Benefit and risk considerations in medical decision making

Douwe Postmus¹, Gert van Valkenhoef, Hans Hillege

Department of Epidemiology, University Medical Center Groningen, The Netherlands

¹Corresponding author. Email: d.postmus@umcg.nl
Medical decision making

- Health policy decision making
  - Given the evidence produced by phase II and phase III studies, should a new anti-depressant be allowed on the market?
  - Which of the available anti-depressants should be eligible for reimbursement?

- Clinical decision making
  - Which anti-depressant should be prescribed to a patient presenting with severe signs and symptoms?
Challenges in drug benefit-risk assessment

- Dealing with multiple comparisons and trade-offs
- Measurement of benefit is closely defined whereas risk is generic
  - Decrease in body weight of 5kg versus 10% increase in the incidence of psychiatric disorders
- Balancing short and long term effects
- Changing from probability statements about the data given the truth (Frequentist) to probability statements about the truth given the data (Bayesian)
Ad-hoc versus rational decision making

Source: Baltussen et al., Cost Effectiveness and Resource Allocation 2006, 4:14
Advantages of the use of MCDA

- It helps to structure the problem
- It makes the need for subjective judgments explicit and the process by which they are taken into account transparent
- It provides a focus and language for discussion, leading to better considered, justifiable, and explainable decisions
- The analysis serves to complement and challenge intuition; it does not seek to replace intuitive judgment or experience
How to balance model complexity and usability?
A simple graphical method

The ‘Lynd & O’Brien’ model:

- Probabilistic simulation method
- Compares 2 alternatives
- On 2 criteria (benefit vs. risk)
- Sample ($\Delta B, \Delta R$) values from a joint distribution
- Plot them on a plane
- Count how many points are below the threshold $\mu$

Benefit-risk plane

\[ p = \frac{a}{a+b} \]

- Benefit A
- Benefit B
- Risk A
- Risk B

µ: B better

A better
Using the graphical method to assess the benefit-risk profile of two second-generation anti-depressants (ADDIS)
Using the graphical method to assess the benefit-risk profile of two second-generation anti-depressants (ADDIS)
Using the graphical method to assess the benefit-risk profile of two second-generation anti-depressants (ADDIS)
Using the graphical method to assess the benefit-risk profile of two second-generation anti-depressants (ADDIS)
Using the graphical method to assess the benefit-risk profile of two second-generation anti-depressants (ADDIS)
Using the graphical method to assess the benefit-risk profile of two second-generation anti-depressants (ADDIS)
Limitations of the graphical method

- The method by Lynd & O’Brien applies to two drugs that are evaluated on two criteria
- In most cases, more than two criteria need to be considered
  - Multiple safety criteria
  - Various measures of therapeutic effect
  - Costs
- How can the multi-criteria assessment be extended to the general $m \times n$ problem without losing the possibility to consider
  - Uncertainty in the criteria measurements
  - Imprecision in the decision maker’s preferences
Stochastic multi-criteria acceptability Analysis (SMAA)

- SMAA is an MCDA method for ranking a set of $m$ alternatives that are evaluated on a set of $n$ criteria.
- It is assumed that the decision makers’ preference structure can be represented by the additive value function

$$V(a) = \sum_{i=1}^{n} w_i v_i(a)$$

- The partial value functions reflect the decision makers’ preferences for different levels of achievement on the individual criteria.
- The weights indicate how much more important the swing from worst to best on one criterion is compared to the swing from worst to best on the other criteria.
Uncertainty in the criteria measurements
Imprecision in the weights

- Total lack of preference information is represented by a uniform distribution over the weight space.

- If some preference information is available, the weight space can be restricted with linear constraints.
SMAA descriptive indices

**Rank acceptability index** share of weights and measurements making an alternative have ranks 1, \ldots, m (most preferred, second most, etc.)

**Central weight vector** center of gravity of the favourable weight space: “Which preferences support an alternative to be the most preferred one?”

**Confidence factor** probability for an alternative to be preferred when preferences equal its central weight vector: “Are the measurements sufficiently precise?”
Case study: second-generation anti-depressants

- Placebo-controlled randomized clinical trial:
  - Fluoxetine
  - Venlafaxine
  - Placebo

- Criteria (selected by expert):
  - Benefit: efficacy (treatment response)
  - Risks: nausea, insomnia, anxiety

Criteria measurements
Preference-free analysis

**Figure:** Rank acceptability indices
Ordinal ranking of the weights for mild depression

Figure: Rank acceptability indices

1. Nausea
2. Anxiety
3. Efficacy
4. Insomnia
Ordinal ranking of the weights for severe depression

**Figure:** Rank acceptability indices
Discussion

- The results of the preference-free analysis showed that there are clear trade-offs among the three drugs.
- However, depending on the scenario considered, it was still difficult to make an informed decision.
  - High uncertainty in the criteria measurements due to a relatively small sample size.
  - An ordinal ranking of the weights resulted in insufficient discrimination for the severe depression scenario and possibly misleading results for the mild depression scenario.
Drug benefit-risk analysis is ideally based on evidence synthesized from multiple trials or possibly a complex network of trials.

**Figure:** Evidence network (25 studies in total)
Pair-wise meta-analyses are ill suited

- Relative effects have to be assessed against a common comparator, and not all evidence structures have a single treatment against which all others are compared
  - Selection bias: arbitrary exclusion of evidence
  - Sensitivity analysis with different comparators
- When a large number of treatments are available, most evidence will be indirect regardless of the chosen common comparator
- Solution: to apply mixed treatment comparison (MTC) for evidence synthesis in SMAA-based drug benefit-risk analysis

Measurement scales

- Meta-analysis results in relative measurements
  - E.g. odds ratio, mean difference
  - Statistically more robust
  - Hard to interpret clinically

- For decision making, we need absolute measurements
  - E.g. risk, change from baseline
  - Choose a baseline treatment and estimate absolute effect
  - Sample effects of other treatments conditional on that

- Problem: how to estimate absolute effect?
  - No general answer, lots of options
MTC/SMAA for drug benefit-risk analysis

identify or perform systematic review

choose criteria

k := 1

select criterion k

run incons. model

[unexplained]

[k < n]

[k < n]

run cons. model

investigate

[k < n]

estimate baseline

[k < n]

[all criteria done (k = n)]

construct SMAA model

choose criteria

run incons. model

investigate

run cons. model

construct SMAA model

k := k + 1

[unexplained]
Incorporating more precise preference information

Drug benefit-risk assessment: current and future challenges

- There has been an increasing interest in MCDA for drug benefit-risk analysis, but developing models that are both theoretically sound and clinically useful has proven to be far from straightforward.
- The ultimate aim will be to arrive at methodologies that allow decision makers to simultaneously explore:
  - Uncertainty in the model structure (i.e. number of alternatives and criteria, level of detail)
  - Uncertainty in the preference statements (i.e. shape of the partial value functions, criteria weights)
  - Uncertainty in the criteria measurements
- We have started to develop a flexible set of tools to address all these aspects (www.drugis.org)
Questions?