single</td>
<td>Using standard analysis procedures relevant for the primary study</td>
<td>[26, 28]</td>
</tr>
<tr>
<td>D1</td>
<td>Single</td>
<td>IPD</td>
<td>Multiple</td>
<td>Using standard multivariate estimation procedures—including correlations</td>
<td>[10, 60]</td>
</tr>
<tr>
<td>A2</td>
<td>Multiple</td>
<td>AD</td>
<td>Single</td>
<td>Meta-analysis; Meta-regression</td>
<td>[20, 30–33, 35, 37, 39, 62]</td>
</tr>
<tr>
<td>B2</td>
<td>Multiple</td>
<td>AD</td>
<td>Multiple</td>
<td>Multivariate meta-analysis (e.g., bivariate random-effects meta-analysis); Mixed treatment comparison</td>
<td>[42–46, 48, 50–58]</td>
</tr>
<tr>
<td>C2</td>
<td>Multiple</td>
<td>IPD</td>
<td>Single</td>
<td>“Mega-analysis” (meta-analysis using IPD)</td>
<td>[61, 64–66, 68, 69]</td>
</tr>
<tr>
<td>D2</td>
<td>Multiple</td>
<td>IPD</td>
<td>Multiple</td>
<td>Multivariate meta-analysis using IPD (e.g., bivariate random-effects meta-analysis)</td>
<td>[71]</td>
</tr>
<tr>
<td>E2</td>
<td>Multiple</td>
<td>Mixture</td>
<td>Single</td>
<td>Two-stage—reduce IPD to AD or reconstruct IPD from AD; One-stage—hierarchical modeling (e.g., meta-analysis using AD and IPD)</td>
<td>[12–16, 74, 75]</td>
</tr>
<tr>
<td>F2</td>
<td>Multiple</td>
<td>Mixture</td>
<td>Multiple</td>
<td>Extensions of previous synthesis models to the hierarchical framework (e.g., bivariate random-effects meta-analysis of IPD)</td>
<td>[13]</td>
</tr>
</tbody>
</table>
Preparing evidence for decision modelling

Considerations relating to the evidence space

Typical evidence space for multi-state decision models

- Observational study
- Observational study
- Judgements
- Evidence on mechanistic relations
- RCT
- RCT

- Multiple sources
- Format of evidence
- Non-data
- Direct info on inputs
- Mechanistic relations
Concerns about modeling

- Inappropriate use of data
- How to deal with biases in observational data
- Difficulties of extrapolation
- Validity of models
- Need extensive validation
  - E.g. NICE appraisal process

Complexity

Also in the analysis of input data:
- correlation between parameters,
- weighting evidence for bias,
- multiparameter evidence synthesis,
- calibration, ...

Early modelling
Thanks!

The challenges of preparing evidence for decision modelling

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