Quantitative Benefit-risk assessment using MultiCriteria Decision Analysis (MCDA) and its extensions: practical applications

Stéphanie Cadour[1], Gaëlle Saint-Hilary[2,3]

[1]Keyrus Biopharma (France)

[2]Politecnico di Torino (Italy)

[3]Institut de Recherches Internationales Servier (France)

Preliminary information

- All the programs to reproduce the results of this presentation will be available on the PSI website

- The R code presented here is intended to be simple and understood by all (more efficient programming ways are certainly possible)
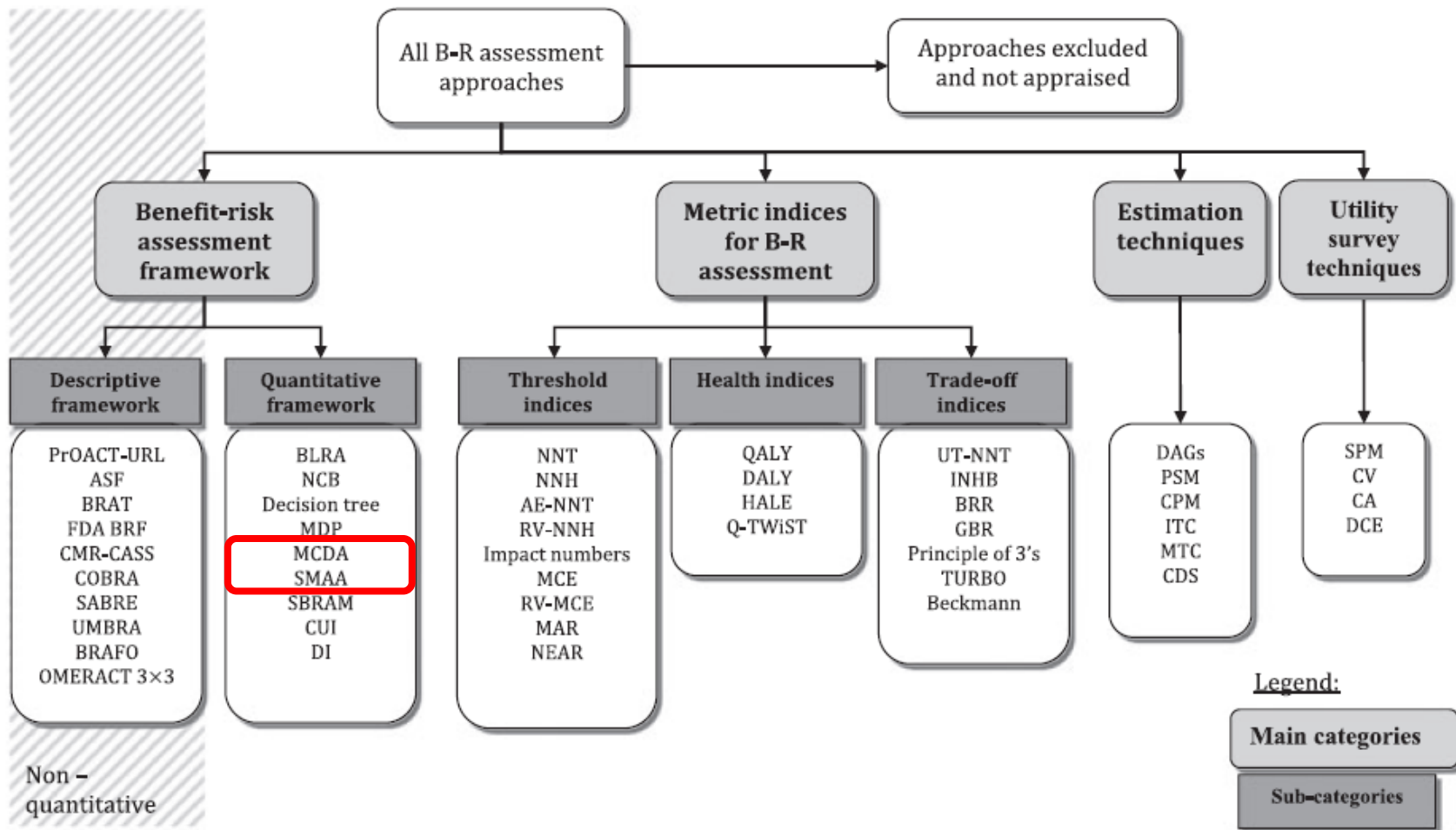
Benefit-Risk assessment Introduction

- **Benefit-risk assessment**: to compare the benefits and the risks of a treatment

- A medicine should be considered only if it has a favorable benefit-risk balance → **Strong predictor for regulatory approval and long-term viability of a medicine**

- Until 2010, most of the drug benefit-risk assessments were qualitative

- Since then, **structured qualitative frameworks** and **quantitative methods** for benefit-risk assessment were developed

    → **more transparency, consistency and better communication**

Main working groups: PhRMA (Pharmaceutical Research and Manufacturers of America) / EMA (European Medicines Agency) / IMI-PROTECT (Innovative Medicines Initiative - Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium) / EFSPI (European Federation of Statisticians in the Pharmaceutical Industry) / PSI (Statisticians in the Pharmaceutical Industry)
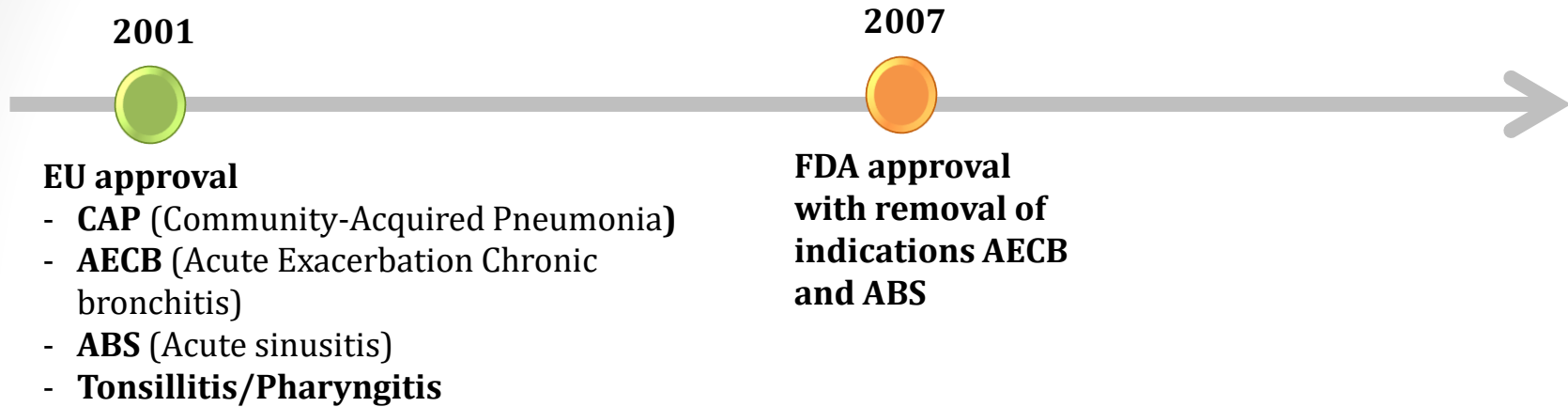
Methodology review
For benefit-risk assessment

Source: Mt-Isa 2014

4

Motivating example: Telithromycin (Ketek®)
IMI PROTECT case study

2001

2007

EU approval
- **CAP** (Community-Acquired Pneumonia**)**
- **AECB** (Acute Exacerbation Chronic bronchitis)
- **ABS** (Acute sinusitis)
- **Tonsillitis/Pharyngitis**

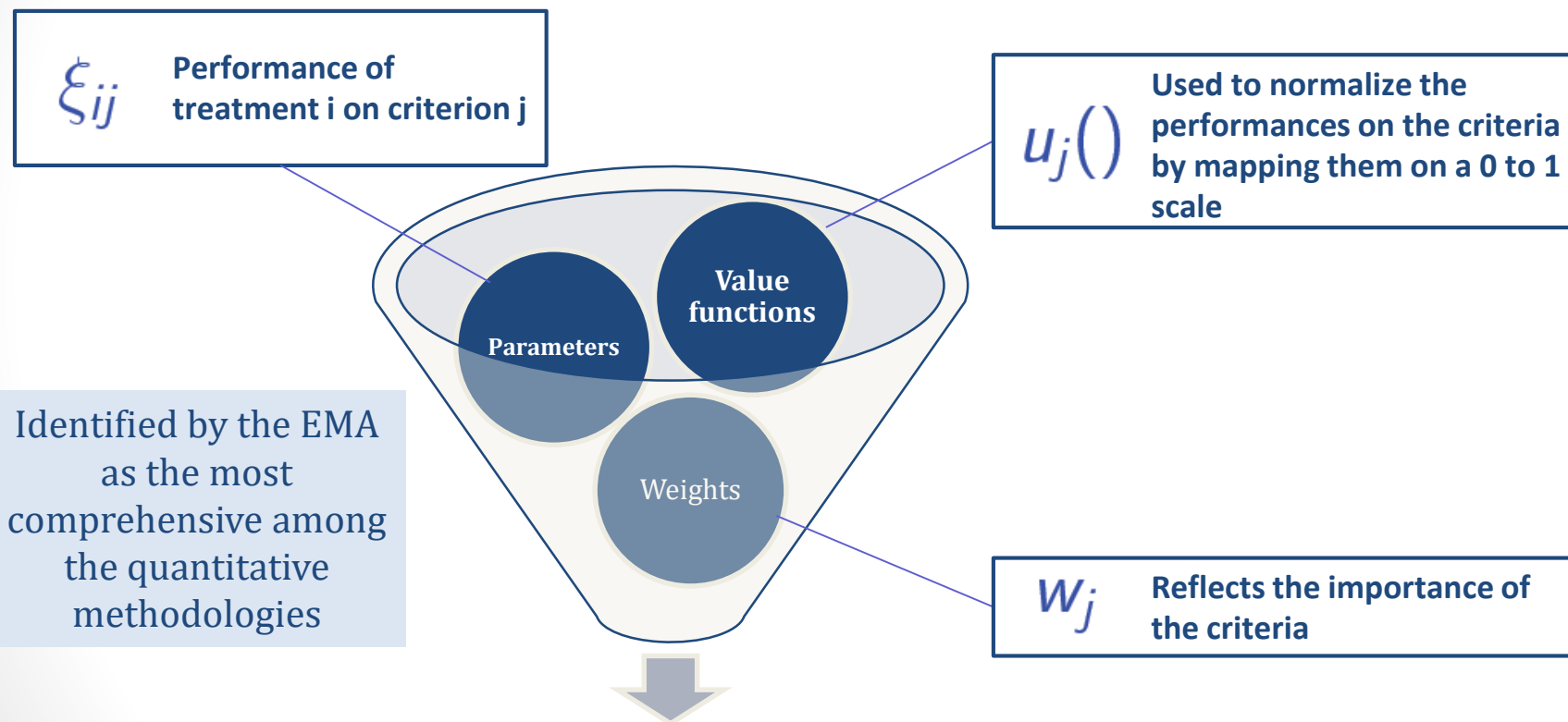**FDA approval with removal of indications AECB and ABS**

Compared to other macrolides, Telithromycin seems to be associated with a somewhat different risk profile including the following adverse reactions (eye disorders, loss of consciousness, acute liver failure, prolonged QT interval).

We will illustrate the use of quantitative approaches for benefit-risk assessment on telithromycin's CAP indication

Multi-Criteria Decision Analysis (MCDA) and its extensions

Principle

| ξ_{ij} | **Performance of treatment i on criterion j** |

| $u_j()$ | **Used to normalize the performances on the criteria by mapping them on a 0 to 1 scale** |

Value functions

Parameters

Identified by the EMA as the most comprehensive among the quantitative methodologies

Weights

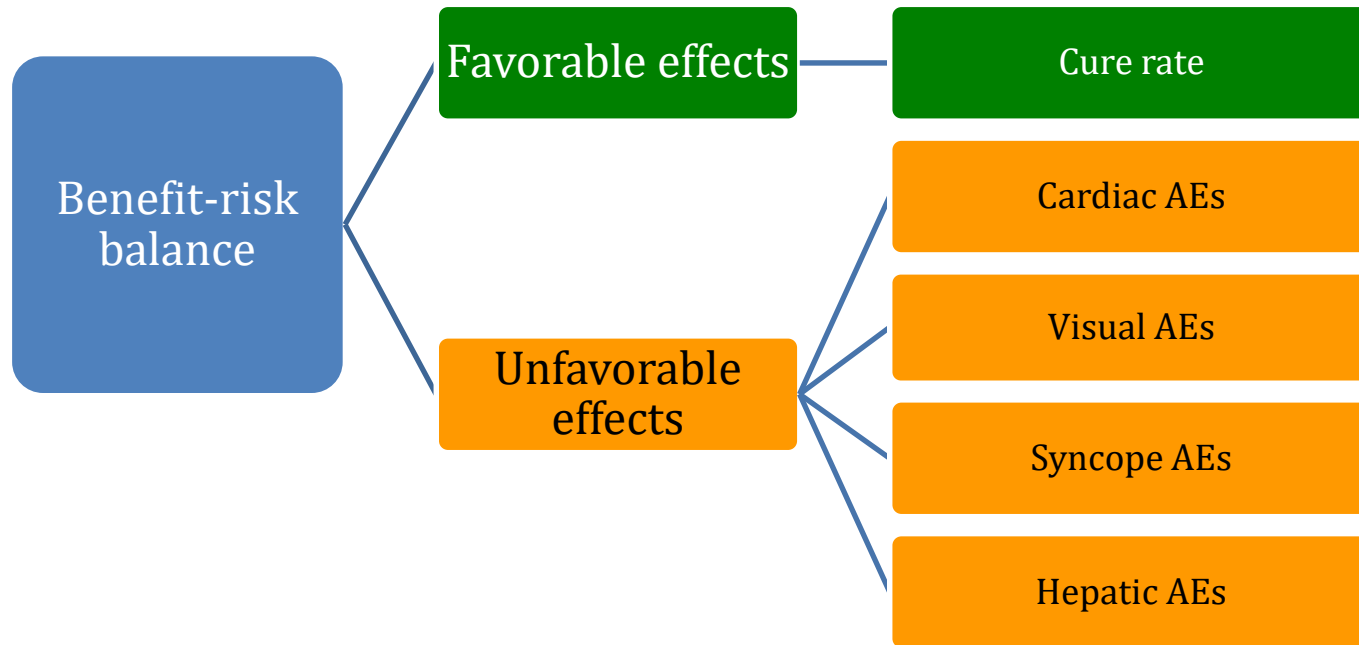| w_j | **Reflects the importance of the criteria** |

Benefit-Risk utility score

$$u(\xi_i, w) = w_1 u_1(\xi_{i1}) + \dots + w_n u_n(\xi_{in})$$

Motivating example: Telithromycin (Ketek®)
IMI PROTECT case study – Indication CAP

Value Tree

AE = Adverse Event

Motivating example: Telithromycin (Ketek®)
IMI PROTECT case study – Indication CAP

- 2 treatments: Ketek & Comparator
- 5 criteria: 1 for favorable effects, 4 for unfavorable effects

Criteria		Ketek®		Comparator	
		n/N	ξ_{1j}	n/N	ξ_{2j}
Favorable effects	**Cure rate**	2185/2417	**90%**	813/926	87,8%
Unfavorable effects	**Hepatic AEs**	57/1320	4,3%	46/1121	**4,1%**
	Cardiac AEs	4/1320	0,3%	3/1121	0,3%
	Visual AEs	14/1320	1,1%	5/1121	**0,4%**
	Syncope AEs	2/1320	**0,2%**	3/1121	0,3%

Data coming from the EPAR.

n = number of events ; N = number of patients ; EPAR = European Public Assessment Report

Different models

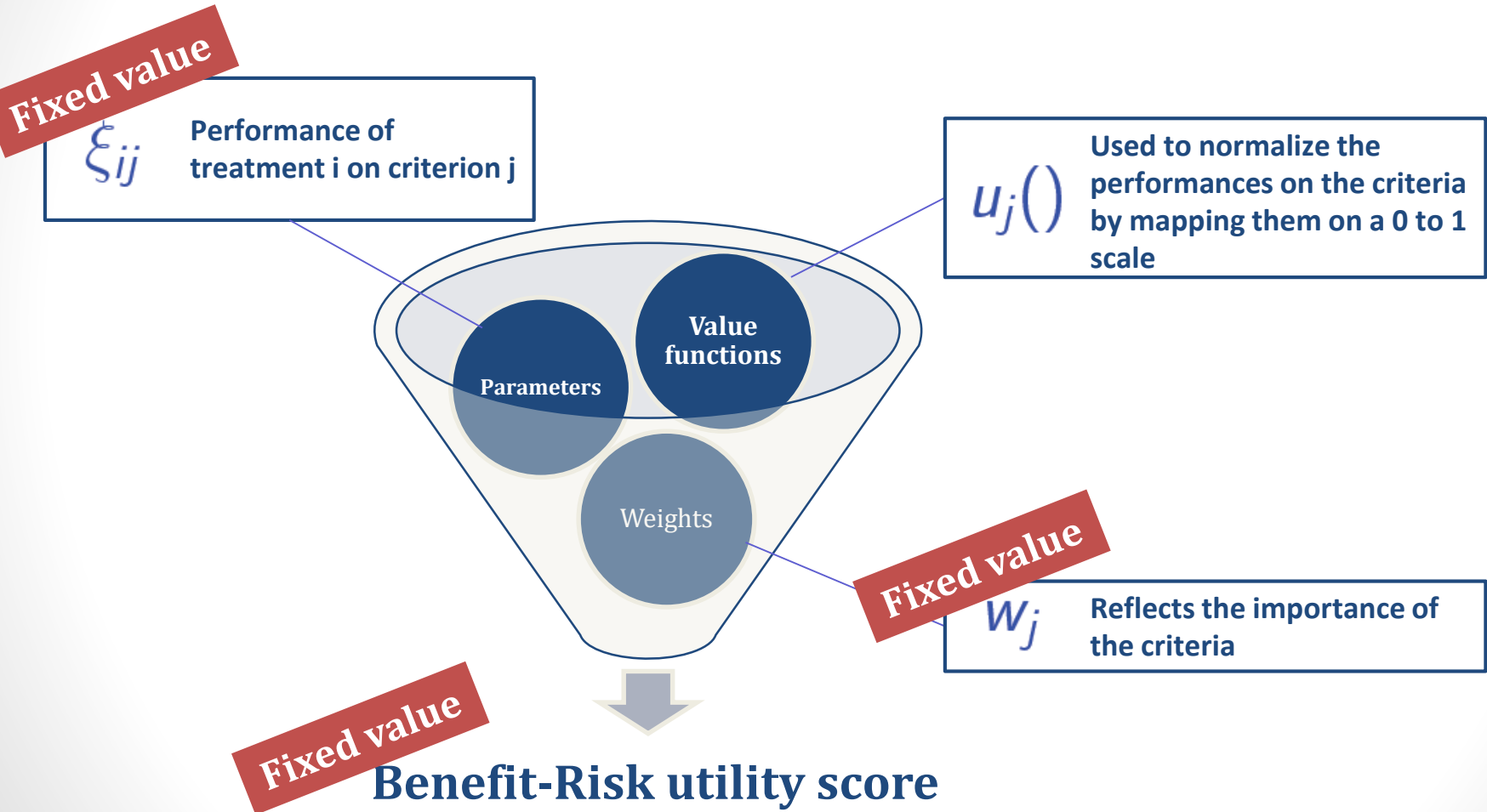- **Deterministic MCDA (dMCDA)**

- **Probabilistic MCDA (pMCDA)**

- **Stochastic Multicriteria Acceptability Analysis (SMAA)**

- **Dirichlet SMAA**

Deterministic MCDA
Mussen et al. (2007)

Fixed value: uncertainty is ignored

Random variable: uncertainty is taken into account

Fixed value

ξ_{ij} — **Performance of treatment i on criterion j**

$u_j()$ — **Used to normalize the performances on the criteria by mapping them on a 0 to 1 scale**

Value functions

Parameters

Weights

Fixed value

w_j — **Reflects the importance of the criteria**

Fixed value

Benefit-Risk utility score

$$u(\xi_i, w) = w_1 u_1(\xi_{i1}) + \ldots + w_n u_n(\xi_{in})$$

Deterministic MCDA
Mussen et al. (2007)

Partial value functions

- Used to **normalize** the performances on the criteria by mapping them on a 0 to 1 scale from **best and worst preferable values of the criteria**

- Linear value functions are often used, but non linear functions can be used

How to define the best and worst preferable values ?

- 95% confidence limits are often used, but it is not advised (data-driven, not reproducible)

- Bounds based on clinical considerations

- Bounds defined on the range of the criteria (e.g. 0-1 for probabilities of event)

Example Telithromycin

Partial value functions

Criteria		Best	Worst	Function
Favorable effects	**Cure rate**	100%	40%	linear
Unfavorable effects	**Hepatic AEs**	0%	10%	inverse linear
	Cardiac AEs	0%	10%	inverse linear
	Visual AEs	0%	10%	inverse linear
	Syncope AEs	0%	10%	inverse linear

Cure rate

Hepatic AEs
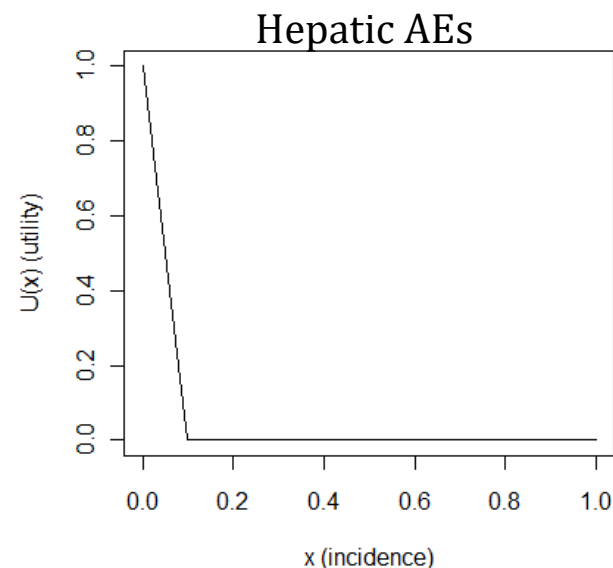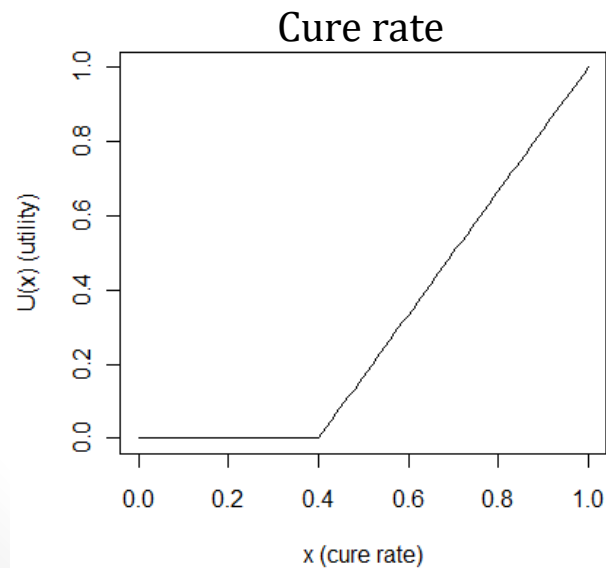
Example Telithromycin

What do we do?

For each model, the application to the motivation example is presented

R Code

Data
Number of events
Number of patients

For the Data column:

```
# Criteria = 1. Cure, 2. Hepatic, 3. Cardiac, 4. Visual, 5. Syncope
# Treatments = 1. Telithromycin, 2. Comparator

events = t(matrix(
  c(2185,  813,
      57,   46,
       4,    3,
      14,    5,
       2,    3), nrow=5, byrow=T))


N = t(matrix(
  c(2417,    926,
    1320,   1121,
    1320,   1121,
    1320,   1121,
    1320,   1121), nrow=5, byrow=T))
```

dMCDA : example Telithromycin

Criterion parameters	
ξ_{ij} deterministic, proportion of events = # events / (# patients)	xi=events/N

Partial value functions	

$u_j(\xi_{ij}) = \dfrac{\xi_{ij} - \xi_{ij}''}{\xi_{ij}' - \xi_{ij}''}$ (linear)
 	
ξ_{ij}' = most preferable value
ξ_{ij}'' = least preferable value
	# Criteria = 1. Cure, 2. Hepatic, 3. Cardiac, 4. Visual, 5. Syncope
	# Most preferable values ; Least preferable values
	most = c(1, 0, 0, 0, 0)
	least = c(0.4, 0.1, 0.1, 0.1, 0.1)
	
	# Partial Value Functions
	pvf <- function(x, most, least) {
	return((x - least) / (most - least))
	}
	values=pvf(xi, most, least)

Weights	
w_j deterministic, elicited by the clinicians / regulators / patients, with guidance from the statisticians (e.g surveys, swing-weighting, MACBETH tool…)	weights=c(0.30, 0.15, 0.15, 0.15, 0.25)

Utility score	
$u(\xi_{ij}, w) = \displaystyle\sum_{j=1}^{n} w_j u_j(\xi_{ij})$	us <- function (v, w) { return (sum(w*v))} us_teli = us(values[,1], weights) us_comp = us(values[,2], weights)

dMCDA : example Telithromycin

Results: dMCDA

Benefit-risk utility score:	Telithromycin	Comparator
	0.863	**0.860**

Conclusion from dMCDA: the benefit-risk balance of telithromycin is better than the benefit-risk balance of the comparator

But...
- Small difference
- Ignore uncertainties
- Sensitivity analyses should be conducted (varying the weights, using different criteria...)

dMCDA: conclusion

dMCDA	✓ Simple summary ✗ Deterministic, all sources of uncertainty are ignored
pMCDA	
SMAA	
Dirichlet SMAA	

Probabilistic MCDA
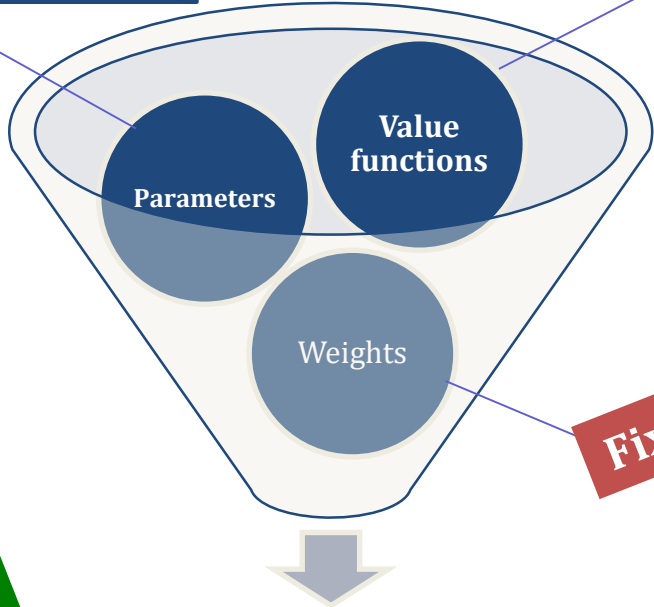## Waddingham et al. (2016)

Fixed value: uncertainty is ignored

Random variable: uncertainty is taken into account

Random variable

ξ_{ij} — **Performance of treatment i on criterion j**

Used to normalize the performances on the criteria by mapping them on a 0 to 1 scale — $u_j()$

Parameters

Value functions

Weights

Fixed value

w_j — **Reflects the importance of the criteria**

Random variable

Benefit-Risk utility score

$$u(\xi_i, w) = w_1 u_1(\xi_{i1}) + \ldots + w_n u_n(\xi_{in})$$

pMCDA : example Telithromycin (1/3)

| Criterion parameters	

$\xi_{ij} \sim Beta(a, b)$
a = # events +1
b = # non-events +1
 	
random variables instead of single summary values
	Ntrt=2 ; Nendpt=5;
	nsim=100000 # nb of simulations to obtain the posterior distributions
	
	# Criteria = 1. Cure, 2. Hepatic, 3. Cardiac, 4. Visual, 5. Syncope
	# Parameters of the posterior beta distribution
	a=events+1
	b=N-events+1
	
	xi = array(0, c(nsim, Ntrt, Nendpt))
	
	for (i in 1:Ntrt) {
	 for(j in 1:Nendpt) {
	  xi[,i,j]=rbeta(nsim, a[i,j], b[i,j])
	 }}

18

pMCDA : example Telithromycin (2/3)

Partial value functions	

$u_j(\xi_{ij}) = \dfrac{\xi_{ij} - \xi_{ij}''}{\xi_{ij}' - \xi_{ij}''}$ (linear)
 	
 ξ_{ij}' = most preferable value
 ξ_{ij}'' = least preferable value
	# Most preferable values
	 most = c(1, 0, 0, 0, 0)
	 # Least preferable values
	 least = c(0.4, 0.1, 0.1, 0.1, 0.1)
	
	 pvf <- function(x, most, least) { return((x - least) / (most - least))}
	 values = array(0, c(nsim, Nendpt, Ntrt))
	 for (i in 1:nsim) {
	   values[i,,]=pvf(t(xi[i,,]), most, least)
	 }

Weights	
w_j remain deterministic	weights=c(0.30, 0.15, 0.15, 0.15, 0.25)

Utility score	

$u(\xi_{ij}, w) = \displaystyle\sum_{j=1}^{n} w_j u_j(\xi_{ij})$
 random variables
	us <- function (v, w) { return (sum(w*v))}
	 us_teli=us_comp=diff=vector(length=nsim)
	 for (i in 1:nsim) {
	   us_teli[i] = us(values[i,,1], weights)
	   us_comp[i] = us(values[i,,2], weights)
	   diff[i]=us_teli[i]-us_comp[i]
	 }

pMCDA : example Telithromycin (3/3)

Results: pMCDA

- Distribution of the B-R utility scores

- Statistics on the B-R utility scores
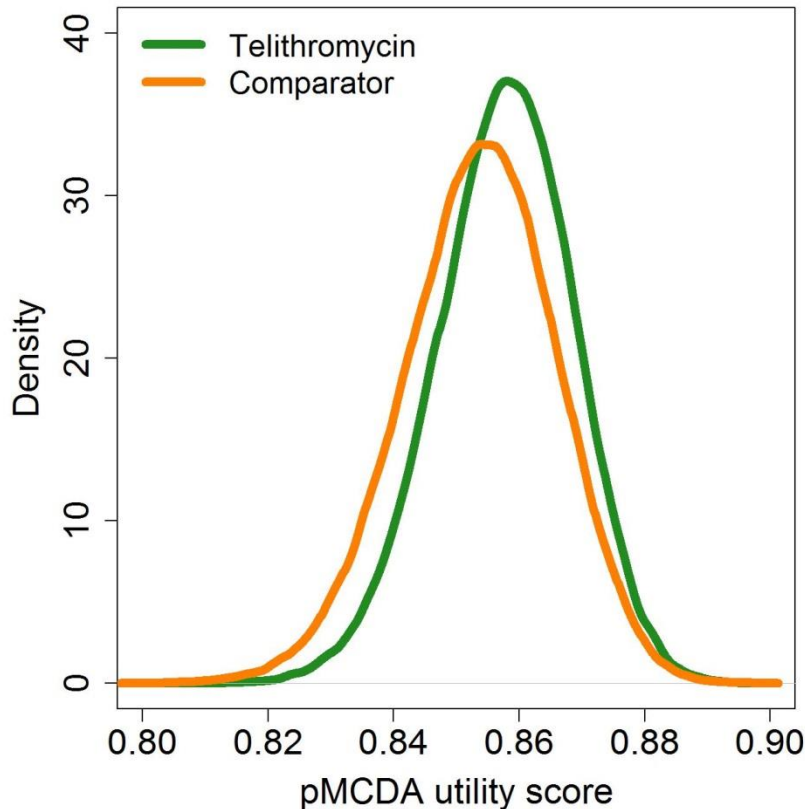
Treatment	Median (95% CrI)
Telithromycin	0.858 (0.836;0.875)
Comparator	0.854 (0.829;0.873)
Difference	0.004 (-0.028;0.032)

- Probability to be better than the comparator

Probability Telithromycin > Comparator
60%

pMCDA: conclusion

dMCDA	✓ Simple summary ✗ Deterministic, all sources of uncertainty are ignored
pMCDA	✓ Takes into account uncertainty in treatment effects on the criteria ✗ Preferences of decision-makers (weights) are explicitly required
SMAA	
Dirichlet SMAA	

SMAA
Tervonen et al. (2011)

Random variable: uncertainty is taken into account

Random variable

ξ_{ij}

Performance of treatment i on criterion j

Value functions

Parameters

Weights

$u_j()$

Used to normalize the performances on the criteria by mapping them on a 0 to 1 scale

Random variable

w_j
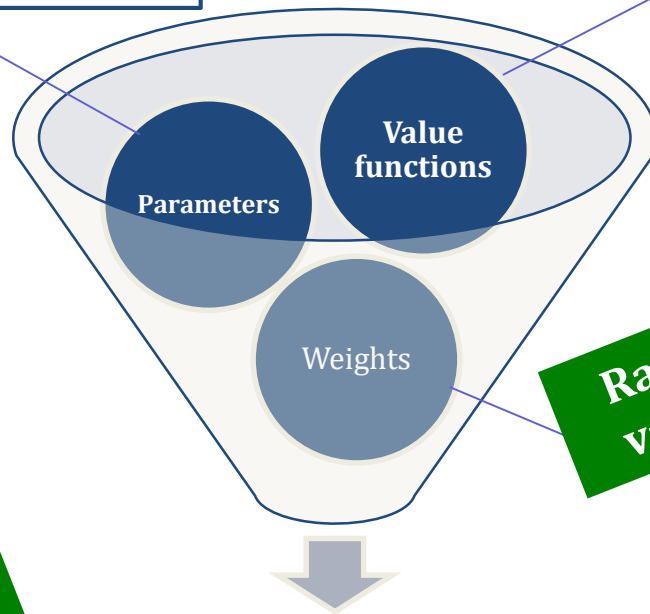
Reflects the importance of the criteria

Random variable

Benefit-Risk utility score

$$u(\xi_i, w) = w_1 u_1(\xi_{i1}) + \ldots + w_n u_n(\xi_{in})$$

SMAA
Tervonen et al. (2011)

Assumption: the weights have a uniform distribution on a space of weights, that needs to be defined

- No information, i.e. no preference between the criteria

$$W = \left\{ w \in \mathbb{R}^n, w > 0, \sum_{j=1}^{n} w_j = 1 \right\}$$

- Restrictions of the space of the weights
  - Upper and/or lower bounds
  - Complete ranking of the criteria
  - Equality of weights between benefits and risks

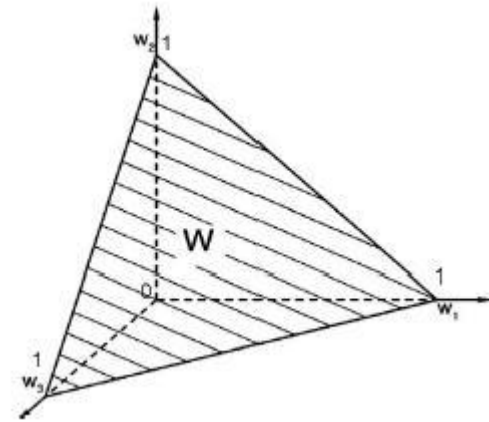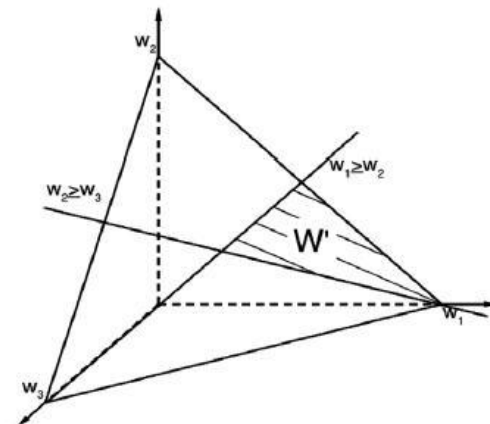*Example for 3 criteria*
w_1, w_2, w_3

Figure: Full space

Figure: Ranking: $w_1 \geq w_2 \geq w_3$

SMAA: example Telithromycin (1/3)

Criterion parameters	

$\xi_{ij} \sim Beta(a, b)$
a = # events +1
b = # non-events +1
 	
random variables instead of single summary values
	Ntrt=2 ; Nendpt=5;
	nsim=100000 # nb of simulations to obtain the posterior distributions
	
	# Criteria = 1. Cure, 2. Hepatic, 3. Cardiac, 4. Visual, 5. Syncope
	# Parameters of the posterior beta distribution
	a=events+1
	b=N-events+1
	
	xi = array(0, c(nsim, Ntrt, Nendpt))
	for (i in 1:Ntrt) {
	 for(j in 1:Nendpt) {
	  xi[,i,j]=rbeta(nsim, a[i,j], b[i,j])
	}}

Partial value functions	

$u_j(\xi_{ij}) = \frac{\xi_{ij} - \xi_{ij}''}{\xi_{ij}' - \xi_{ij}''}$ (linear)
ξ_{ij}' = most preferable value
ξ_{ij}'' = least preferable value
	# Most preferable values
	most = c(1, 0, 0, 0, 0)
	# Least preferable values
	least = c(0.4, 0.1, 0.1, 0.1, 0.1)
	
	pvf <- function(x, most, least) { return((x - least) / (most - least))}
	values = array(0, c(nsim, Nendpt, Ntrt))
	for (i in 1:nsim) { values[i,,]=pvf(t(xi[i,,]), most, least)}

SMAA: example Telithromycin (2/3)

| Weights		
w_j **random variables** with a joint uniform distribution on a weight space W	**# Example: use simplex.sample from package hitandrun to # generate uniform unit simplexes** **library(hitandrun)** **weights=simplex.sample(Nendpt, nsim, sort=FALSE)$samples**	
Utility score		

$$u(\xi_{ij}, w) = \sum_{j=1}^{n} w_j u_j(\xi_{ij})$$
<center>random variables</center>
	us <- function (v, w) { return (sum(w*v))}
	us_teli=us_comp=diff=vector(length=nsim)
	for (i in 1:nsim) {
	  us_teli[i] = us(values[i,,1], weights**[i,]**)
	  us_comp[i] = us(values[i,,2], weights**[i,]**)
	  diff[i]=us_teli[i]-us_comp[i]
	}	

SMAA: example Telithromycin (3/3)

Results: SMAA

Without weight elicitation

- Distribution of the difference in B-R utility scores

- Statistics on the difference in B-R utility scores
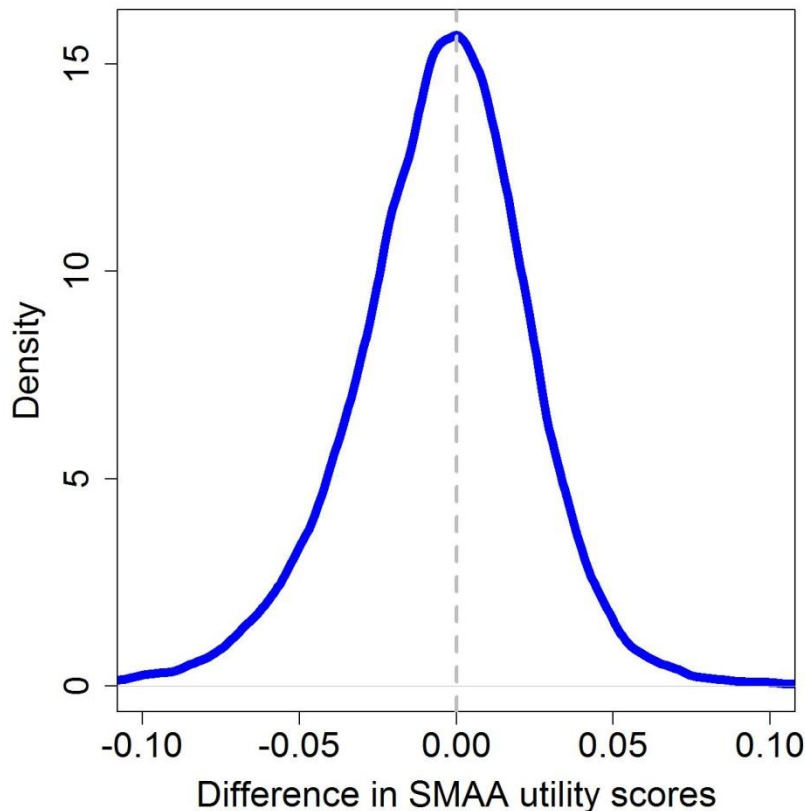
Treatment	Median (95% CrI)
Difference	-0.005 (-0.067;0.04)

- Probability to be better than the comparator

Probability Telithromycin > Comparator
45%

SMAA: conclusion

dMCDA	✓ Simple summary ✗ Deterministic, all sources of uncertainty are ignored
pMCDA	✓ Takes into account uncertainty in treatment effects on the criteria ✗ Preferences of decision-makers (weights) are explicitly required
SMAA	✓ Takes into account uncertainty in treatment effects on the criteria ✓ Does not require the elicitation of preferences to weigh the criteria ✗ Interpretation less straightforward ✗ High degree of uncertainty in the results
Dirichlet SMAA	

Dirichlet SMAA
Saint-Hilary et al. (2017)

Fixed value: uncertainty is ignored

Random variable: uncertainty is taken into account

Random variable

ξ_{ij} — **Performance of treatment i on criterion j**

Used to normalize the performances on the criteria by mapping them on a 0 to 1 scale — $u_j()$

Value functions

Parameters
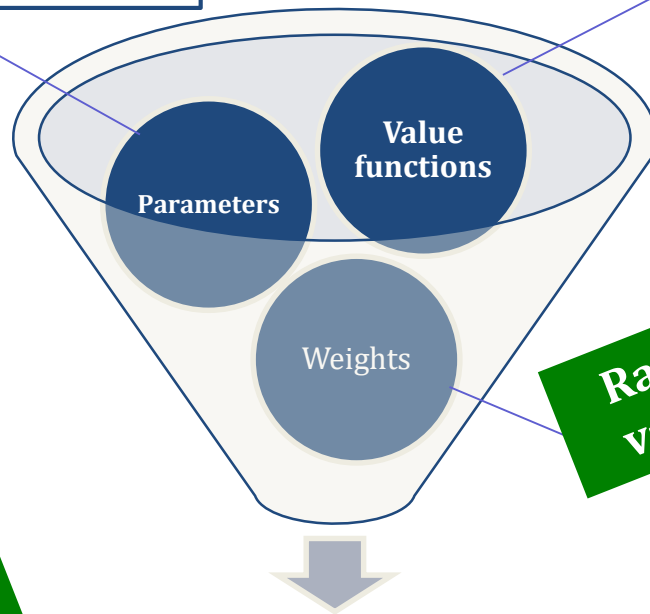
Weights

Random variable

w_j — **Reflects the importance of the criteria**

Random variable

Benefit-Risk utility score

$$u(\xi_i, w) = w_1 u_1(\xi_{i1}) + \ldots + w_n u_n(\xi_{in})$$

Dirichlet SMAA
Saint-Hilary et al. (2017)

- w_j : weights are **random variables,** following a **Dirichlet distribution**

$$(w_1, \dots, w_n) \sim Dirichlet(\alpha_1, \dots, \alpha_n)$$

Property:

the means of all w_i stay the same if all α_i are scaled with the same multiplicative constant, with variances getting smaller as the parameters α_i grow.

- We rewrite the Dirichlet distribution as follows:

$$(\boldsymbol{w_1}, \dots, \boldsymbol{w_n}) \sim \boldsymbol{Dirichlet}\left(\boldsymbol{c} . \left(\boldsymbol{w_1^0}, \dots, \boldsymbol{w_n^0}\right)\right)$$

With: (*i*) $0 \leq w_1^0, \dots, w_n^0 \leq 1$ with $\sum_{j=1}^{n} w_j^0 = 1$

(*ii*) c, a scaling constant, that can vary from 0 to $+\infty$

Dirichlet SMAA
Saint-Hilary et al. (2017)

- The variances of w_j are inversely proportional to c.
- They equal to infinity when $c = 0$ and to zero when $c = +\infty$.

- **Dirichlet SMAA** corresponds to:
  - pMCDA, when $c = +\infty$, as weights are deterministic $(w_j = w_j^0, j = 1, \dots, n)$
  - SMAA, without weight elicitation when $w_1^0 = \dots = w_n^0 = 1/n$ and $c = n$

- c : **confidence level** of the decision-makers in the elicitation of their preferences, which impact on the results can be assessed using different values of c.

Dirichlet SMAA: example Telithromycin (1/3)

Criterion parameters	

$\xi_{ij} \sim Beta(a, b)$
a = # events +1
b = # non-events +1
 	
random variables instead of single summary values
	Ntrt=2 ; Nendpt=5;
	nsim=100000 # nb of simulations to obtain the posterior distributions
	
	# Criteria = 1. Cure, 2. Hepatic, 3. Cardiac, 4. Visual, 5. Syncope
	# Parameters of the posterior beta distribution
	a=events+1
	b=N-events+1
	
	xi = array(0, c(nsim, Ntrt, Nendpt))
	for (i in 1:Ntrt) {
	  for(j in 1:Nendpt) {
	    xi[,i,j]=rbeta(nsim, a[i,j], b[i,j])
	  }}

Partial value functions	

$u_j(\xi_{ij}) = \dfrac{\xi_{ij} - \xi_{ij}''}{\xi_{ij}' - \xi_{ij}''}$ (linear)
ξ_{ij}' = most preferable value
ξ_{ij}'' = least preferable value
	# Most preferable values
	most = c(1, 0, 0, 0, 0)
	# Least preferable values
	least = c(0.4, 0.1, 0.1, 0.1, 0.1)
	
	pvf <- function(x, most, least) { return((x - least) / (most - least))}
	values = array(0, c(nsim, Nendpt, Ntrt))
	for (i in 1:nsim) { values[i,,]=pvf(t(xi[i,,]), most, least)}

Dirichlet SMAA: example Telithromycin (2/3)

Weights	
w_j **random variables** with a Dirichlet distribution c = confidence factor, **level of confidence** of the decision-makers in their weight elicitation	**library(gtools)** **# Example for c=50** **c=50** **weights=rdirichlet(nsim,c(0.30, 0.15, 0.15, 0.15, 0.25)*c)**
Utility score	

$$u(\xi_{ij}, w) = \sum_{j=1}^{n} w_j u_j(\xi_{ij})$$ random variables	us <- function (v, w) { return (sum(w*v))}
	us_teli=us_comp=diff=vector(length=nsim)
	for (i in 1:nsim) {
	  us_teli[i] = us(values[i,,1], weights[i,])
	  us_comp[i] = us(values[i,,2], weights[i,])
	  diff[i]=us_teli[i]-us_comp[i]
	}

Dirichlet SMAA: example Telithromycin (3/3)

Results: Dirichlet SMAA

For a given confidence factor (here, c=50)

- Distribution of the difference in B-R utility scores

- Statistics on the difference in B-R utility scores
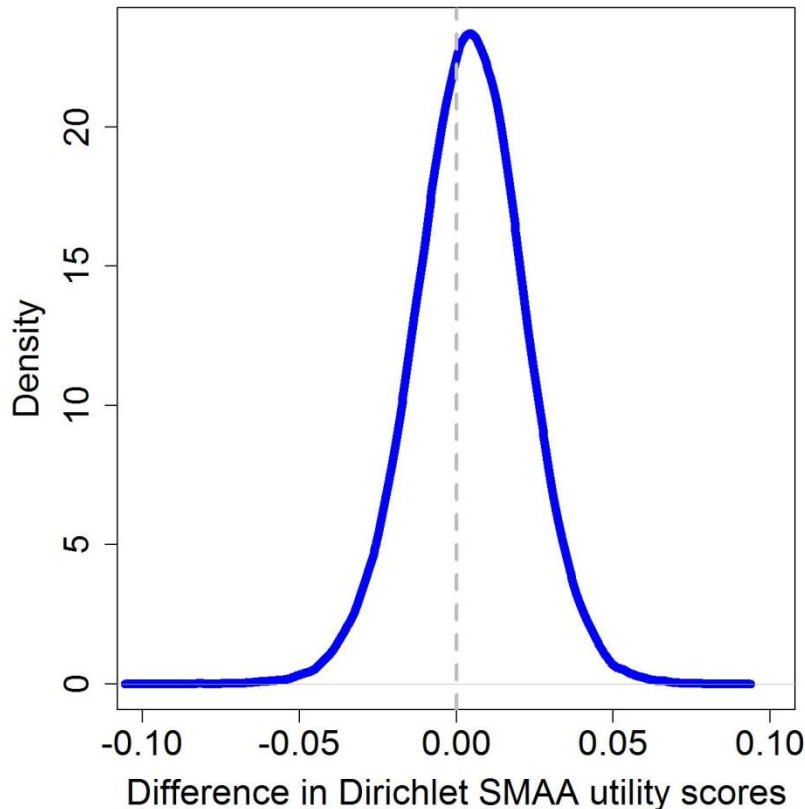
Treatment	Median (95% CrI)
Difference	0.004 (-0.031;0.033)

- Probability to be better than the comparator

Probability Telithromycin > Comparator
60%

Dirichlet SMAA: example Telithromycin (3/3)

Results: Dirichlet SMAA

Varying confidence factor

- Probability to be better than the comparator

  *Taking into account the **uncertainty** of the decision-makers in their weight elicitation*

Best-guess weights
- Cure: 0.30, Hepatic: 0.15, Cardiac: 0.15, Visual: 0.15, Syncope: 0.25
- Cure: 0.20, Hepatic: 0.20, Cardiac: 0.20, Visual: 0.20, Syncope: 0.20

Y-axis: P(telithromycin > comparator)

X-axis: c = strength of confidence in weight elicitation

SMAA c=5 ... 1, 11, 22, 35, 51, 72, 100, 150, 233, 399, 892, 10^5 ... pMCDA c=+∞
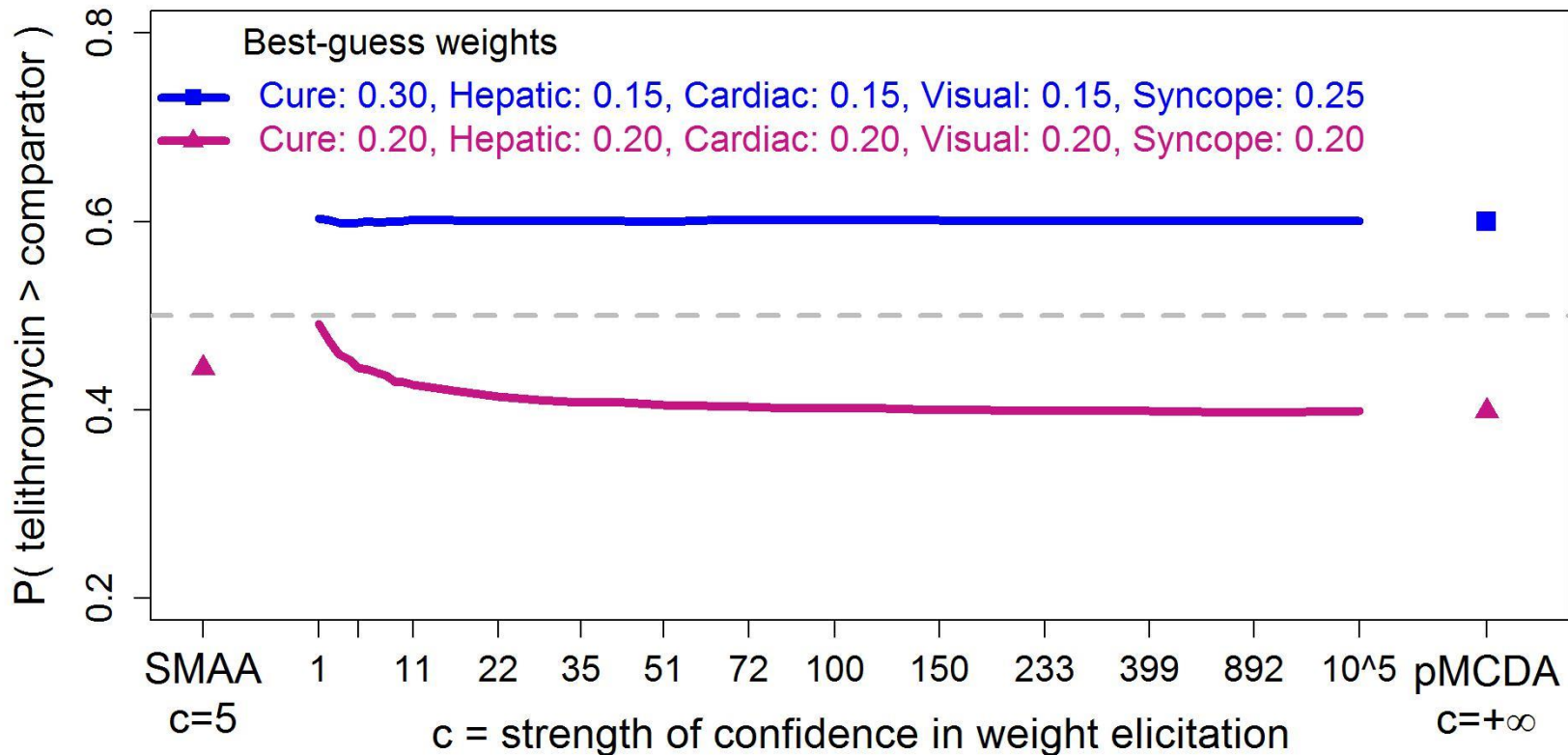
Dirichlet SMAA: conclusion

dMCDA	✓ Simple summary ✗ Deterministic, all sources of uncertainty are ignored
pMCDA	✓ Takes into account uncertainty in treatment effects on the criteria ✗ Preferences of decision-makers (weights) are explicitly required
SMAA	✓ Takes into account uncertainty in treatment effects on the criteria ✓ Does not require the elicitation of preferences to weigh the criteria ✗ Interpretation less straightforward ✗ High degree of uncertainty in the results
Dirichlet SMAA	✓ Takes into account uncertainty in treatment effects on the criteria ✓ Takes into account uncertainty in weight elicitation, and allows flexibility by making the variance of the weights vary ✓ Permits to account for a new source of uncertainty: the level of confidence of the decision-makers in their weight elicitation ✓ All parameters have a natural interpretation: treatment effects, decision-makers' preferences and their strength of confidence

Other examples in backup slides

- dMCDA: Gardasil$^®$ vaccine for preventing anal cancer in males

- pMCDA: Natalizumab for the treatment of Relapsing Remitting Multiple Sclerosis (RRMS)

- Dirichlet SMAA: fictive case-study in depression (inspired by a real case)

MCDA and its extensions
Conclusion

- Powerful quantitative **decision-making** tools
  - Recognized by the EMA

- **Subjectivity**: input from clinical/regulatory/patients needed to determine the criteria and their relative importance, as well as the range of preferences
  - Sensitivity analyses should be performed
  - Need to consider the various sources of uncertainty

- Relative **complexity**
  - Collecting and summarizing the data on multiple criteria, possibly from different sources

- Usually used late in the development → could be applied in **Early development** using biomarkers

Main references (1/2)

- EMA (2010). Benefit–risk methodology project. Work package reports: applicability of current tools and processes for regulatory benefit–risk assessment. Available at http://www.ema.europa.eu/

- IMI PROTECT Work package 5: benefit–risk integration and representation. Available at http://protectbenefitrisk.eu/

- EFSPI-SIG Benefit-risk http://www.benefit-risk-assessment.com/welcome-to-the-benefit-risk-blog-of-the-efspi-benefit-risk-sig/

- Mt-Isa, S., Ouwens, M., Robert, V., Gebel, M., Schacht, A., and Hirsch, I. (2015). Structured benefit–risk assessment: a review of key publications and initiatives on frameworks and methodologies. *Pharmaceutical Statistics* **15**, 324–332. doi: 10.1002/pst.1690

- Mt-Isa, S. *et al.* (2014). Balancing benefit and risk of medicines: a systematic review and classification of available methodologies. *Pharmacoepidemiology and Drug Safety* **23**, 667-678. doi: 10.1002/pds.3636

- Mussen, F., Salek, S., and Walker, S. (2007). A quantitative approach to benefit–risk assessment of medicines—part 1: the development of a new model using multi-criteria decision analysis. *Pharmacoepidemiology and Drug Safety* **16**, S2–S15.

Main references (2/2)

- Nixon, R., Dierig, C., Mt-Isa, S., Stockert, I., Tong, T., Kuhls, S., Hodgson, G., Pears, J., Waddingham, E., Hockley, K., and Thomson, A. (2016). A case study using the PrOACT-URL and BRAT frameworks for structured benefit risk assessment. *Biometrical Journal* **58**, 8–27.

- Tervonen, T., Van Valkenhoef, G., Buskens, E., Hillege, H. L., and Postmus, D. (2011). A stochastic multicriteria model for evidence-based decision making in drug benefit–risk analysis. *Statistics in Medicine* 30, 1419–1428. DOI: 10.1002/sim.4194.

- Waddingham, E., Mt-Isa, S., Nixon, R., and Ashby, D. (2016). A Bayesian approach to probabilistic sensitivity analysis in structured benefit–risk assessment. *Biometrical Journal* **58**, 28–42.

- **Saint-Hilary, G.**, Cadour, S., Robert, V. and Gasparini, M. (2017). A simple way to unify multicriteria decision analysis (MCDA) and stochastic multicriteria acceptability analysis (SMAA) using a Dirichlet distribution in benefit–risk assessment. *Biometrical Journal (early view online).* doi: 10.1002/bimj.201600113

- Marcelon, L., Verstraeten, T., Dominiak-Felden, G., Simondon, F. (2016). Quantitative benefit-risk assessment by MCDA of the quadrivalent HPV vaccine for preventing anal cancer in males. *Expert Rev Vaccines* **15** (1): 139 - 48. doi: 10.1586/14760584.2016.1107480

Back-up slides

Example 1: Gardasil® vaccine for preventing anal cancer in males

Assessment report 25 April 2014

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH
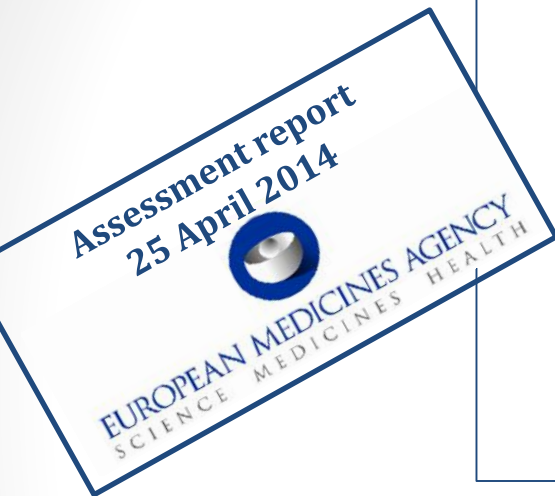
(...) the MAH has used the 'problem, objectives, alternatives, consequences, trade-offs, uncertainty, risk attitude, linked decisions' (PrOACT-URL) and the multi criteria decision analysis' (MCDA) approaches, which are two similar and well-structured approaches to estimate the overall benefit-risk balance, both on a **qualitative (PrOACT** and MCDA) **and a quantitative (MCDA)** point of view. **These two approaches allow taking into consideration all the potential benefits and all the potential risks within a single evaluation.**

Quantitative benefit–risk assessment by MCDA of the quadrivalent HPV vaccine for preventing anal cancer in males

Lydie Marcelon, Thomas Verstraeten, Geraldine Dominiak-Felden & François Simondon

EXPERT **REVIEW**
OF VACCINES

To cite this article: Lydie Marcelon, Thomas Verstraeten, Geraldine Dominiak-Felden & François Simondon (2016) Quantitative benefit–risk assessment by MCDA of the quadrivalent HPV vaccine for preventing anal cancer in males, Expert Review of Vaccines, 15:1, 139-148, DOI: 10.1586/14760584.2016.1107480

Example 1: Gardasil® vaccine for preventing anal cancer in males

PrOACT-URL
Generic **qualitative** framework to structure decision problems

dMCDA
Quantitative approach to synthetize the results

Problem
Objective
Alternatives
Consequences
Trade-off
Uncertainty
Risk tolerance
Linked decisions

Parameters

Value functions
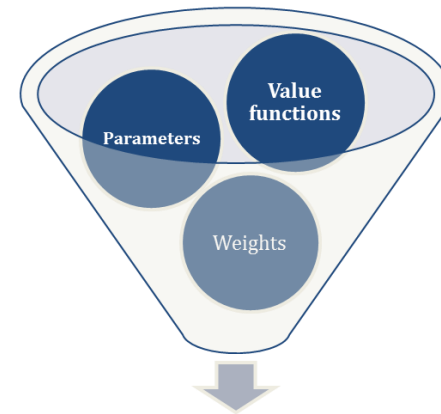
Weights

Benefit-Risk utility score

$$u(\xi_i, w) = w_1 u_1(\xi_{i1}) + \ldots + w_n u_n(\xi_{in})$$

Example 1: Gardasil® vaccine for preventing anal cancer in males

Data sources

Identification of key benefits and risks	Weights	Treatment performances on the criteria
1) Sanofi Pasteur MSD clinicians and epidemiologists, with working experience on the qHPV vaccine 2) Panel of six external experts		• Merck/Sanofi Pasteur MSD-sponsored clinical trials • Post-authorization study reports

Treatment groups

• Gardasil®
• No vaccination

Example 1: Gardasil® vaccine for preventing anal cancer in males

Criteria and weights

Weights

Criterion			Weight
Benefits	Direct effects	Anal cancer	**16.1%**
		Genital warts	**12.9%**
	Indirect effects	HPV transmission	**8.1%**
Risks	Adverse Effects	Overall incidence of AEs	**6.5%**
		Overall incidence of SAEs	**20.2%**
	Important Identified risk	Syncope	**5.0%**
		Hypersensitivity	**10.1%**
	Important Potential risk	Autoimmune disorder	**20.2%**
	Potential for non-demonstrated risk	Unanticipated safety signal	**1%**

Benefit-risk balance

44
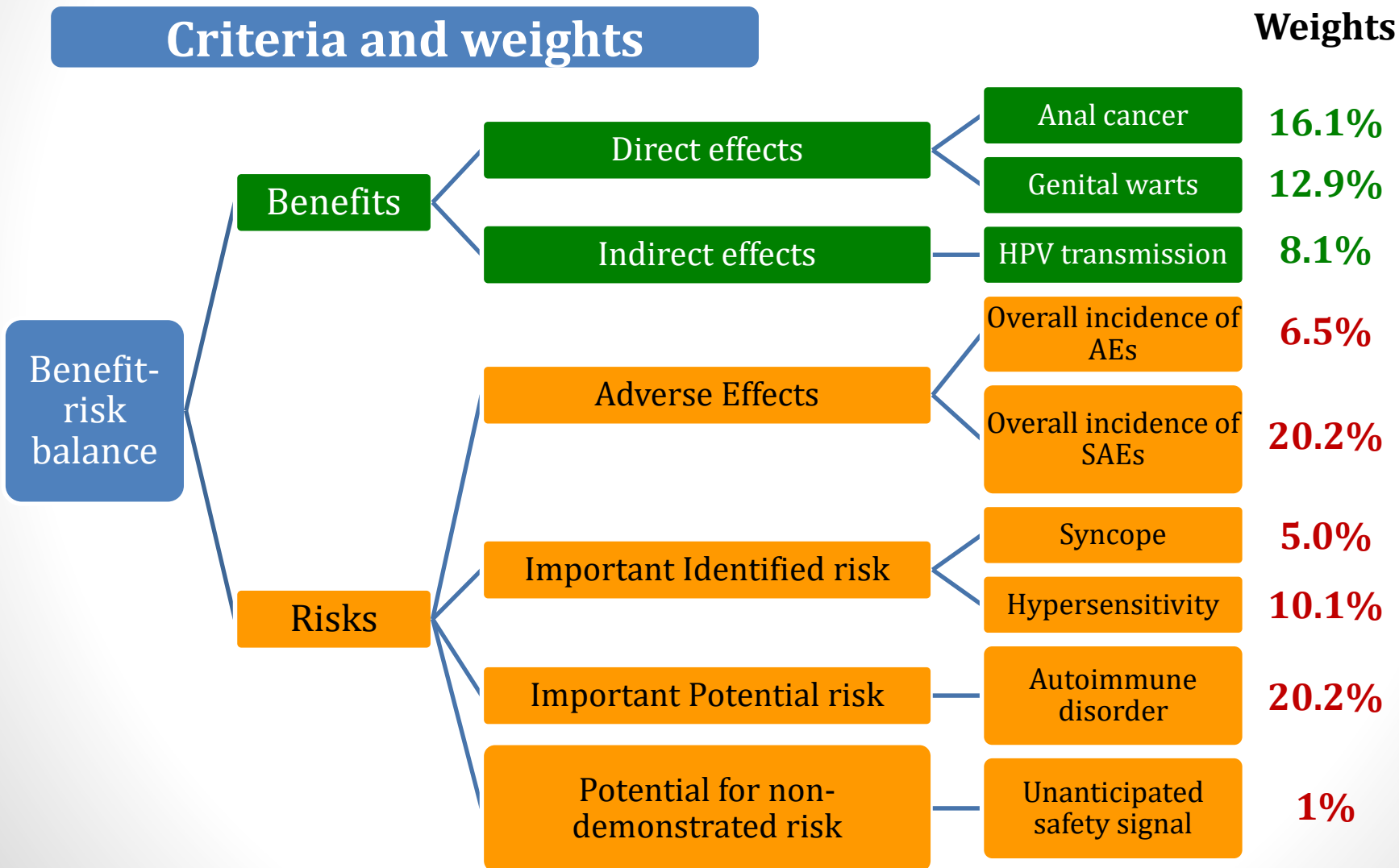
Example 1: Gardasil® vaccine for preventing anal cancer in males

Results: dMCDA

Benefit-risk utility score:	Gardasil®	No vaccination
	66	**46**

Sensitivity analyses: results are robust to changes in
- the **weight** assigned to the individual criteria or nodes
- the **model parameters** (e.g. inclusion of data less favorable to the vaccine or excluding all beneficial effects other than anal cancer prevention)

Assessment report
25 April 2014

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES H

"MCDA is a method considered to be **useful as a complementary and supportive tool**. Through a number of steps the purpose is to **bring together evaluations of options on both benefits and risks into one overall evaluation** taking into account what is considered best current evidence."

Example 1: Gardasil® vaccine for preventing anal cancer in males
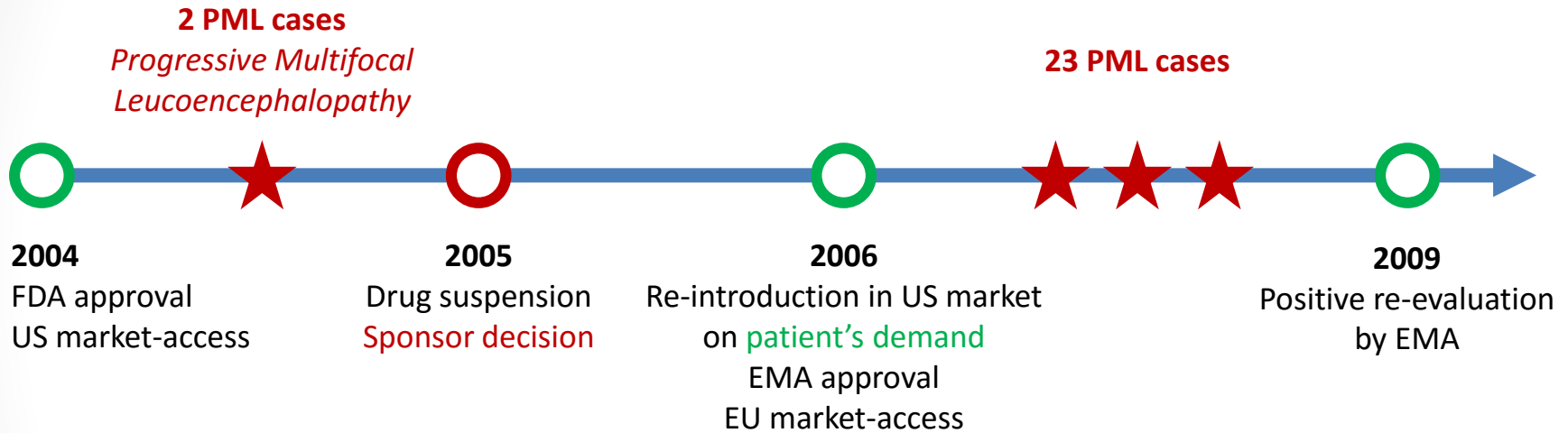
Conclusion

**Assessment report
25 April 2014**

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

"The benefit-risk balance [of Gardasil®] is considered positive."

APPROVED

Example 2: Natalizumab for the treatment of Relapsing Remitting Multiple Sclerosis (RRMS)

2 PML cases
Progressive Multifocal Leucoencephalopathy

23 PML cases

2004
FDA approval
US market-access

2005
Drug suspension
Sponsor decision

2006
Re-introduction in US market
on patient's demand
EMA approval
EU market-access

2009
Positive re-evaluation
by EMA

→ Rare serious side effect in an effective treatment for a serious disease

Was the decision right to keep natalizumab on the market given that increased episodes of PML were observed?

Webinar

G. Saint-Hilary, S. Cadour
Quantitative benefit-risk assessment

47

Example 2: Natalizumab for the treatment of Relapsing Remitting Multiple Sclerosis (RRMS)

Data sources

Identification of key benefits and risks	Weights	Treatment performances on the criteria
Individual experts (based largely on data from the SPC and the EPAR for natalizumab)	Patient representatives (Decision conference held on 23 Sept 2011)	Mainly: • EPARs • Literature search

EPAR: European public assessment reports
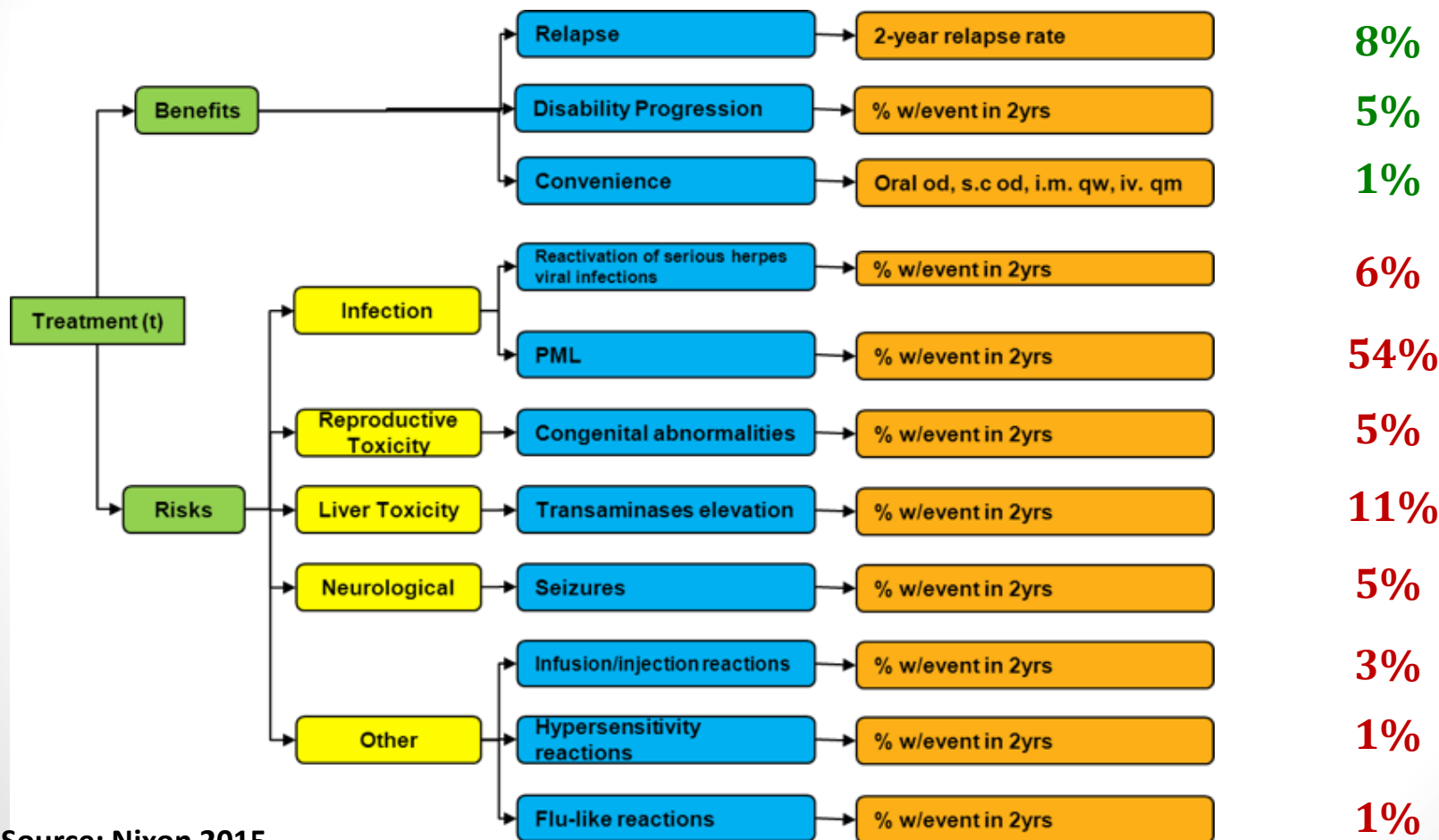SPC: Summary of Product Characteristics

Treatment groups

- Natalizumab
- Placebo
- Glatiramer Acetate
- Beta-interferon

48

Example 2: Natalizumab for the treatment of Relapsing Remitting Multiple Sclerosis (RRMS)

Criteria and weights

Weights

| Criteria	Measure	Weight
Relapse	2-year relapse rate	**8%**
Disability Progression	% w/event in 2yrs	**5%**
Convenience	Oral od, s.c od, i.m. qw, iv. qm	**1%**
Reactivation of serious herpes viral infections	% w/event in 2yrs	**6%**
PML	% w/event in 2yrs	**54%**
Congenital abnormalities	% w/event in 2yrs	**5%**
Transaminases elevation	% w/event in 2yrs	**11%**
Seizures	% w/event in 2yrs	**5%**
Infusion/injection reactions	% w/event in 2yrs	**3%**
Hypersensitivity reactions	% w/event in 2yrs	**1%**
Flu-like reactions	% w/event in 2yrs	**1%**

Source: Nixon 2015

Example 2: Natalizumab for the treatment of Relapsing Remitting Multiple Sclerosis (RRMS)

Results: pMCDA

- Distribution of the B-R utility scores
- Statistics on the B-R utility scores
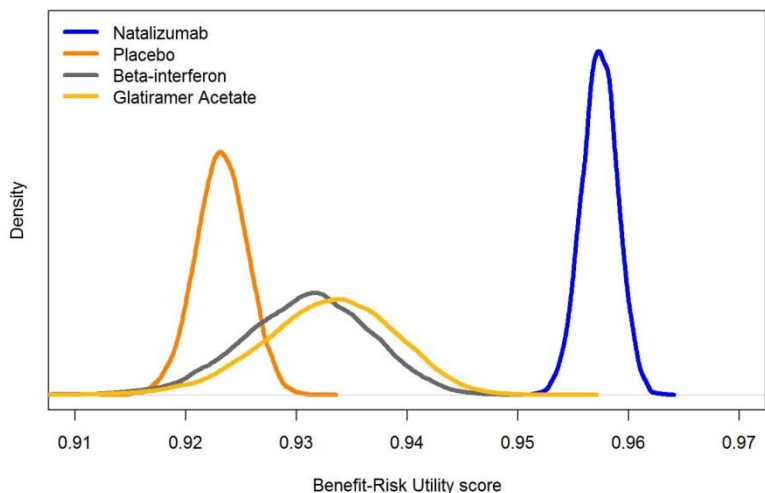
Treatment	Median (95% CrI)
Placebo	0.92 (0.92;0.93)
Natalizumab	0.96 (0.95;0.96)
Beta-interferon	0.93 (0.92;0.94)
Glatiramer Acetate	0.93 (0.92;0.94)

- Probability to be better than the control

Treatment	Probability Treatment > Placebo
Natalizumab	100%
Beta-interferon	80%
Glatiramer Acetate	79%

Source: Waddingham 2016

Webinar

G. Saint-Hilary, S. Cadour
Quantitative benefit-risk assessment

Example 2: Natalizumab for the treatment of Relapsing Remitting Multiple Sclerosis (RRMS)
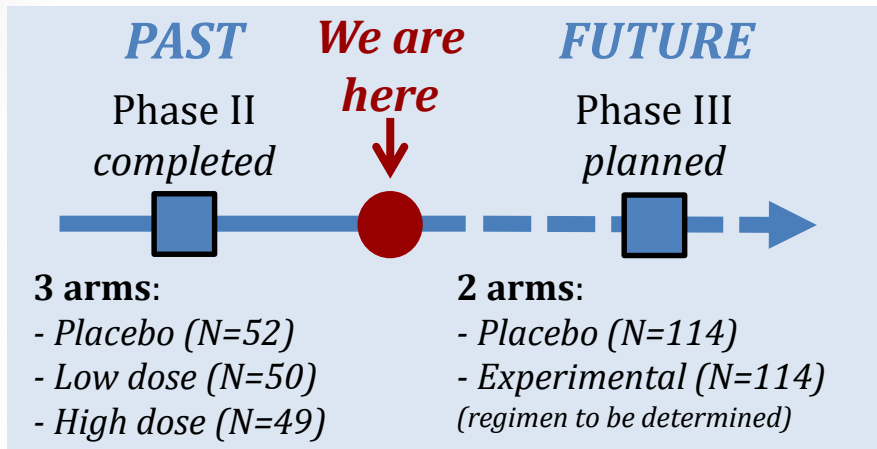
Conclusion

- Despite the incidence of the serious rare adverse events PML, Natalizumab has the best benefit-risk profile

Example 3: Fictive case-study in depression
(inspired by a real case)

Context: Go/No-Go Ph III

PAST
Phase II *completed*

We are here

FUTURE
Phase III *planned*

3 arms:
- *Placebo (N=52)*
- *Low dose (N=50)*
- *High dose (N=49)*

2 arms:
- *Placebo (N=114)*
- *Experimental (N=114)*
(regimen to be determined)

Results from Ph II

- Effective treatment
- **Dose-response relationship** for efficacy and safety
- Hypokalemia may be a **serious adverse effect**

Considered strategies for Ph III

- Low dose
- High dose

- Low dose with possible dose-increase
- High dose with potassium supplementation

Which dose/regimen has the best chance to have a positive Benefit-Risk balance versus Placebo in Phase III?

Example 3: Fictive case-study in depression
(inspired by a real case)

Data sources

Identification of key benefits and risks	Weights	Treatment performances on the criteria
Sponsor multidisciplinary team (clinical, pharmacovigilance, regulatory, statistics etc.)		Phase II trial

Treatment groups

- Low dose
- High dose

- Low dose with possible dose-increase
- High dose with potassium supplementation

Note: details about the combination of new hypotheses with the data (dose-increase, potassium supplementation) and about predictions of the next study are not included in this presentation
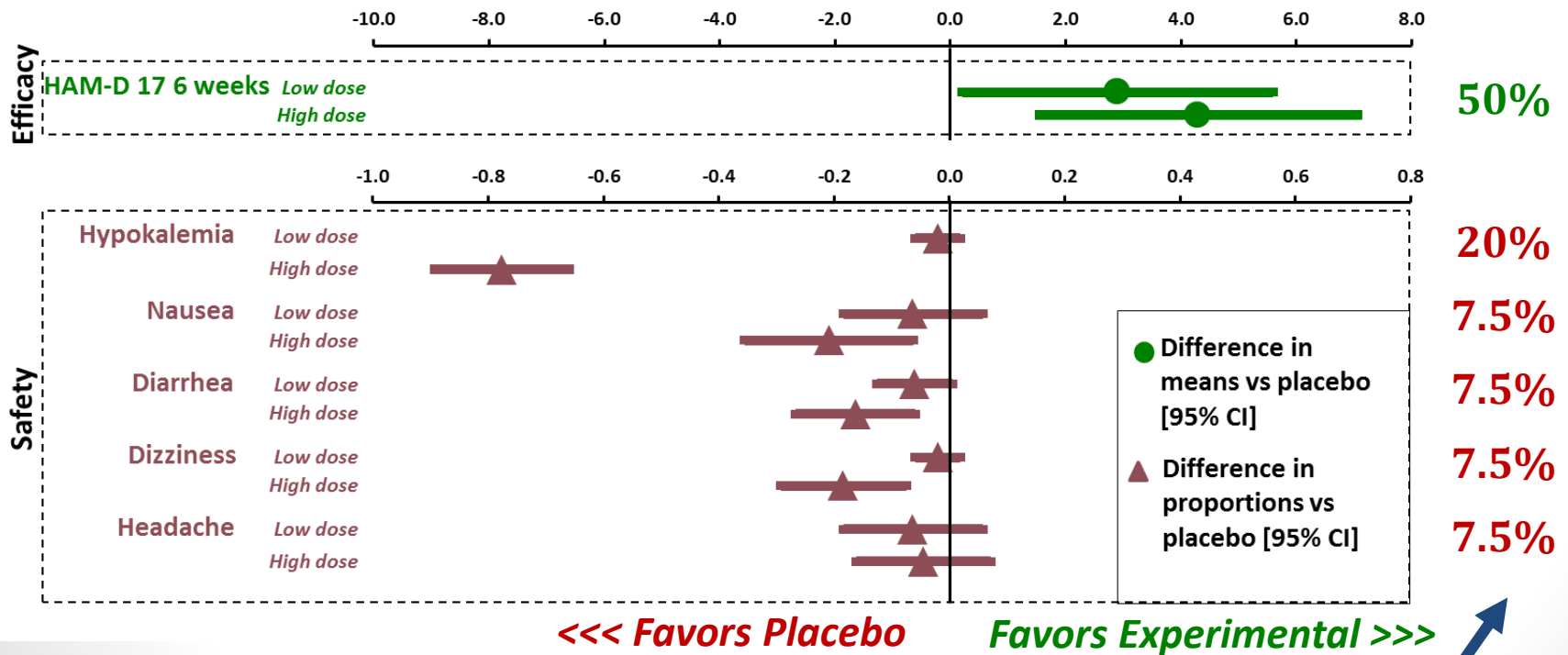
Example 3: Fictive case-study in depression
(inspired by a real case)

Criteria and weights

Results from Phase II
Primary efficacy criterion and 5 more frequent adverse events

Weights

Efficacy — HAM-D 17 6 weeks *Low dose* / *High dose* — **50%**

Safety:
- Hypokalemia *Low dose* / *High dose* — **20%**
- Nausea *Low dose* / *High dose* — **7.5%**
- Diarrhea *Low dose* / *High dose* — **7.5%**
- Dizziness *Low dose* / *High dose* — **7.5%**
- Headache *Low dose* / *High dose* — **7.5%**

Legend:
● Difference in means vs placebo [95% CI]
▲ Difference in proportions vs placebo [95% CI]

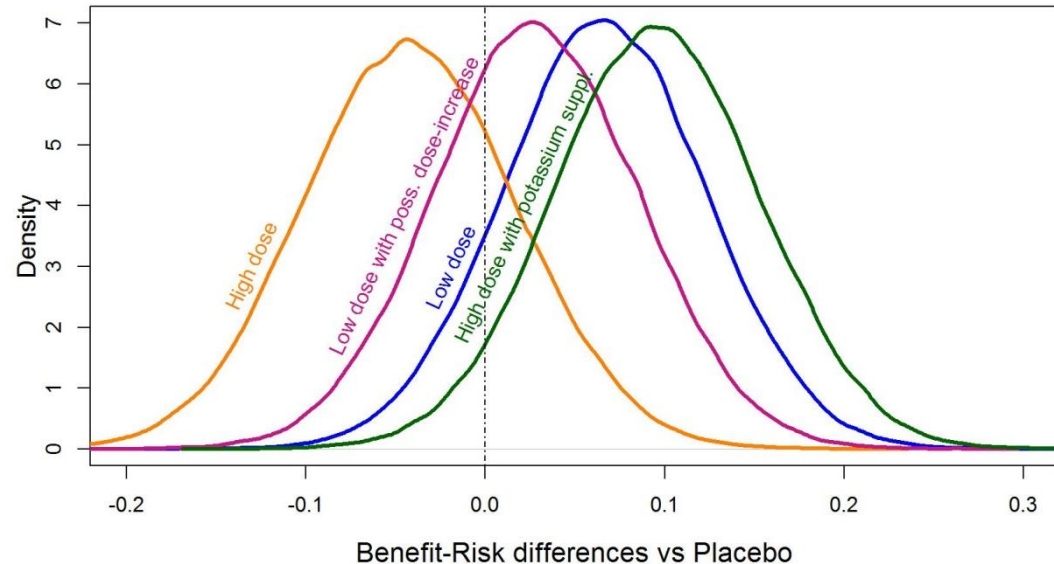*<<< Favors Placebo*   *Favors Experimental >>>*

But decision-makers are not quite confident in their weight elicitation...

54

Example 3: Fictive case-study in depression

(inspired by a real case)

Results: Dirichlet SMAA

- Predictive distribution of the differences in B-R utility scores vs Placebo

- Statistics on differences in B-R utility scores vs Placebo

| Treatment	Diff vs Placebo Median (95% CrI)
Low dose	0.07 (-0.04;0.18)
High dose	-0.04 (-0.16;0.08)
Dose-increase	0.03 (-0.08;0.14)
High dose suppl	0.10 (-0.02;0.21)

Example 3: Fictive case-study in depression
(inspired by a real case)

Results: Dirichlet SMAA

- Probability to be better than placebo in the next Ph III

*Taking into account the **uncertainty** of the decision-makers in their elicitation of preferences (weights)*
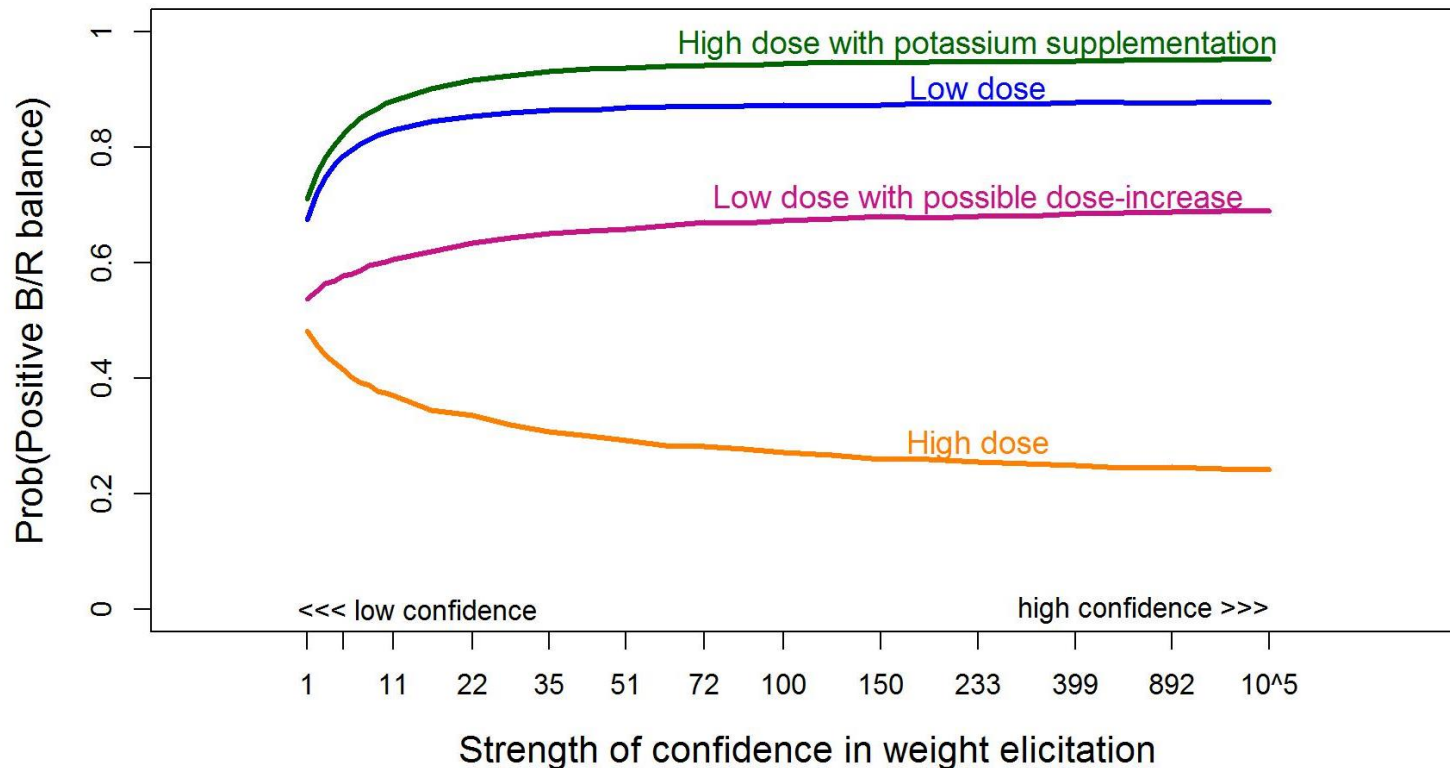
Example 3: Fictive case-study in depression
(inspired by a real case)

Conclusion

- High dose with potassium supplementation seems to be the regimen with the best benefit-risk balance vs placebo

G. Saint-Hilary, S. Cadour
Quantitative benefit-risk assessment

57