Scale Loss Score (SLoS): a novel measure of drug benefit-risk assessment

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Introduction

- **MultiCriteria Decision Analysis (MCDA)** is a popular quantitative method to assess the **benefit-risk (BR) balance** of treatments: it permits to summarize the benefits and the risks of a drug in a **single utility score**
- The utility score is often derived using a **linear model** which might lead to **counter-intuitive conclusions**, for example, a recommendation of a non-effective drug
- We propose **Scale Loss Score (SLoS)** as a new tool for benefit-risk assessment: it is based on strong theoretical principles, addresses the issues of the linear MCDA model and can lead to more **meaningful recommendations**

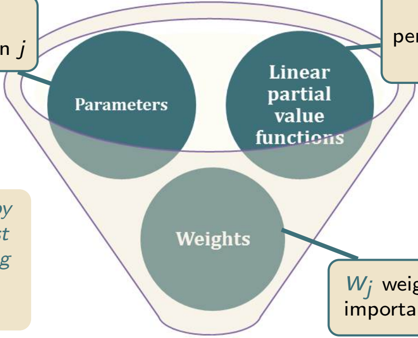
Outine

- **Introduction**
- **Linear MultiCriteria Decision Analysis (MCDA)**
  - Model
  - Counter-intuitive conclusions
- **Scale Loss Score (SLoS)**
  - Model
  - Differences with Linear MCDA
  - Weight mapping
  - Case-study: telithromycin
  - Simulation study
- **Conclusion**

Linear Multi-Criteria Decision Analysis (MCDA)

ξ_{ij} performance of treatment i on criterion j

$u_j(\xi_{ij})$ map the performances on criterion j to a $(0,1)$ scale



MCDA is identified by the EMA as the most comprehensive among the quantitative methodologies

w_j weight reflecting the importance of criterion j

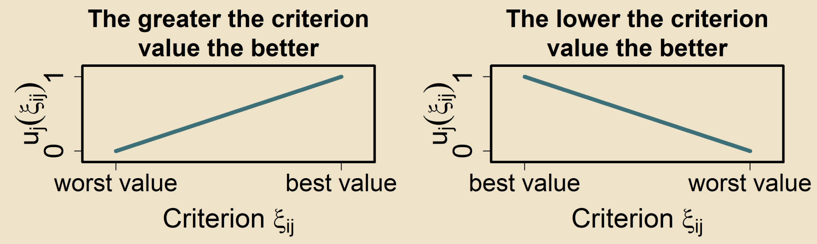
MCDA linear utility score

$$u(\boldsymbol{\xi}_i, \mathbf{w}) \quad := \quad \sum_{j=1}^{n} w_j u_j(\xi_{ij})$$

Higher utility score $\rightarrow$ more preferable BR balance

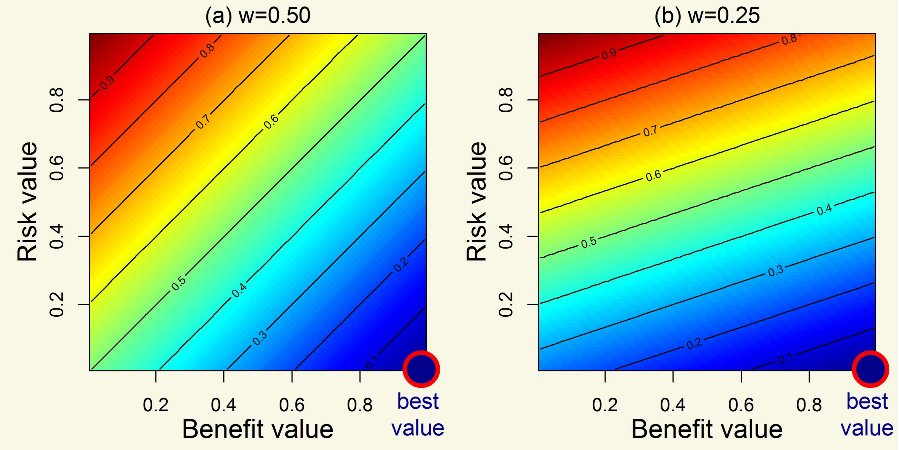
$u_j(\xi_{ij})$: linear partial value functions - map the performances on criterion j to a $(0,1)$ scale

$$u_j(\xi_{ij}) = \frac{\xi_{ij} - \xi'_{ij}}{\xi''_{ij} - \xi'_{ij}}, \ \xi'_{ij} \text{ and } \xi''_{ij} \text{ the worst and best values}$$



Example with two criteria

Contours of $1 - u(\xi_{i1}, \xi_{i2}, w)$

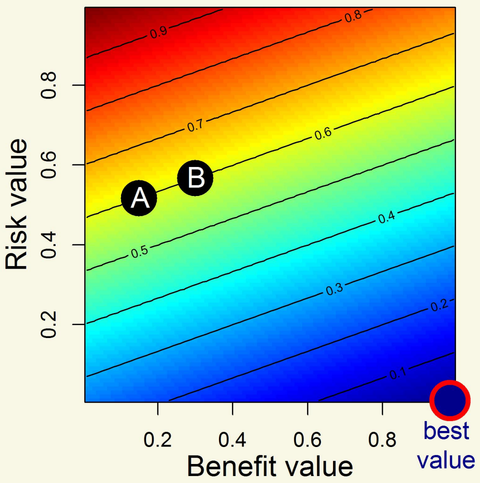


Linear Multi-Criteria Decision Analysis (MCDA)

Might lead to counter-intuitive conclusions

(1) The benefit–risk trade-off is the same for all levels of risk/benefit

Contours of $1 - u(\xi_{i1}, \xi_{i2}, w = 0.25)$



- Drug B increases the benefit from 0.15 to 0.30 compared to A ($\times 2$)
- An increase of $+5\%$ in risk could be tolerated to have the same utility

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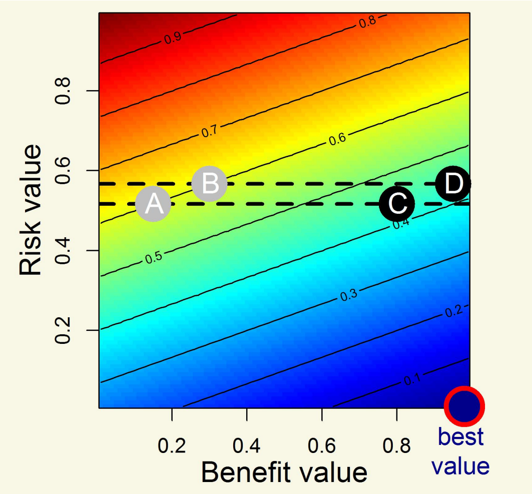


- Drug D increases the benefit from 0.80 to 0.95 compared to C ($\times 1.1875$)
- An increase of $+5\%$ in risk could be tolerated to have the same utility

The same benefit increase is not as relatively large, only a smaller increase in risk may usually be tolerated

(2) Drugs with no benefit or extreme risk can be recommended

2 criteria, fixed parameter values and $w = 0.25$

	Example 1 Low benefit and risk		Example 2 High benefit and risk	
	Drug 1	Drug 2	Drug 1	Drug 2
Benefit	0%	30%	96%	50%
Risk	9%	20%	100%	85%
MCDA utility	0.6825	0.6750	0.2400	0.2375

Even if none of those drugs are likely to be taken to the market, these examples reveal some counter-intuitive conclusions

Linear Multi-Criteria Decision Analysis (MCDA)

Might lead to counter-intuitive conclusions

With Linear MCDA:
(1) The benefit–risk trade-off is the same for all levels of risk/benefit
(2) Drugs with no benefit or extreme risk can be recommended

We advocate two properties of a benefit–risk analysis measure:

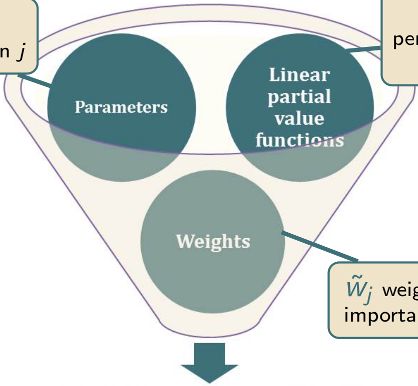
- For a given increase in benefit, one can tolerate a larger increase in risk if the amount of benefit is small than if it is high
  $\rightarrow$ Convex preferences (i.e. concavity of equal loss contours)

- One is not interested in the level of risk (benefit) if the drug does not treat (harm all) patients
  $\rightarrow$ Strong penalisation of extreme low benefit values and extreme high risk values

Scale Loss Score (SLoS)

ξ_{ij} performance of treatment i on criterion j

$u_j\left(\xi_{ij}\right)$ map the performances on criterion j to a $(0,1)$ scale



$\tilde{w}_j$ weight reflecting the importance of criterion j

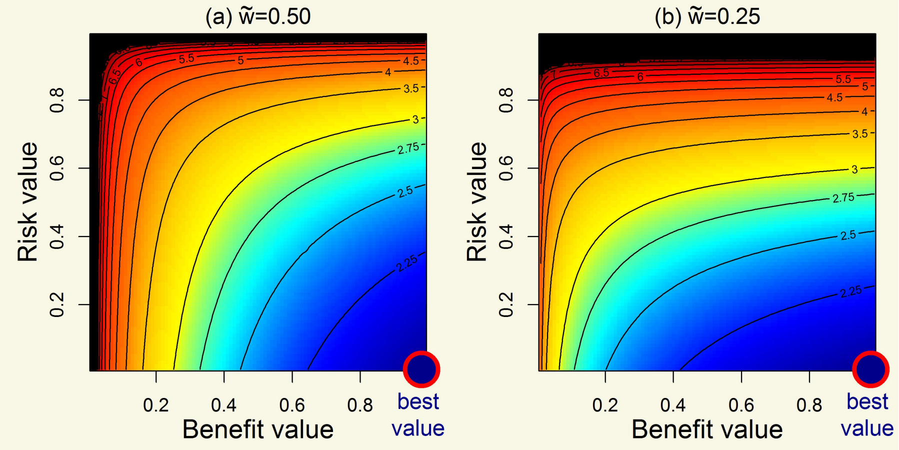
Scale Loss Score (SLoS)

$$l(\boldsymbol{\xi}_i, \tilde{\boldsymbol{w}}) \quad := \quad \sum_{j=1}^{n} \left(\frac{1}{u_j(\xi_{ij})}\right)^{\tilde{w}_j}$$

Lower loss score $\rightarrow$ more preferable BR balance

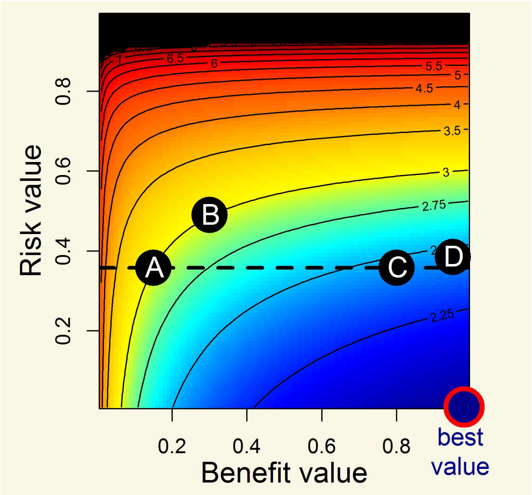
Example with two criteria

Contours of $I(\xi_{i1}, \xi_{i2}, \tilde{w})$



Addresses the counter-intuitive conclusions of Linear MCDA

Contours of $I(\xi_{i1}, \xi_{i2}, \tilde{w} = 0.25)$



- Drug B increases the benefit from 0.15 to 0.30 ($\times 2$) compared to A
- Drug D increases the benefit from 0.80 to 0.95 ($\times 1.1875$) compared to C

For a given increase in benefit, a **smaller** increase in risk is tolerated if benefit is high than if it is low

Scale Loss Score (SLoS)

Addresses the counter-intuitive conclusions of Linear MCDA

2 criteria, fixed parameter values and $w = \tilde{w} = 0.25$

	Example 1		Example 2	
	Low benefit and risk		High benefit and risk	
	Drug 1	Drug 2	Drug 1	Drug 2
Benefit	0%	30%	96%	50%
Risk	9%	20%	100%	85%
MCDA utility	0.6825	0.6750	0.2400	0.2375
SLoS	$+\infty$	2.5334	$+\infty$	5.3381

$\rightarrow$ SLoS strongly penalizes extremely low benefit values and extremely high risk values

Drugs with no benefit or extreme risk **can never be recommended**

Weight mapping

Comprehensive work was already published or is on-going on weight elicitation for MCDA

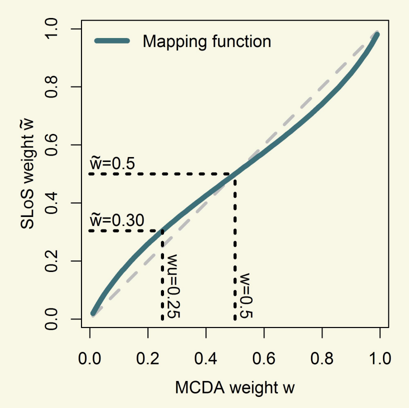
→ **We propose a simple way to map MCDA weights w_j to SLoS weights $\tilde{w}_j$**

With two criteria:

$$\frac{\tilde{w}_j}{1-\tilde{w}_j} \cdot 2^{2\tilde{w}_j - 1} = \frac{w_j}{1-w_j},$$

No analytical solution, but $\tilde{w}_j$ can be approximated by line search

Weight mapping



Case study: telithromycin

IMI PROTECT Benefit-Risk Group example

2001 — EU approval

2004 — FDA approval

Including indications CAP and ABS

2007 — CHMP reassessment, FDA removal of indication ABS

Proba(telithromycin $>$ β-lactam antiobiotics)

	Community Acquired Pneumonia (CAP)	Acute Bacterial Sinusitis (ABS)
MCDA	59%	71%
SLoS	51%	55%

$\rightarrow$ SLoS results are more in line with the regulatory authorities concerns on ABS indication

Simulations (1/2)

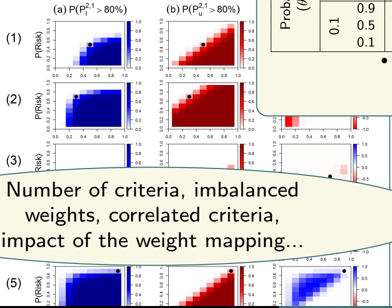
Comprehensive simulation study investigating the performances of MCDA and SLoS in many different scenarios

Simulation scenarios with two criteria

Probability of Risk θ_{i2}	Probability of Benefit θ_{i1}: 0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
0.9	◇●	◇	◇	◇	◇	◇	◇	◇	◇●
0.8	◇	◇	◇	◇	◇	◇	◇	◇	◇
0.7	◇	◇	◇●	◇	◇	◇	◇●	◇	◇
0.6	◇	◇	◇	◇	◇	◇	◇	◇	◇
0.5	◇	◇	◇	◇	◇●	◇	◇	◇	◇
0.4	◇	◇							
0.3	◇	◇							
0.2	◇	◇							
0.1	◇●	◇							

● = treatr

Simulation results with two

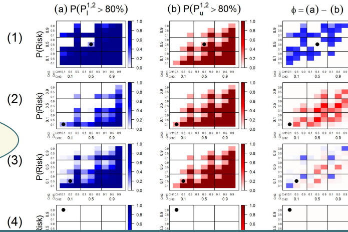


Simulation scenarios with four criteria

Probability of Risk (θ_{i3} and θ_{i4})		Probability of Benefit (θ_{i1} and θ_{i2}): 0.1 / 0.1	0.1 / 0.5	0.1 / 0.9	0.5 / 0.1	0.5 / 0.5	0.5 / 0.9	0.9 / 0.1	0.9 / 0.5	0.9 / 0.9
0.9	0.9	◇●	◇	◇	◇	◇	◇	◇	◇	◇●
0.9	0.5	◇	◇●	◇	◇	◇	◇	◇	◇●	◇
0.9	0.1	◇	◇	◇	◇	◇	◇	◇	◇	◇
0.5	0.9	◇	◇	◇	◇	◇	◇	◇	◇	◇
0.5	0.5	◇	◇	◇	◇	◇●	◇	◇	◇	◇
0.5	0.1	◇	◇	◇	◇	◇	◇	◇	◇	◇
0.1	0.9	◇	◇	◇	◇	◇	◇	◇	◇	◇
0.1	0.5	◇	◇●	◇	◇	◇	◇	◇	◇●	◇
0.1	0.1	◇●								

● =

Simulation results with four criteria



Number of criteria, imbalanced weights, correlated criteria, impact of the weight mapping...

Simulations (2/2)

Comprehensive simulation study investigating the performances of MCDA and SLoS in many different scenarios

Main conclusions from the simulation study:

- Both are robust to correlations between outcomes
- Similar conclusions in many cases
- Clear advantage of SLoS when drugs have no benefit or extreme risk

Discussion

- **Scale Loss Score (SLoS)** offers the same advantages as Linear MCDA to summarise the drug benefit–risk balance in a **single measure**

- SLoS has additional **desirable properties**:
  - Avoids recommendations of non-effective or extremely unsafe drugs
  - Tolerates larger increases in risk for a given increase in benefit when the amount of benefit is small than when it is high

  $\rightarrow$ **Better reflects human's natural preferences**

- Alternative approach: handling non-constant trade-offs by varying the shape of the partial value functions (non-linear MCDA)
  - Non-trivial approach, and eliciting non-linear partial value functions is very challenging

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Thank-you!