Critical choices to be made in Benefit/Risk assessments of vaccines

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The 7 steps of MCDA

1. Define the decision context
2. Identify the options (2 or more)
3. Set the criteria against which the options will be evaluated
4. Measure the performance of the options
5. Assign weights to the criteria
6. Determine the scores
7. Run the necessary sensitivity analyses
MCDA ≅ PrOACT-U(RL)

PrOACT – URL
- Problem
- Objective
- Alternatives
- Consequences
- Trade-offs
- Uncertainty
- Risk
- Linked decisions

MCDA

- Decision context
- Options
- Criteria
- Performance options
- Weights
- Weighted scores
- Sensitivity analyses
(Most) critical choices

MCDA
• Decision context
• Options
• Criteria
• Performance options
• Weights
• Weighted scores
• Sensitivity analyses

Value Tree
Effects Table
Weighting
Value functions
The value tree: the art of trimming

2 steps:

- First, a big tree with all potential effects:
  - General model proposed by Mussen\(^1\)
  - For vaccines, need to add indirect effects
  - Potential and identified effects can be taken from Risk Management Plan

- Next, ‘prune’ the tree to a simplified, more workable tree

\(^1\) Filip Mussen, Sam Salek, Stuart R. Walker: Benefit-risk appraisal of medicines: a systematic approach to decision-making (2009)
The value tree: the art of trimming

Why not simply keep all (imaginable) effects?

• Most likely not all have been (can be) measured or are accepted (eg neck- and head cancers)
• Avoid overlap (double counting, eg immunogenicity and efficacy)
• The number of leaves matters!!!
• The box becomes too black
Value tree: art to science

• Define the trimming criteria
• Keep it simple
• If in doubt, be conservative (e.g., Quality of Life)
• Assess which option is favored, if not conservative -> sensitivity analysis
The effects tables: the art of choosing

Possible choices:

• Published only or also unpublished studies? Not all data are published (eg postmarketing safety)
• Intent-to-treat or per-protocol?
• Internal reports: what level of scrutiny?
• Pre-licensure only or also post-licensure?
• Clinical only or also observational studies?
• Do an additional systematic literature search? If so, how robust is the data?
• Do meta-analyses?
Define the data selection strategy upfront:

• Define the hierarchy (e.g., clinical > observational, pre-licensure > post-licensure etc)

• Assess which option is favored, if not conservative -> sensitivity analysis

• Document and QC, QC, QC …
Effects table Gardasil males: strategy

First choice: a study performed in boys of around 12 years of age, the age at which Gardasil would hypothetically be recommended for mass vaccination of boys.

If not available or of limited value, mostly because of sample size restrictions

Next best alternative: a study in males of a different age group.

If not available or of limited value, mostly because of sample size restrictions

Last alternative: a study in females
Time horizon (how long do effects of vaccination last)

- Protective effect Gardasil: 20 years\(^1\)
- Risks:

<table>
<thead>
<tr>
<th>Event</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs</td>
<td>15 days</td>
</tr>
<tr>
<td>SAEs</td>
<td>6 months</td>
</tr>
<tr>
<td>Syncope</td>
<td>1 day</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>1 day</td>
</tr>
<tr>
<td>Auto-immune disease</td>
<td>1 year</td>
</tr>
</tbody>
</table>

Value functions: the art of comparing apples and pears (step 1)

2 important aspects:

1. Setting the limits (scales)
2. Defining the value function
   a. Linear
   b. Non-linear
From a measure to a score:

Vaccination: 4 cases  = 73 points  X 0.20  = 14.6

No vaccination: 14 cases = 7 points  X 0.20  = 1.4

Scale

0  Best

15  Worst
Scales

- If > 2 options: relative scales possible. Best option = 100, worst option = 0, the rest proportional to these.
- If 2 options: fixed scales: “best and worst performance which could realistically occur”.
Scales: art to science

Define a logic, eg:

• Choose extremes which reflect a reasonable rate

• Choose extremes based on prior experience with other vaccines

• Choose extremes which are relatively close to the actual observed values.

• Aim for comparable scales for different outcomes: this facilitates the weighting process.
From a measure to a score:

**Scale**
- 0: Best
- 15: Worst

**Value**
- Vaccination: 4 cases = 73 points
- No vaccination: 14 cases = 7 points

**x Weights**
- Vaccination: 4 cases x 0.20 = 14.6
- No vaccination: 14 cases x 0.20 = 1.4
From a measure to a score:

<table>
<thead>
<tr>
<th>Scale</th>
<th>Value</th>
<th>x Weights</th>
<th>= Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best</td>
<td>Vaccination: 4 cases</td>
<td>= 100 points</td>
<td>X 0.20</td>
</tr>
<tr>
<td>Worst</td>
<td>No vaccination: 14 cases</td>
<td>= 0 points</td>
<td>X 0.20</td>
</tr>
<tr>
<td>Scale</td>
<td>Value</td>
<td>x Weights</td>
<td>Score</td>
</tr>
<tr>
<td>---------------</td>
<td>------------------------</td>
<td>-----------</td>
<td>--------</td>
</tr>
<tr>
<td>Best</td>
<td>100 points</td>
<td>X 0.20</td>
<td>19.2</td>
</tr>
<tr>
<td>Worst</td>
<td>0 points</td>
<td>X 0.20</td>
<td>17.2</td>
</tr>
</tbody>
</table>

Vaccination: 4 cases = 96 points

No vaccination: 14 cases = 86 points

No vaccination: 14 cases

Vaccination: 4 cases
Weights: the art of comparing apples and pears (step 2)

- At all levels of the tree (leaves and nodes)
- Complex (and no easy way to make it simple)
- Also need to agree on manner of summarizing weights (top-down or bottom-up)
Top-down and bottom-up weighting

**Top-down**

- **Benefit-risk balance**
- **Benefit**
- **Indirect Effect**
- **Direct Effect**
- **Overall incidence of AEs**
- **Unanticipated safety signal**
- **Anal cancer**
- **Genital warts**
- **HPV transmission**

**Node level 1:** assigned

**Weight**

**Node level 2:** assigned x weight level 1

**Weight outcome:** assigned x weight level 1 x weight level 2
Top-down and bottom-up weighting

Weight
Node level 1: sum of the weights below

Weight
Node level 2: sum of the weights below

Weight Outcome: assigned
Weights: art to science

Swing-weighting!!!

Bottom up easier to follow (but beware of multiple endpoints)

Check, re-check and re-re-check the results as you go up the tree

And … be brave
Summary

• MCDA can do the job
• Best friends:
  – Swing weighting
  – Sensitivity analyses
  – Mussen et al
• Terminology not yet ideal (values, scores, measures, scales open for interpretation)
Which box is blacker?
Visit us at ISPE


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