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Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

An IMI PROTECT case study: Telithromycin

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EFSPI/PSI – Structured Benefit-Risk Assessment

17th September

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Acknowledgments

- The research leading to these results was conducted as part of the PROTECT consortium (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium, www.imi-protect.eu) which is a public-private partnership coordinated by the European Medicines Agency.
- The PROTECT project has received support from the Innovative Medicine Initiative Joint Undertaking (www.imi.europa.eu) under Grant Agreement n° 115004, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.

Disclaimer

"The processes described and conclusions drawn from the work presented herein relate solely to the **testing** of methodologies and representations for the evaluation of benefit and risk of medicines.

This report neither replaces nor is intended to replace or comment on any regulatory decisions made by national regulatory agencies, nor the European Medicines Agency."

And yet another disclaimer ….

- Models for Benefit-Risk Assessment are NOT tools that can make choices
- They are rather a set of principles, guidelines and tools to support the decision maker in:
  - Planning
  - Preparing
  - Analysing
  - Exploring
  - Decision and dissemination

  The decision problem

Thelithromycin – case study

Active drug	Thelithromycin
Indication	Community acquired pneumonia Acute exacerbation chronic bronchitis **Acute bacterial sinusitis** Tonsilitis/Pharyngitis
Severe side effects	Cardiac syncope, Liver failure
Regulatory history	Approved July 2001, Restriction and warning revised 2007 License renewed 2011
Data source	EPARs
Comparators	Standard treatment antibiotics

Methods

Methods recommended for further testing	Telithromycin
PrOACT-URL	✓
BRAT	✓
MCDA	✓
SMAA	✓
NNT & NNH	
Impact Number	
QALY	
Q-TWiST	
INHB	
BRR	✓
PSM	✓
MTC	
DCE	
Other:	SBRAM, Swing-weighting

PrOACT-URL Framework

- A generic framework to structure the decision problem
- Divide into 8 steps
- Emphasis on uncertainty via sensitivity analysis

PrOACT-URL - Problem

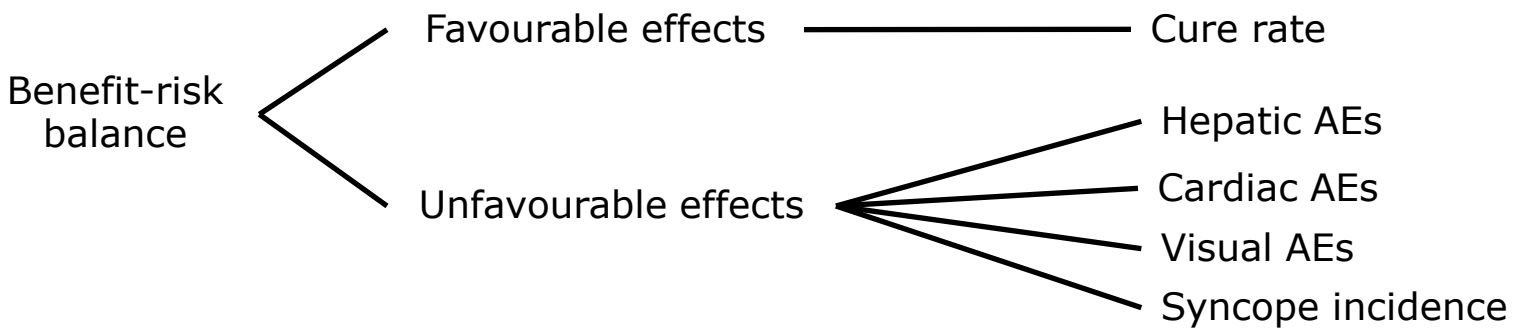
Active drug	Telithromycin - ketolide antibiotic, a class related to macrolides
Indication	Acute bacterial sinusitis (ABS) in patients 18 year or older, contraindication for patients with myasthenia gravis

Severity of indication	• Prevalence of ABS among adults with symptoms of sinusitis about 50%.
	• Potential complications ABS:
	  • Local extension (e.g. infection of the intracranial cavity)
	  • spread of bacteria to the central nervous system (e.g. meningitis).
	• With antimicrobial treatment severe complications are 1 per 10,000 cases of ABS.

Unmet medical need	Resistance of commonly used antibiotic has reached significant levels in several European countries.
Severe side affects	Associated with different risk profile; Cardiac, syncope and liver failure
Data source	EPAR

PrOACT-URL - Objectives

Aim:	Evaluate benefit-risk balance for telithromycin, based on from EPAR 2007 including both phase III and phase IV. Assess if a change in benefit-risk balance could give reason for recommending restriction to the authorization.
Favourable effects	• Cure rate
Unfavoruable effects	• Hepatic AE • Cardiac AE • Visual AE • Syncope



PrOACT-URL - Alternatives

Alternative decisions	No changes in indication Restrict indication Retract approval
Drug	Telithromycin
Comparators	**Comparators** are taken as a single alternative which are standard treatment antibiotics, this is done since all safety data are pooled in the EPAR.

PrOACT-URL - Consequence

	Name	Study	Phase	Telithromycin			Comparators		
				Total	events	Rate (%)	Total	Events	Rate (%)
Cure	Cure rate	A3005	III	146	110	75.3	137	102	74.5
		A3011	III	189	161	85.2	89	73	82.0
Unfavourable Effects	Hepatic AE	Pooled	III	750	13	1.7	366	2	0.5
			IV	565	0	0.0	579	1	0.0
	Cardiac AE	Pooled	III	750	0	0.0	366	1	0.3
			IV	565	1	1.2	579	0	0.0
	Visual AE	Pooled	III	750	9	1.2	366	3	0.8
			IV	565	7	1.2	579	1	0.2
	Syncope	Pooled	III	750	0	0.0	366	1	0.3
			IV	565	0	0.0	579	0	0.0
	AESI*	Pooled	III	750	21	2.8	366	7	1.9
			IV	565	8	1.4	579	2	0.3

*Sum of Hepatic AE, Cardiac AE, Visual AE and Syncope.

PrOACT-URL

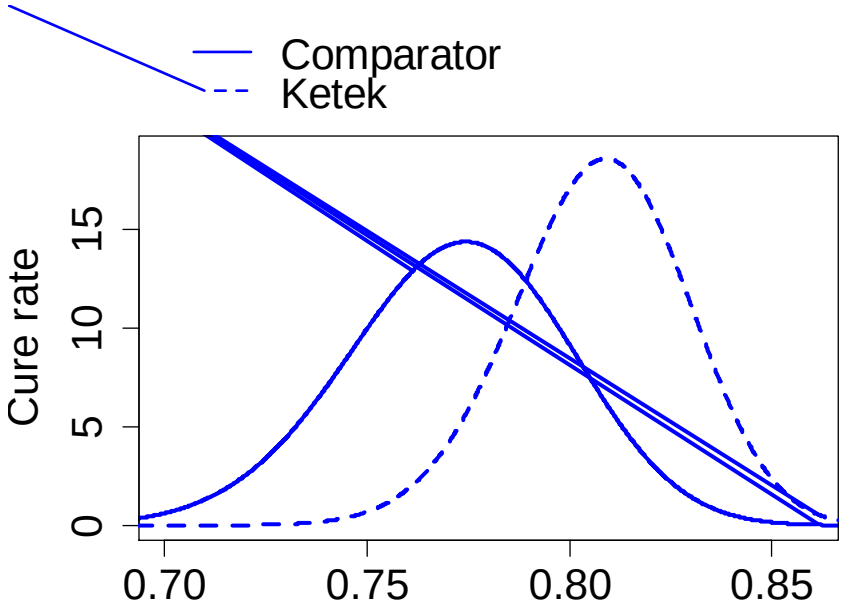
Tread-off & Uncertainty	
	The methods SMAA and BRR are used to explore different trade-off between benefit and risk • Uncertainty related to sampling variation • Uncertainty related to preference weights

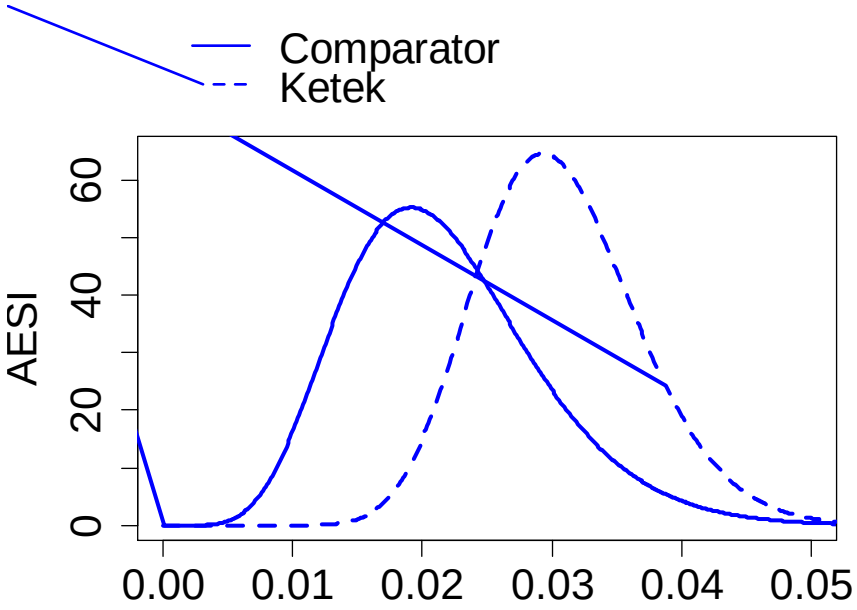
Benefit-risk ratio for ABS

$$BRR = \frac{p_t - p_c}{q_t - q_c},$$

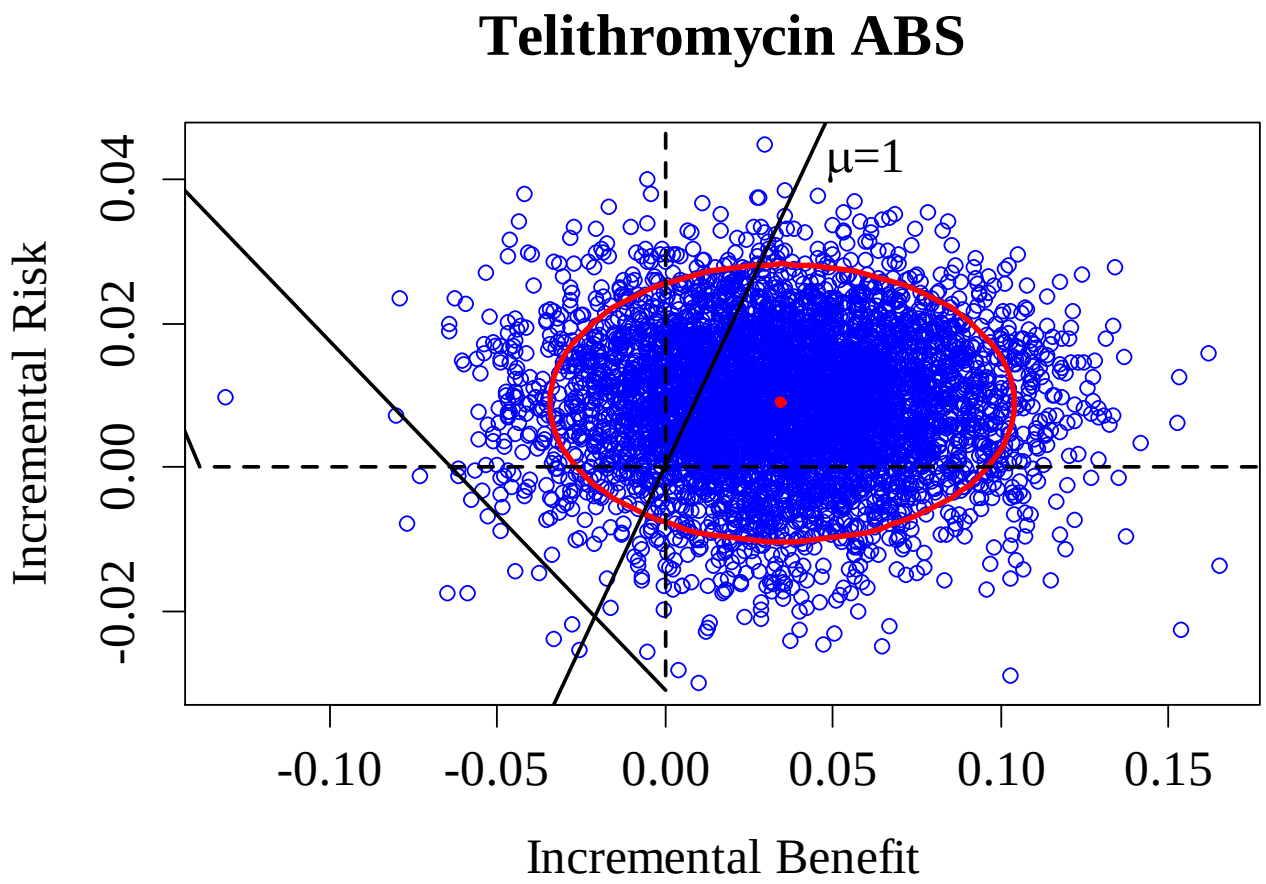
- p_t and p_c probability of benefit for telithromycin and comparators, respectively
- q_t and q_c probability of risk for telithromycin and comparators, respectively
- Benefit criteria is cure rate
- Risk element is Adverse Event of Special Interest (AESI) (Hepatic, Cardiac, Syncope and Visual).
- Data pooled randomized controlled Phase III trials of telithromycin vs. comparator.

Data


Comparator
Ketek
Cure rate
0
5
10
15
0.70
0.75
0.80
0.85


Comparator
Ketek
AESI
0
20
40
60
0.00
0.01
0.02
0.03
0.04
0.05

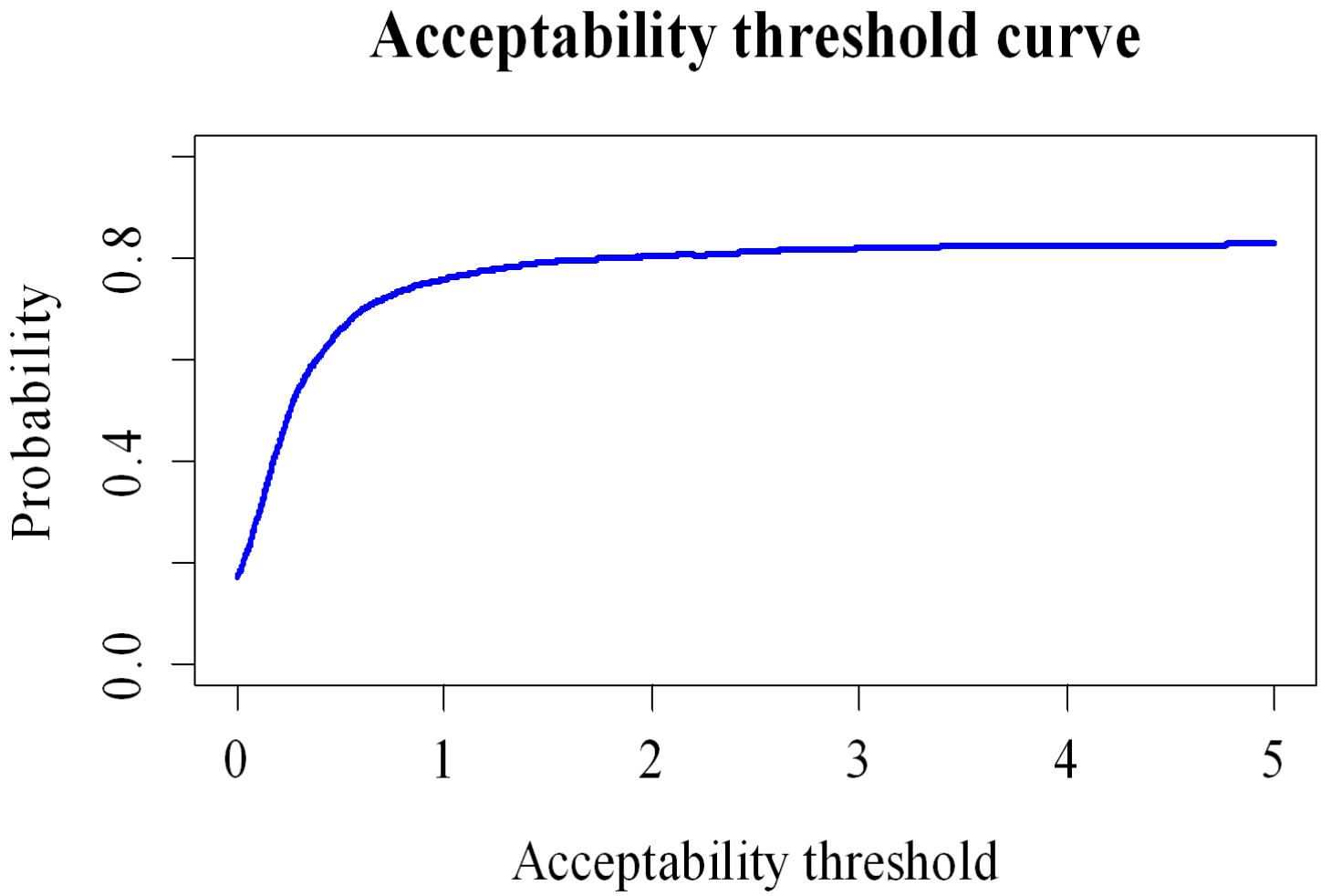
Benefit-risk plane



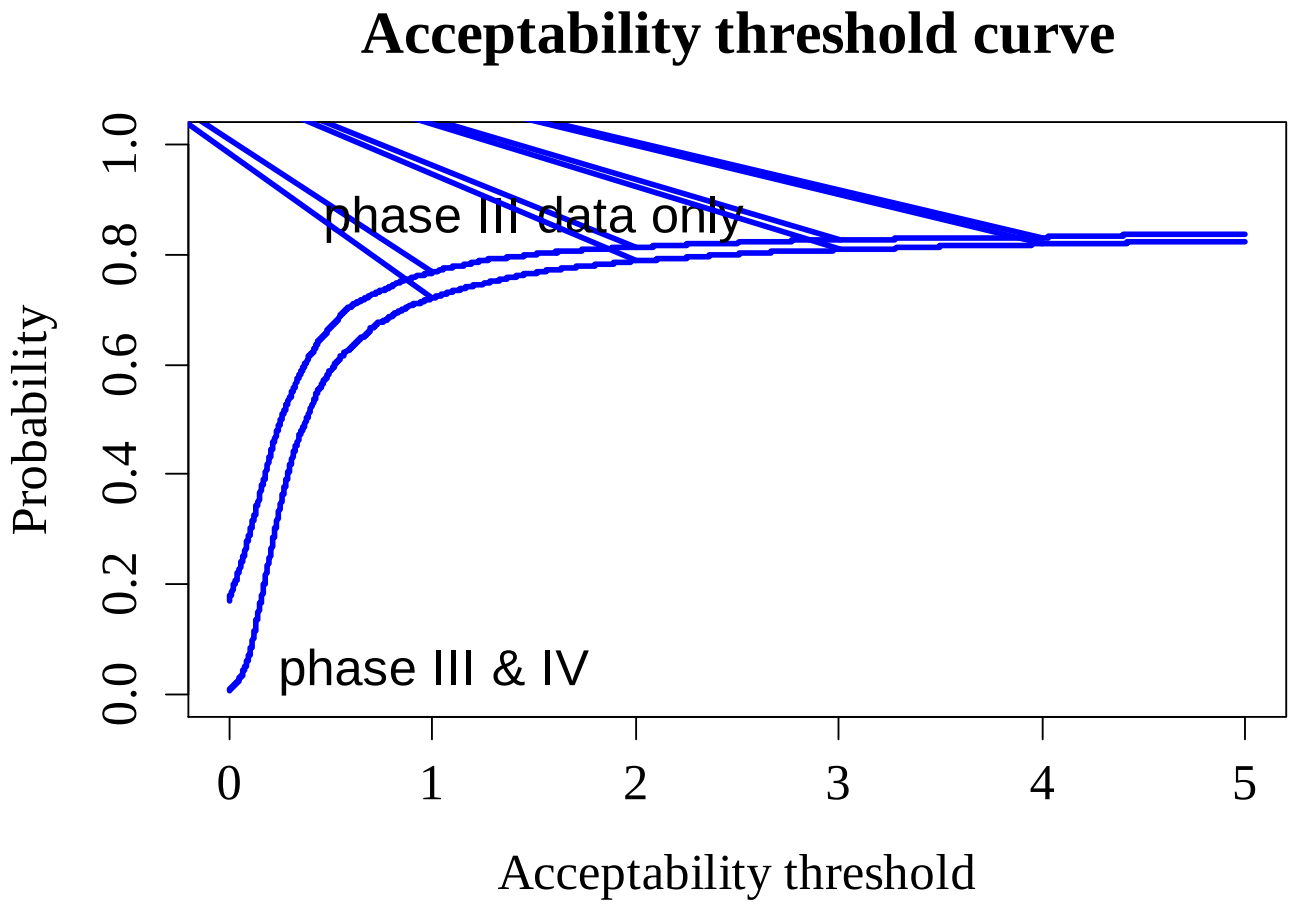
Acceptability threshold μ = 1, - probability of favourable BR for telithromycin is 0.76

Acceptability threshold μ = 0.25, - probability of favourable BR for telithromycin is 0.50

Probability of favourable BR



Phase III (only) and phase III & IV



Acceptability threshold μ = 1,
Phase III only - probability of favourable BR for telithromycin is 0.76
Phase III and IV – probability of favourable BR for telithromycin is 0.72

Applicability and acceptability

- The methods provide the necessary visualization and representation of benefit and risk information and incorporate uncertainty into analysis.
- A challenge collapsing benefits and risks into single measures (i.e. BRR)
- Can only incorporate binary measure of benefit and risk.
- Can only compare two alternatives at the time
- In simulations, criteria are assumed to be independent of each other (not a limitation of method)

SMAA

Stochastic Multi-criteria Acceptability Analysis

- Similar to MCDA
- Requires utilities, probabilities, weights
- Allows uncertainty and missing weights
- There is no formal framework but could be used with PrOACT-URL or BRAT
- Stochastic analysis

SMAA

Let $f_X(\xi)$ = density function on the space of all consequence X

$f_W(w)$ = density function of weight space W

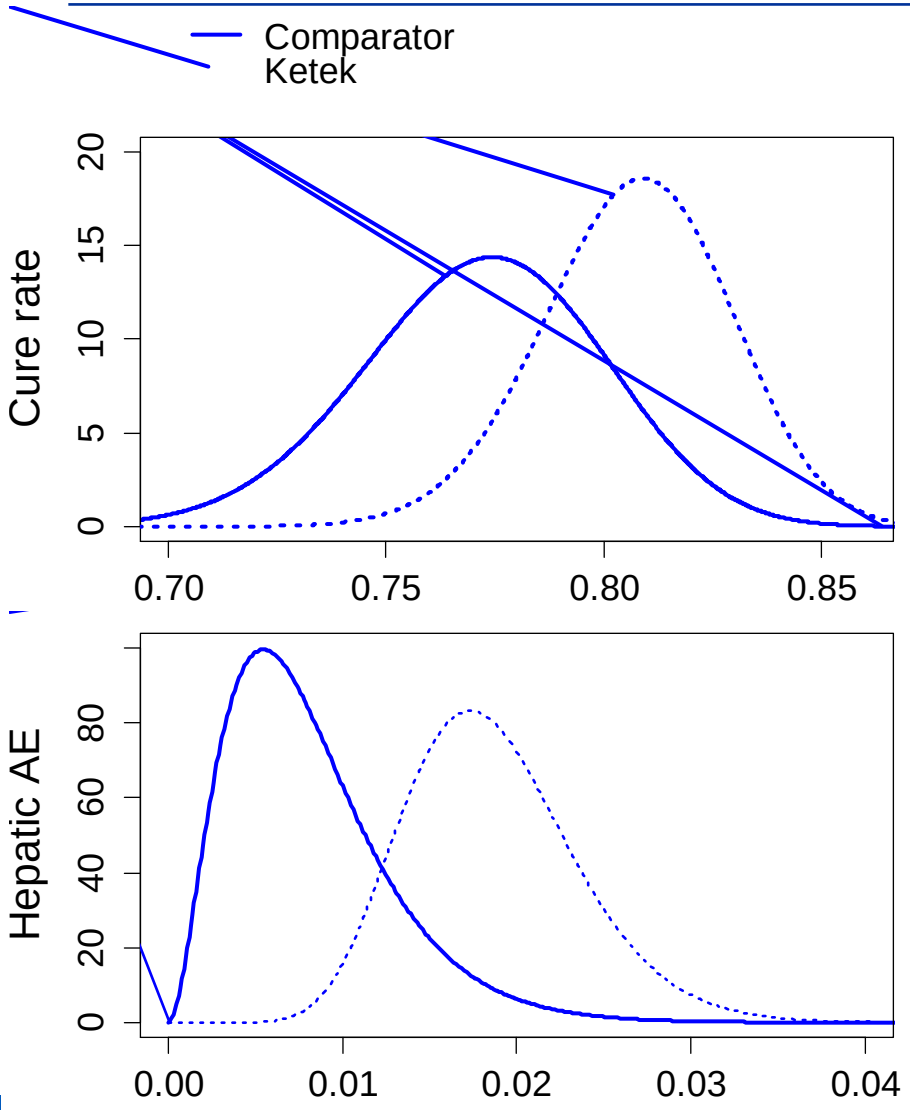
$W_i^1(\xi)$ = alternative i favourable weight space

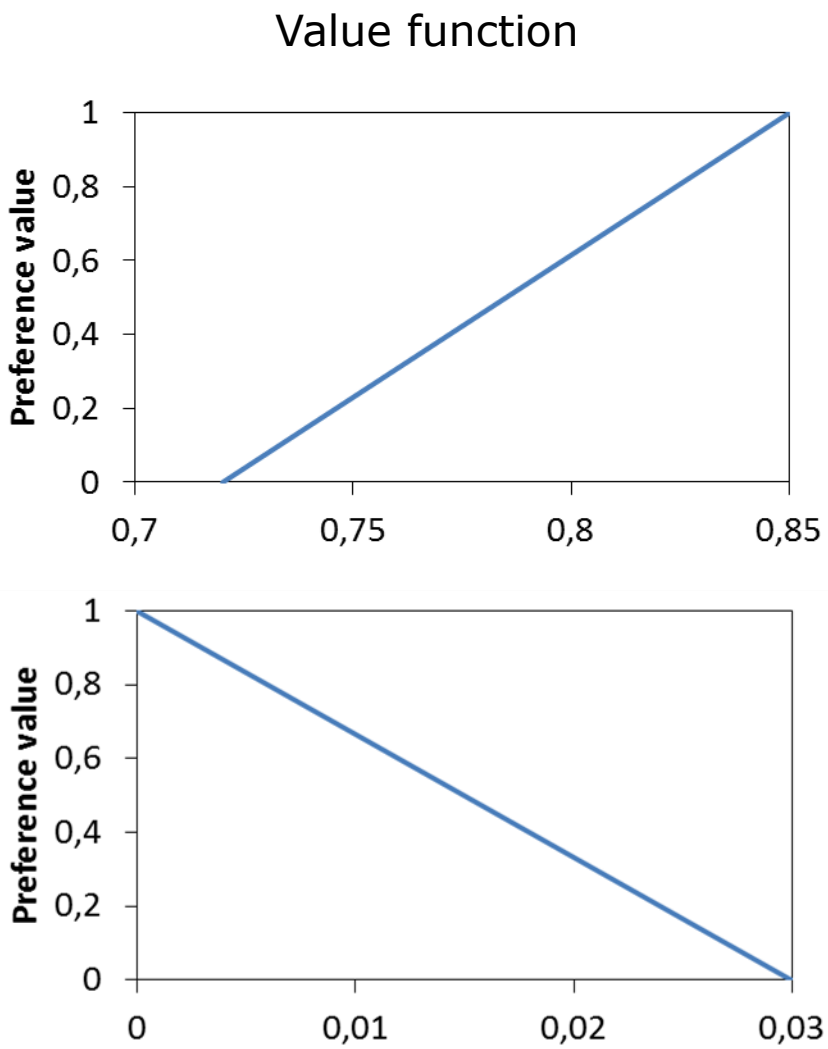
For $X \subset R^{i \times j}$ (i alternatives and j criteria) and $w \in W_i^1(\xi)$

Then the probability of alternative i ranked first is

$$b_i^1 = \int_{\xi \in X} f_X(\xi) \int_{w \in W_i^1(\xi)} f_w(w)\, dw d\xi$$

Data and Value Function



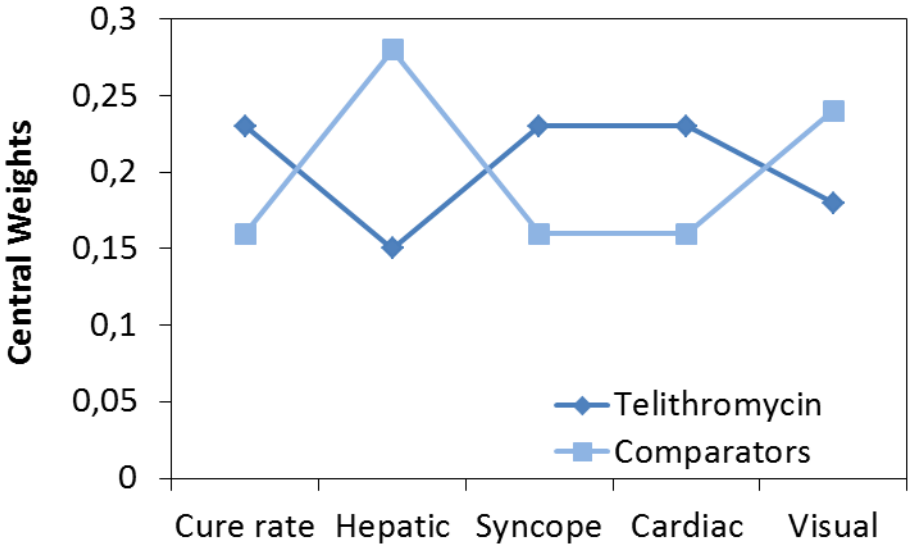


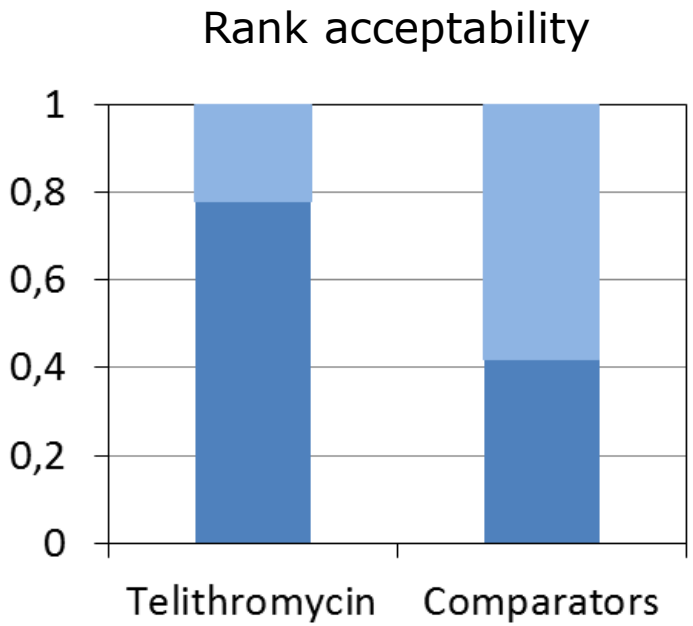
SMAA analysis

- Weights corresponding to PSM analysis with acceptability threshold, $\mu=1$
  - The consequence of one point increase in probability of the benefit criterion equals the consequent of one point decrease in the probability of any of the risk criteria

Alternative	Rank 1	Rank 2
Telithromycin	0,76	0,34
Comparators	0,24	0,76

Missing weight analysis - central weights





Applicability and acceptability

- SMAA extends MCDA by bringing in analysis the sampling variation and preference uncertainty, which are almost inevitable in real practices. The utility used in SMAA and MCDA can be very general. If a decision maker is not
- In simulations, criteria are assumed to be independent of each other (not a limitation of method)

JSMAA software

- Software for SMAA is still in development stage and choices (utility functions, choices of most preferred and least preferred values etc) are limited.

PrOACT-URL

Risk tolerance	
	Medical need is covered by several other therapeutic options
	Increasing infection by beta-lactam and/or macrolide resistant strains

Linked decisions	
	Considerations to different risk profile to drug class

Take home messages

Challenges:

- To define consistent criteria across decision options, find data matching these criteria
- To elicit preference values

A BR methodology does not give you the answer

- It is a framework for decomposing and understanding a problem
- Communicates issues in a transparent, rational and consistent way
- Assesses the main value drivers of a decision
- Allows sensitivity analysis around different perspectives