BENEFIT-RISK ASSESSMENT IN HTA

Shahrul Mt-Isa (MSD), Susan Talbot (Amgen), Jixian Wang (Celgene)

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Disclaimer

The views expressed herein represent those of the presenters and do not necessarily represent the views or practices of their companies or the views of the general Pharmaceutical Industry. The work presented here is a voluntary effort of the members of the EFSPI Joint BR-HTA SIG.

Key points

- Many benefit-risk assessment methods but no one-size-fits-all
- Planning and evidence are key drivers to good structured benefit-risk assessments throughout product lifecycle
- Robust analyses of quality evidence contributes to greater transparency and well-informed decision-making
- Benefit-risk balance depends on perspective
- More considerations are given by regulators and HTA agencies in terms of preference methodologies to assess BR balance

CURRENT STATE OF KNOWLEDGE

Regulatory Benefit-Risk (BR) Assessment

- should be based on the available tests and clinical trials carried out on the product designed to test the efficacy and safety; and accounting for the potential impact on the evaluation of benefits and risks through the pharmacovigilance activities

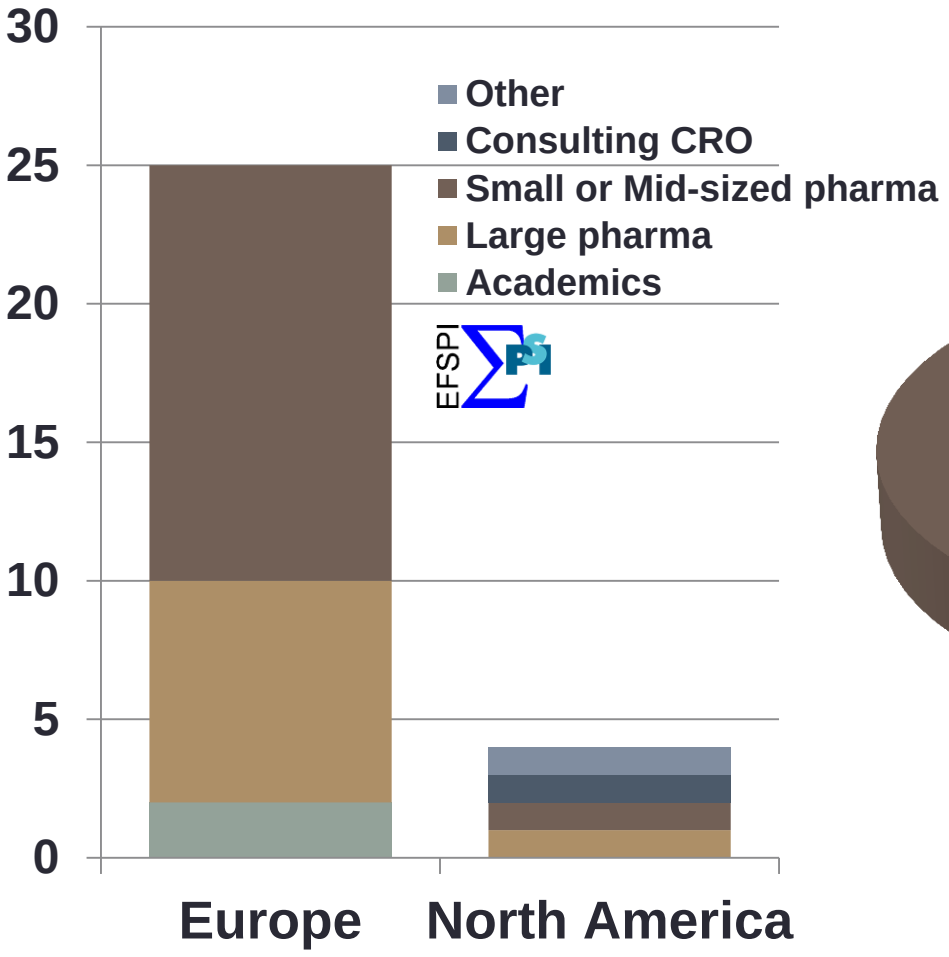
[Directive 2001/83/EC*]

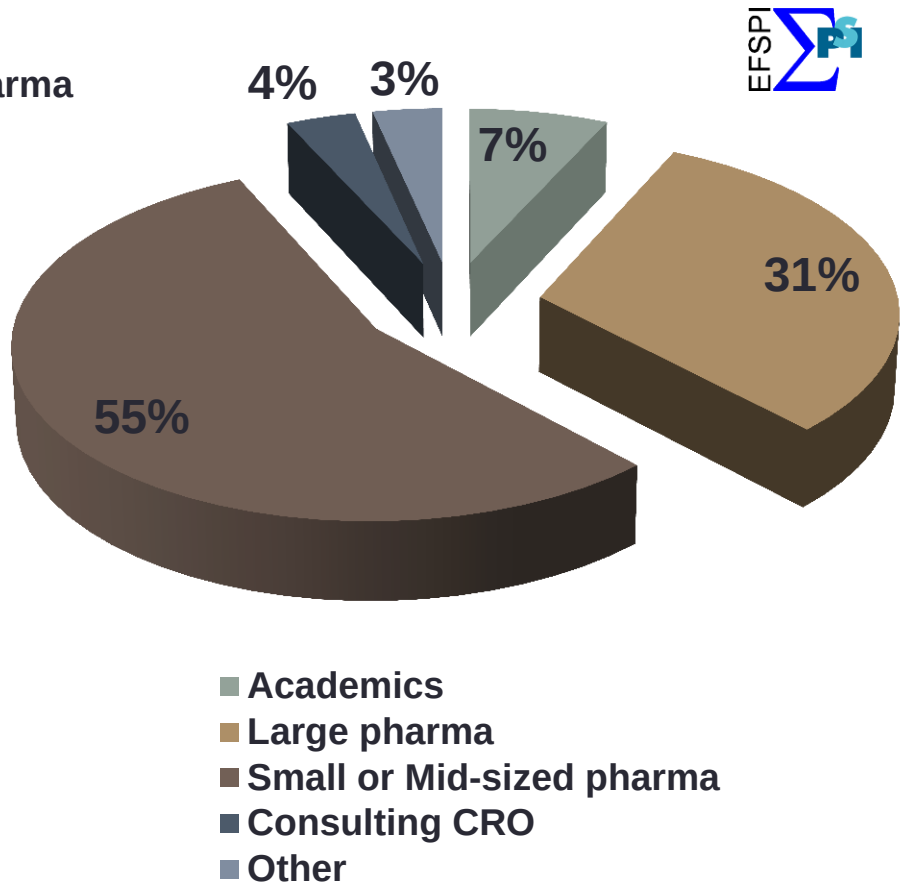
- authorisation decisions should be based on quality, safety and efficacy, and not including economic and other considerations such as “cost-effectiveness”.

[Community law (Regulation EC 726/2004)*]

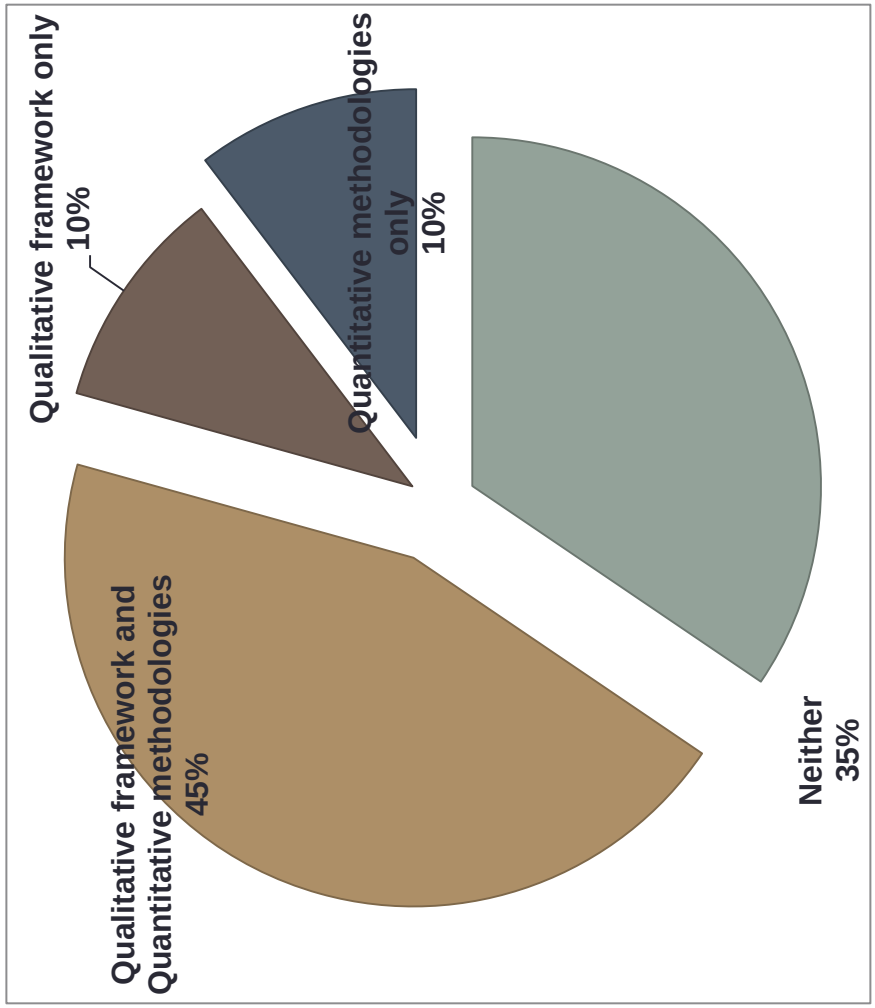
* Of the European Parliament and of the Council

EFSPI BR SIG Survey 2016 – Responders





EFSPI BR SIG Survey 2016 – Experience



Methodologies Quantitative and/or Qualitative	n	%
Multi-Criteria Decision Analysis (MCDA)	11	58%
Number Needed to Treat (NNT)	9	47%
Benefit-Risk Action Team (BRAT) framework	8	42%
Quality of life measures (QALYs, DALYs, Q-TWiST)	6	32%
Stochastic Multi Acceptability Analysis (SMAA)	5	26%
Benefit-Risk Ratio (BRR)	4	21%
PrOACT-URL	4	21%
Net clinical benefit	1	5%
Network Meta Analysis	1	5%
Our own qualitative framework (mixture of BRAT & ProACt)	1	5%
Project Team meetings	1	5%

Benefit-Risk Assessment Roadmap

Planning

- critical issues
- think & discuss purpose and context
- documentation
- foundations for future analyses and updates

Evidence gathering and data preparation

- relevant evidence
- data collection
- data aggregation
- missing/incomplete data

Analysis

- Evaluate data
- Quantify benefits and risks
- Weigh or integrate

Exploration

- robustness
- sensitivity
- assumptions and uncertainties
- other consequences
- impact or added value to the RMPs

Conclusion and dissemination

- communicate results/consensus
- any influence on future actions
- transparent audit trail
- ensures "big picture" is not lost

Hughes D, et *al*. Recommendations for the methodology and visualisation techniques to be used in the assessment of benefit and risk of medicines. IMI-PROTECT Website 2014.

EMA Effects Table

- The European Medicines Agency recommends the use of an Effects Table for Day 80 Critical Assessment Report.

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Acronym of short identifier of the effect, e.g. RR for response rate.	A very short description of how the effect was measured. Further description may be added as footnotes.	Unit of measurement for each effect, e.g. mmHg, months, %	Summary of key effects of the index drug driving the BR discussion. Separate column may be added for each relevant comparator. Reference(s) to specific studies may be added in footnotes.		Description of strength of evidence and any major uncertainty or limitation for each effect.	Optional. Use especially where complex issues have arisen to provide reference to specific part of the text.

Source: http://www.benefit-risk-assessment.com/

Ref: EMA. Guidance document on the content of the Rapporteur day 80 critical assessment report. Overview and lists of question. 2015. EMA/90842/2015. Available from http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004800.pdf.

An Example of an Effects Table (Partially)

Effect	Short description	Unit	Natalizumab	Placebo	Uncertainties / Strength of evidence	References
Favourable effects (benefits)						
Disability progression	Proportion of patients with EDSS score progression in two years	NA	11.3	23.0	No CIs because # patients and events are not available in the data sent	[1;2;3]
Unfavourable effects (risks)						
PML	Proportion of patients experiencing PML in 2 years	%	0.2	0.0	3 cases of PML for Tysabri in 4500 patient years; Take mean of 3/2250 (assumption 2250 patients treated for two years) and 3/4500 (assumption 4500 patients treated for one year) -> 0,001	[1;2;3]
Flu-like reactions	Proportion of patients experiencing flu-like reactions in 2 years	%	39.9 (95% CI 31.8 – 47.9)	39.9 (95% CI 31.8 – 47.9)	# Patients and # events for Tysabri and Placebo were set to # Patients and # events for Placebo from Avonex study as no difference is assumed	[1;2;3]
http://protectbenefitrisk.eu/						

FDA Structured Benefit-Risk Framework Table

Benefit-Risk Summary Assessment

Decision Factor	**Evidence and Uncertainties** *Facts and uncertainties + any assumptions on BR*	**Conclusions and Reasons** *The implications of "Evidence and Uncertainties"*
Analysis of Condition	*therapeutic area's current state of knowledge on the severity of the condition*	
Current Treatment Options	*therapeutic area's current state of knowledge on other therapies available to treat the condition*	
Benefit	*product-specific key benefit considerations, including but not limited to clinical trials results, clinical meaning of primary and secondary endpoints, and appropriate analysis of subpopulations*	
Risk	*product-specific key risk considerations, including but not limited to adequacy of the safety database, severity of adverse events, reversibility of adverse events, potential for sub-optimal management in post-market setting*	
Risk Management	*product-specific efforts that could help to mitigate the identified safety concerns, and ensure drug is directed to patients for whom the risk is considered acceptable*	

Source: http://www.benefit-risk-assessment.com/

An Example of a FDA sBR Table

Benefit-Risk Summary Assessment

… The review team found the risk-benefit assessment to be acceptable. This application is supported by the results of two well designed, well controlled, randomized trials of ruxolitinib in patients with MF demonstrating a clinically significant benefit with ruxolitinib. The major side effect of thrombocytopenia can be limited by dose adjustment…

Decision factor	Evidence and uncertainties	Conclusions and reasons
Analysis of condition: MF Clinical manifestations Median survival (all groups)…	Splenomegaly and symptoms… 57 months…	MF is a serious, life-threatening condition in which death is due to evolution into AML (12%), …
Current treatment options Off-label use of interferon-alpha, anagrelide,…	No approved therapy. Allograft is the only curative therapy...	For most patients, there is no curative therapy, and no effective treatment…
Benefit 2 randomized, well controlled trials were conducted…	42% and 29% of ruxolitinib treated patients… >=35% reduction of splenic volume…	… trials met efficacy endpoints… uncertain… benefits will last… toxicity of long-term…
Risk Early deaths… SAEs…	Ruxolitinib arms Not increased Not increased…	Thrombocytopenia was successfully managed by… Anemia was managed by….
Risk management Need of studies for toxicity of long-term therapy	Two phase III trials showed significant benefit and minimal risks… Need PMC for longer term follow-up…	PMR for follow-up… PMC for post-marketing… efficacy and safety outcomes…

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202192Orig1s000ODMemo.pdf

Why create an Effects Table / FDA sBR Table?

- It drives alignment on key benefits and risks
- It clarifies the way to measure and/or present key benefits and risks
- It permits an opportunity to rank key benefits and risks
- It can be used to look for consistency of the benefit-risk ratio across subgroups
- It is an efficient tool to aid communication
- The regulators will be creating one
- It will facilitate internal governance reviews
- It may help in payer discussions

Adapted from http://www.benefit-risk-assessment.com/what-is-this-effects-table-and-why-should-i-create-one/

Notable Aspects of ICH CTD §2.5.6

- Written to be consistent with regulatory post-marketing requirements (e.g. PBRER); creates a continuity
- Utilization of findings beyond traditional “primary study endpoints” (secondary and exploratory endpoints, e.g. convenience or PRO QoL)
- Information about the patient perspective may be considered:
  - May be obtained directly from patients or indirectly from other stakeholders (eg, parents and caregivers) using qualitative, quantitative, or descriptive methods
- An applicant may choose to use methods that quantitatively express the underlying judgments and uncertainties in the assessment. Analyses that compare and/or weigh benefits and risks using the submitted evidence may be presented

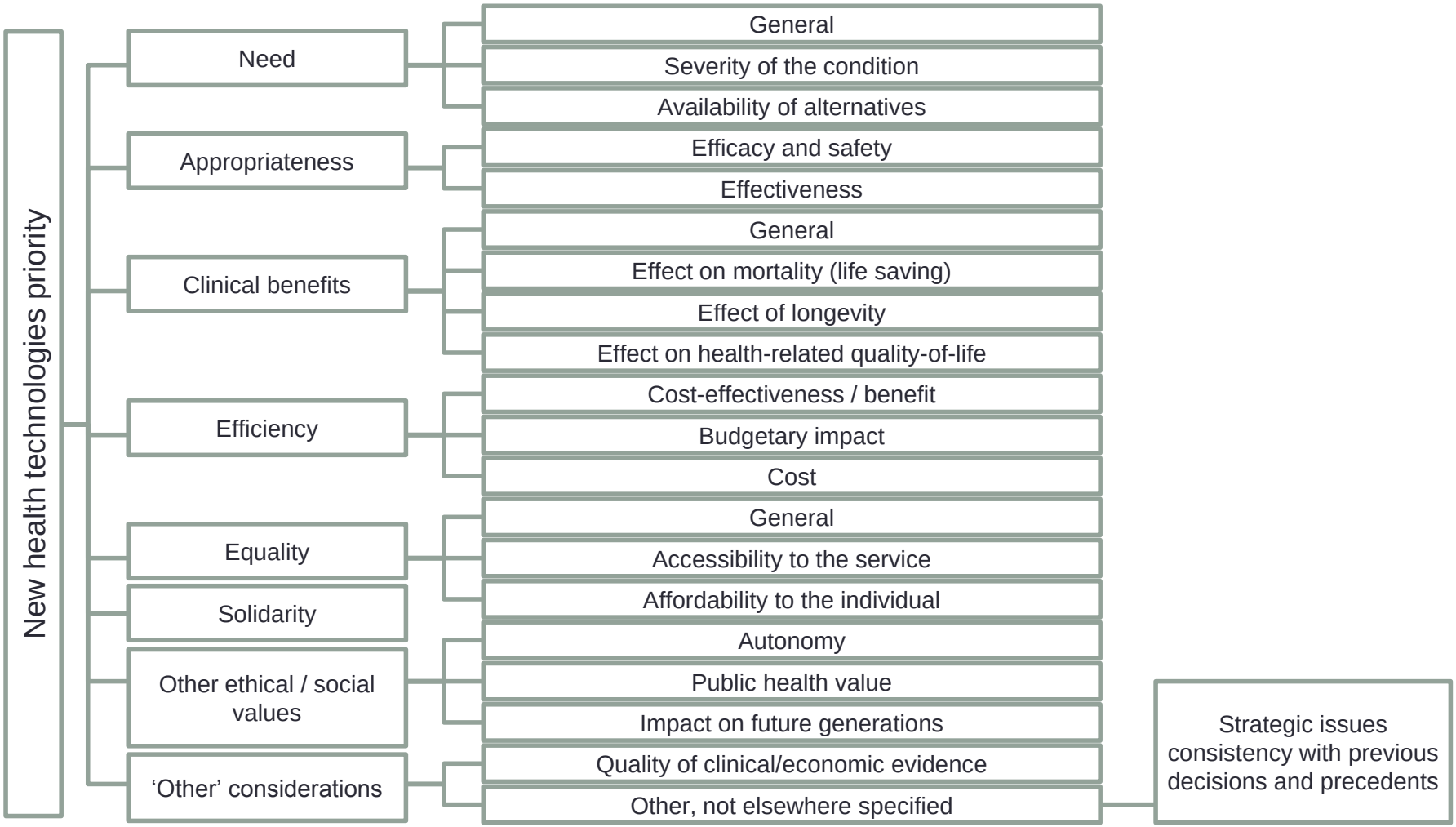
Source: Hammad, T. Overview of Benefit-Risk Assessment in Medical Product Development: Context for Patient Engagement. DIA Pharmacovigilance and Risk Management Strategies. Jan 23-25 2017. Washington DC.

European Commission's view on HTA

- "HTA is way of assessing the ways science & technology are used in healthcare and disease prevention. It covers medical, social, economic, and ethical issues"
- "It provides policy-makers with objective information, so they can formulate health policies that are safe, effective, patient-focused and cost-effective"
- "HTA should be transparent, unbiased, robust and systematic - firmly rooted in research and the scientific method."

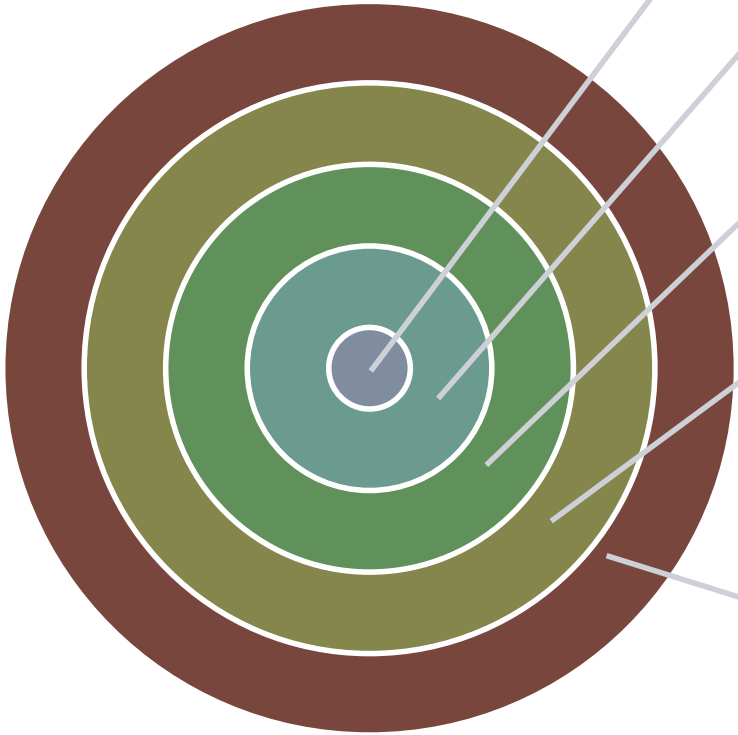
https://ec.europa.eu/health/technology_assessment/policy_en

Considerations in HTA decisions



Golan, *et* al. Health technology prioritization: Which criteria for prioritising new technologies and what are their relative weights? Health Policy 2011. 102(2-3): 126-135. http://dx.doi.org/10.1016/j.healthpol.2010.10.012

(Some of) The Decision-Makers



Patients / Carers

- Make decisions for themselves / patients

Healthcare providers

- Make decisions based on prescribing lists

Health Technology Assessors / Payers

- Make decisions on cost-effectiveness etc.

Regulators

- Make decisions on quality, safety, efficacy and benefit-risk balance to individuals and public health

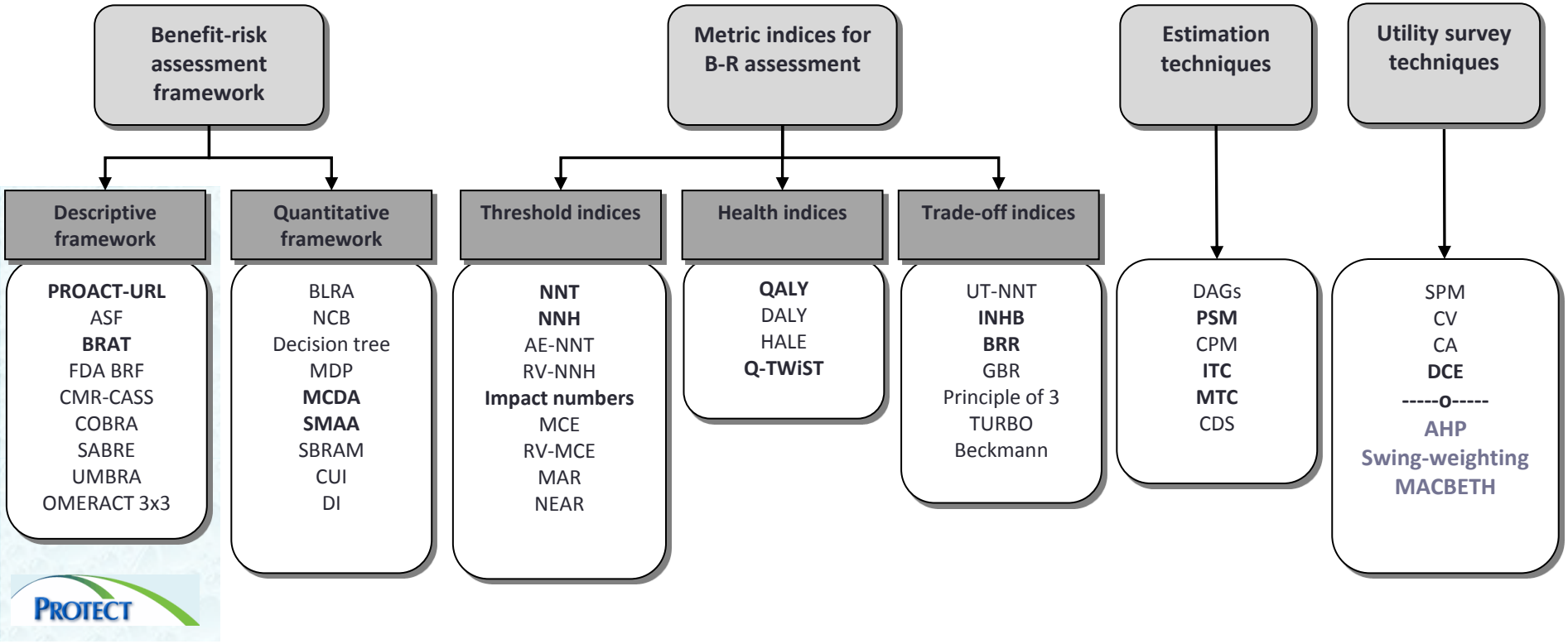
Pharmaceutical companies

- Make decisions on what to develop for which licenses to apply

Adapted from http://www.protectbenefitrisk.eu

METHODOLOGIES AND IMPACT

Taxonomy of BR Assessment Methodologies



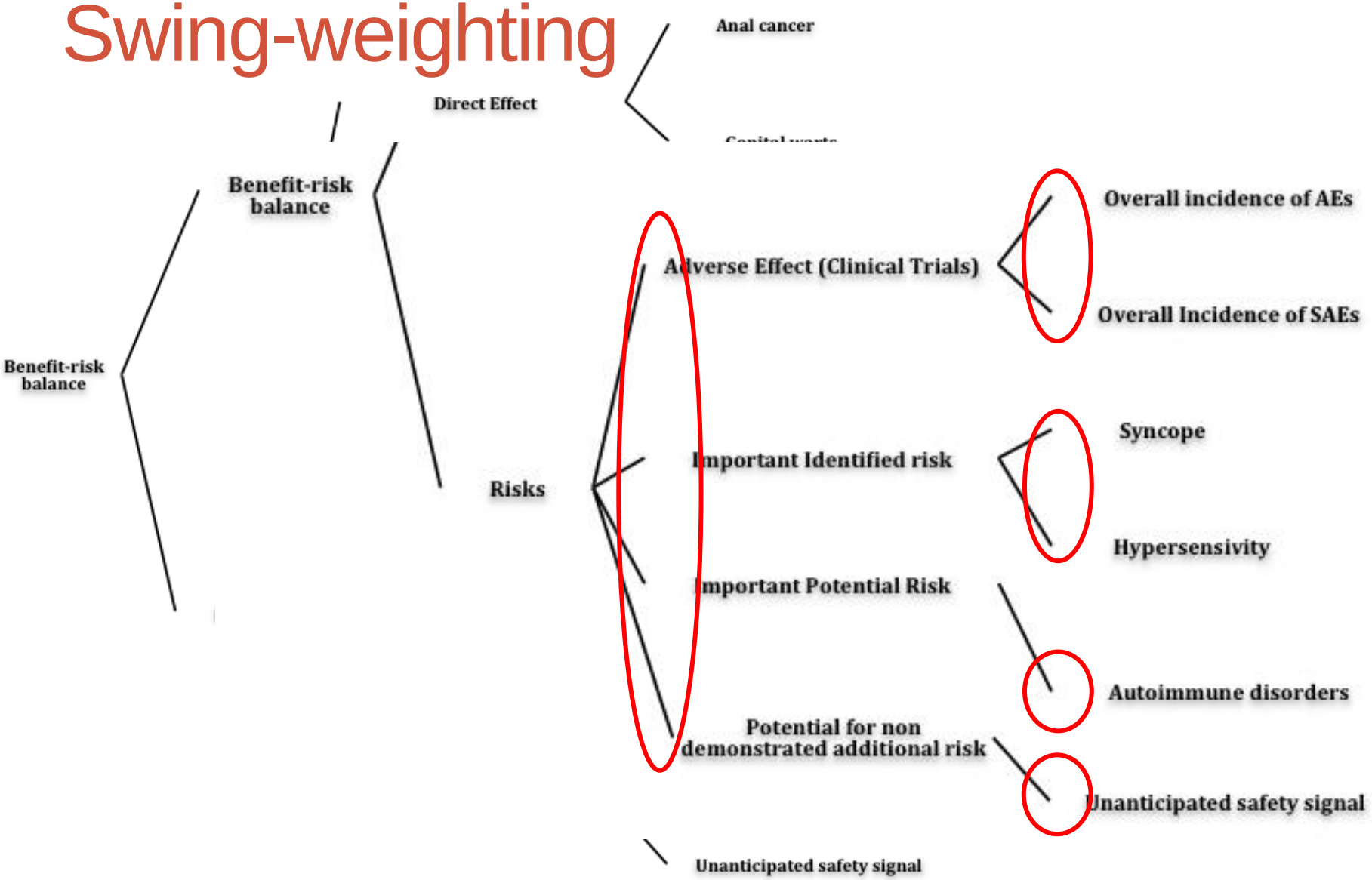
Mt-Isa *et al*. Balancing benefit and risk of medicines: a systematic review and classification of available methodologies. Pharmacoepidemiology and Drug Safety 2014. DOI: 10.1002/pds.3636.
http://protectbenefitrisk.eu/

Ex 1: qHPV Vaccine

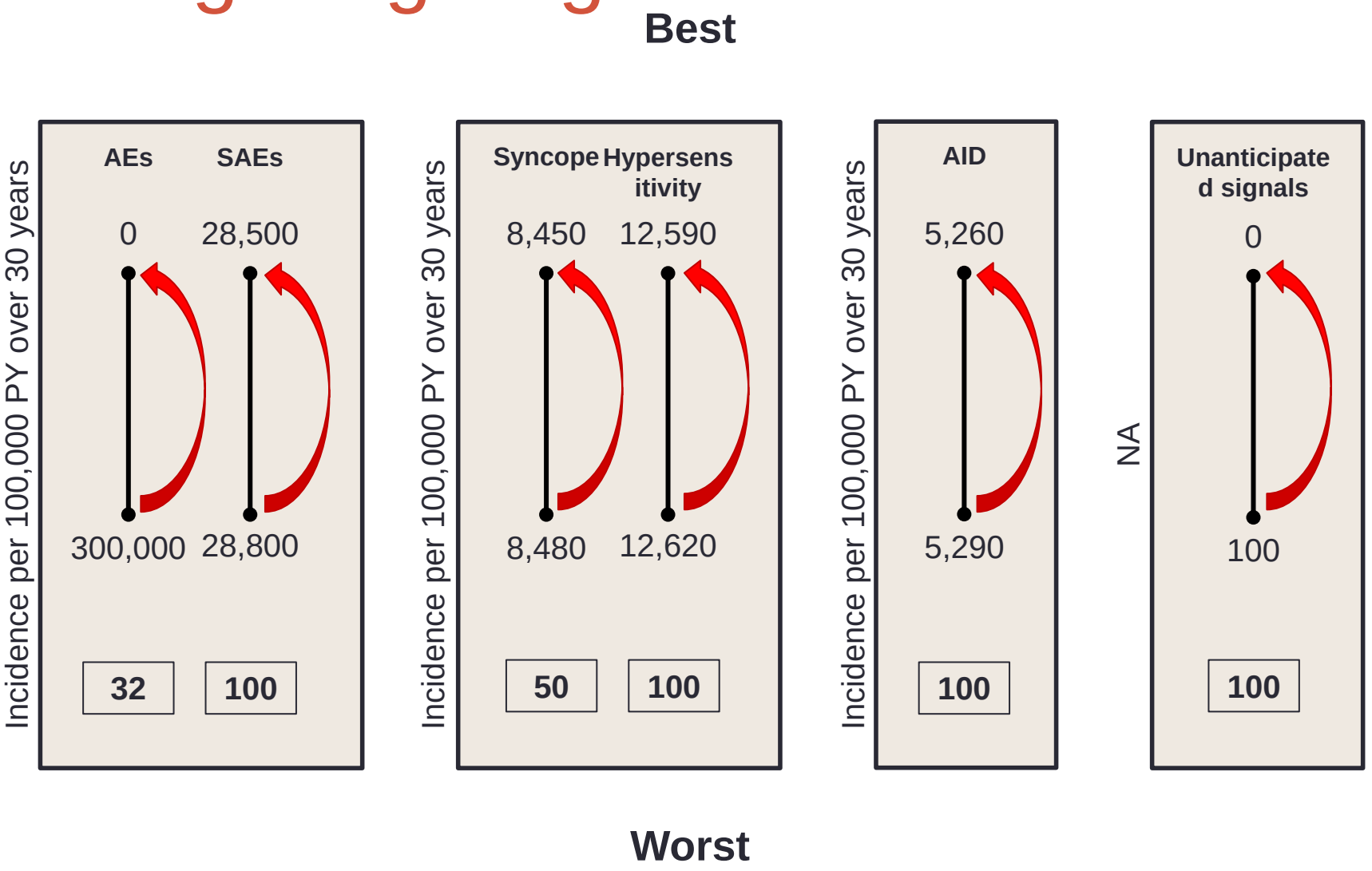
- Provides relative preference weights based on “swing” from worst to best state

- Human papillomavirus (HPV) – SPMSD
- The original HPV vaccines, Gardasil and Cervarix, were licensed in 2006 with an indication for the prevention of HPV-related genital cancers (cervical, vulvar and vaginal), and in the case of Gardasil also genital warts.
- A variation in 2011 requesting to add the anal cancer prevention to the Gardasil SPC for males was refused, mainly in the absence of proven benefits in the general population.

Swing-weighting

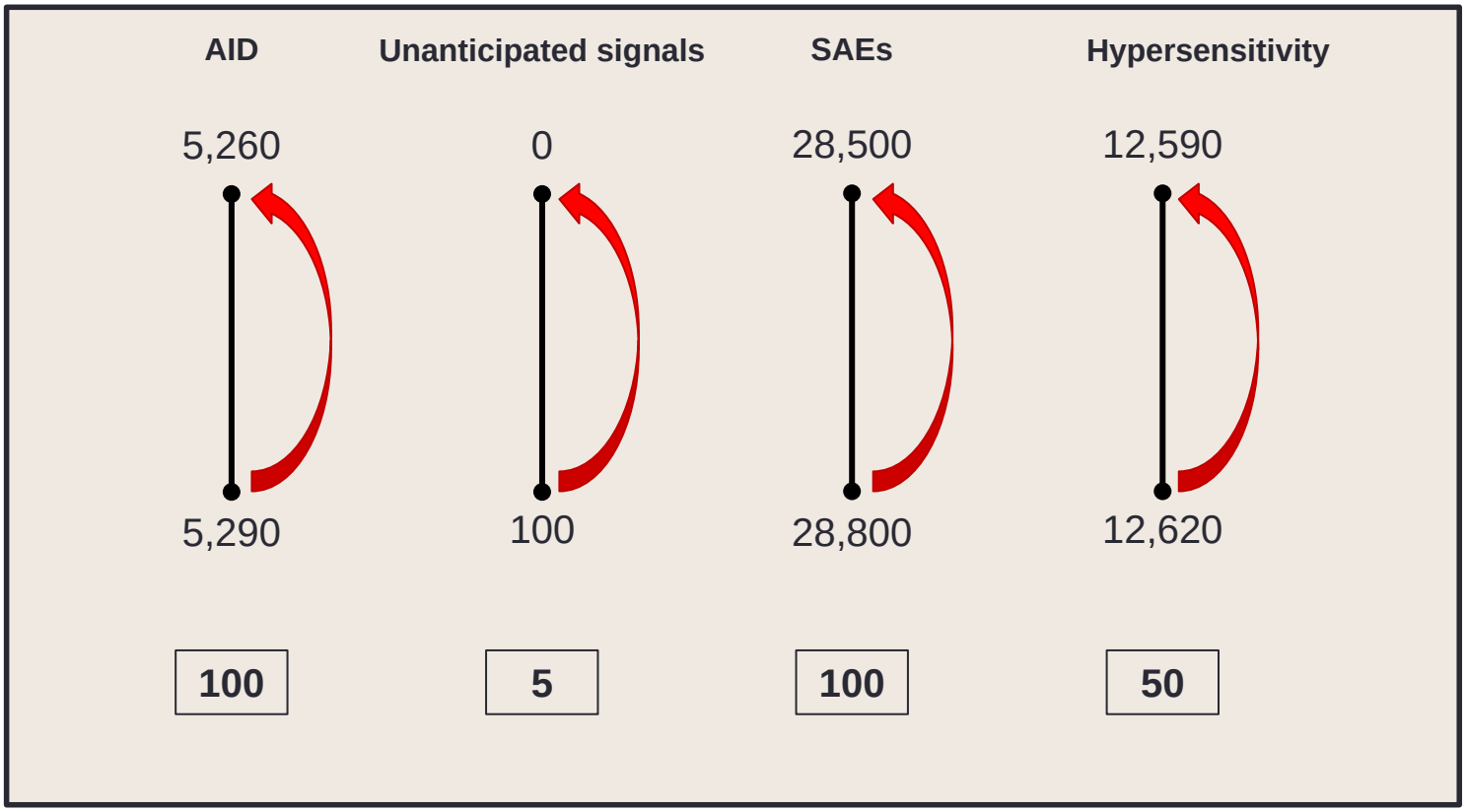


Swing-weighting



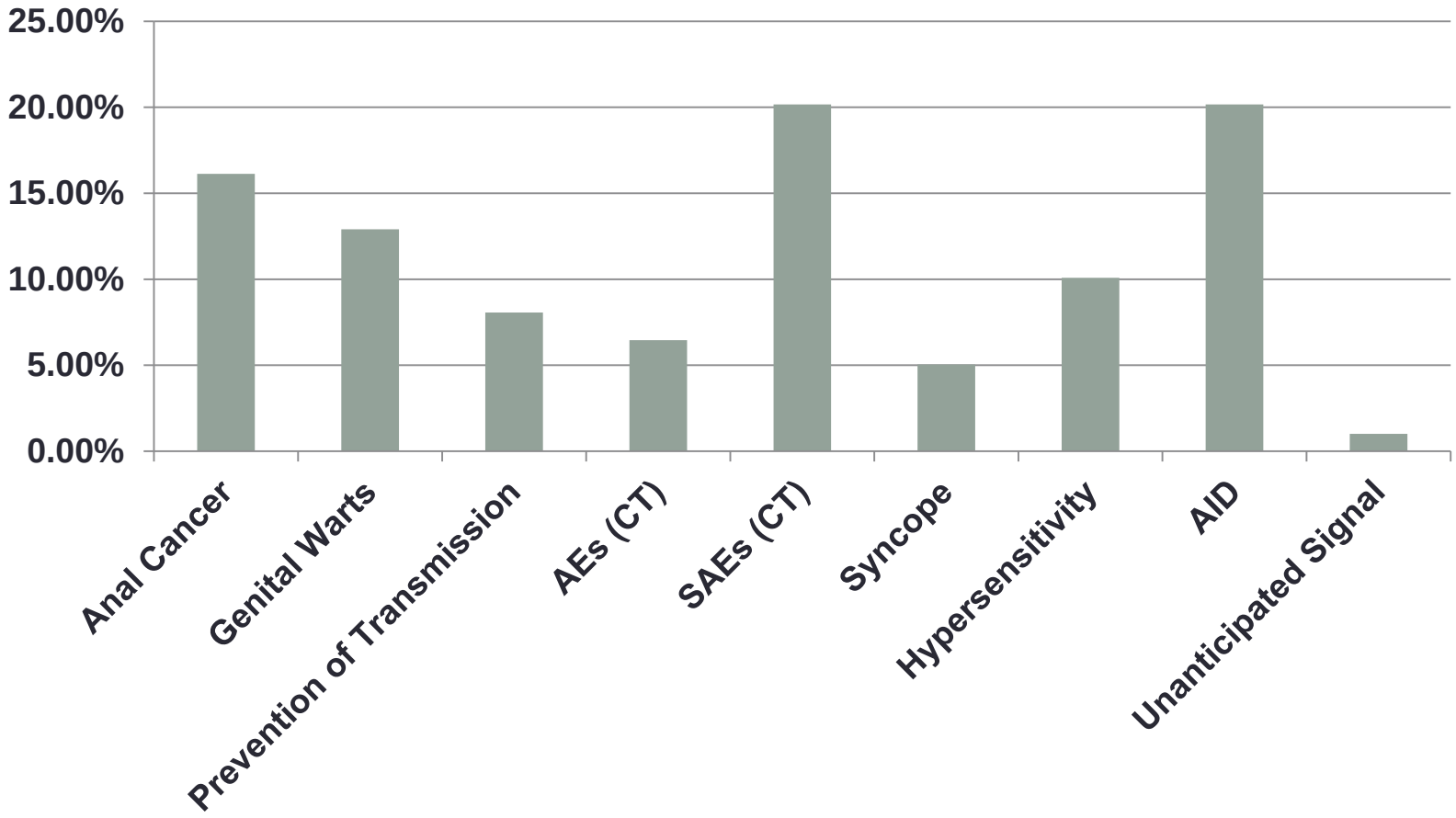
Swing-weighting

Best



Worst

Final Elicited Preference Weights



Lydie Marcelon, Thomas Verstraeten, Geraldine Dominiak-Felden & François Simondon. Quantitative benefit–risk assessment by MCDA of the quadrivalent HPV vaccine for preventing anal cancer in males. Expert Review of Vaccines Vol. 15 , Iss. 1,2016

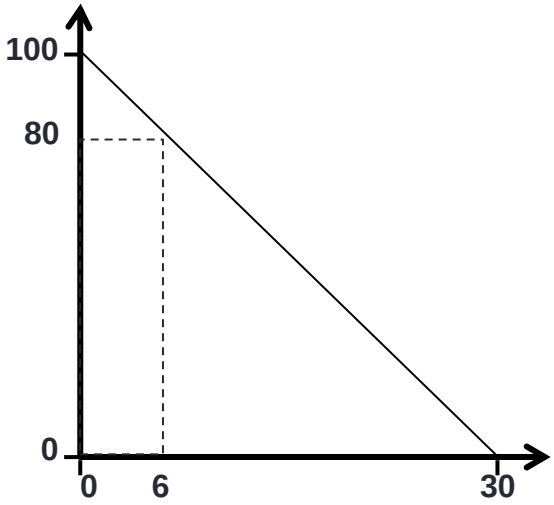
BRA of multiple attributes using MCDA

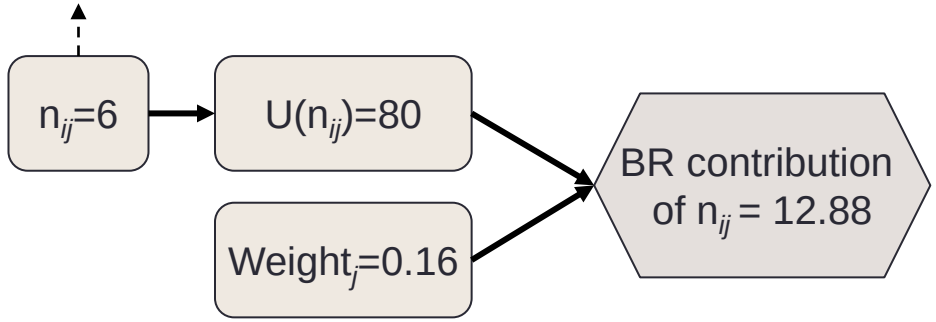
- Common MCDA approaches use multi-attribute value/utility functions to measure overall utility.
- Often, multiple attributes are assumed additive (Preference Independence). Let z_i $(i = 1, \ldots, n)$ be the i^{th} attribute, $v_i(z_i)$ its real value, and ω_i its weight. The overall value is

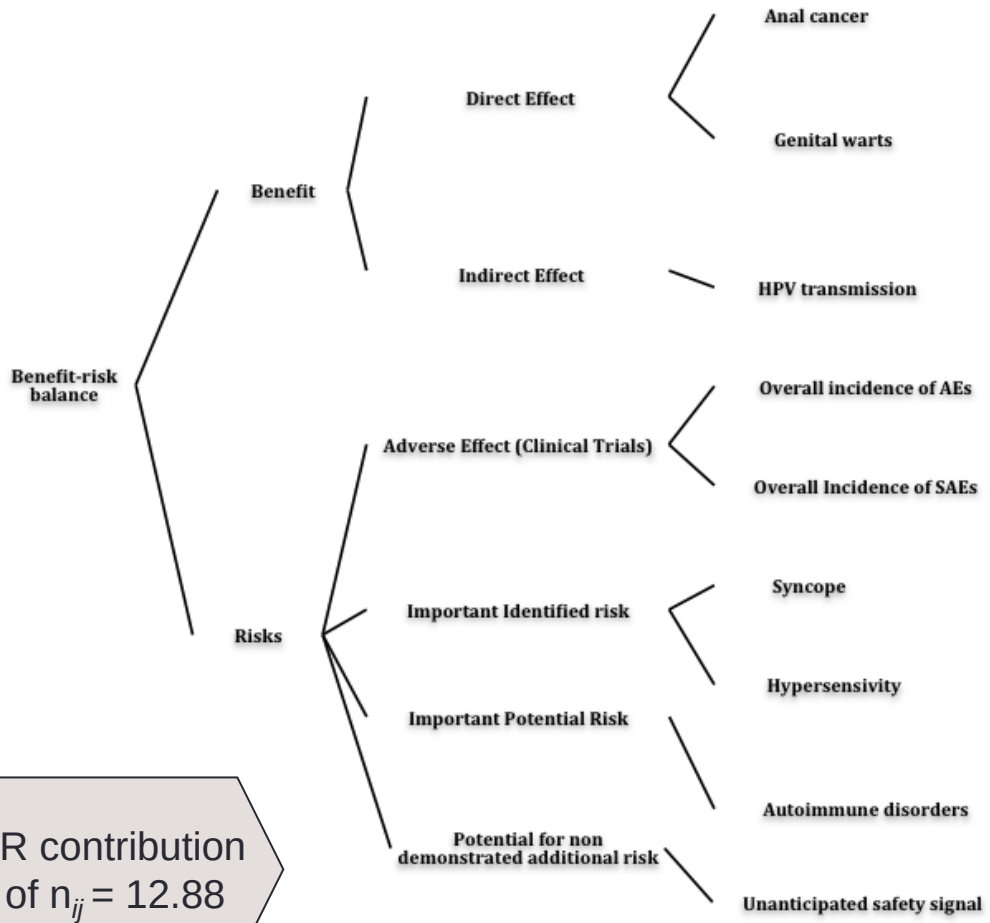
$$\boldsymbol{V(\cdot) = \sum_{i=1}^{n} \omega_i v_i(z_i)} \quad ; \text{where} \sum_{i=1}^{n} \boldsymbol{\omega_i = 1}$$

MCDA and weights

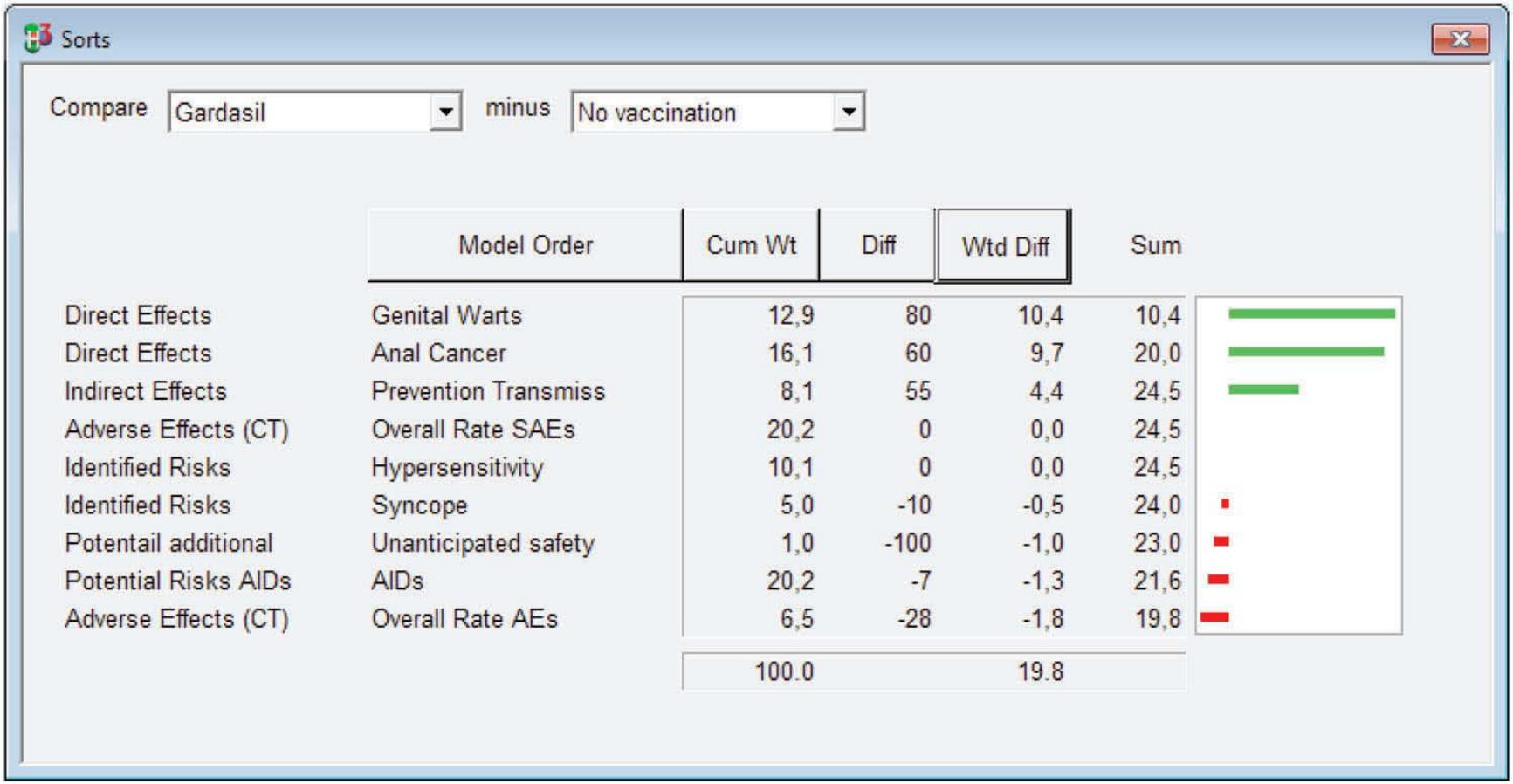
- Partial value function







MCDA: Contribution of criteria to BRA of qHPV vaccine among males



	Model Order	Cum Wt	Diff	Wtd Diff	Sum
Direct Effects	Genital Warts	12,9	80	10,4	10,4
Direct Effects	Anal Cancer	16,1	60	9,7	20,0
Indirect Effects	Prevention Transmiss	8,1	55	4,4	24,5
Adverse Effects (CT)	Overall Rate SAEs	20,2	0	0,0	24,5
Identified Risks	Hypersensitivity	10,1	0	0,0	24,5
Identified Risks	Syncope	5,0	-10	-0,5	24,0
Potentail additional	Unanticipated safety	1,0	-100	-1,0	23,0
Potential Risks AIDs	AIDs	20,2	-7	-1,3	21,6
Adverse Effects (CT)	Overall Rate AEs	6,5	-28	-1,8	19,8
		100.0		19.8	

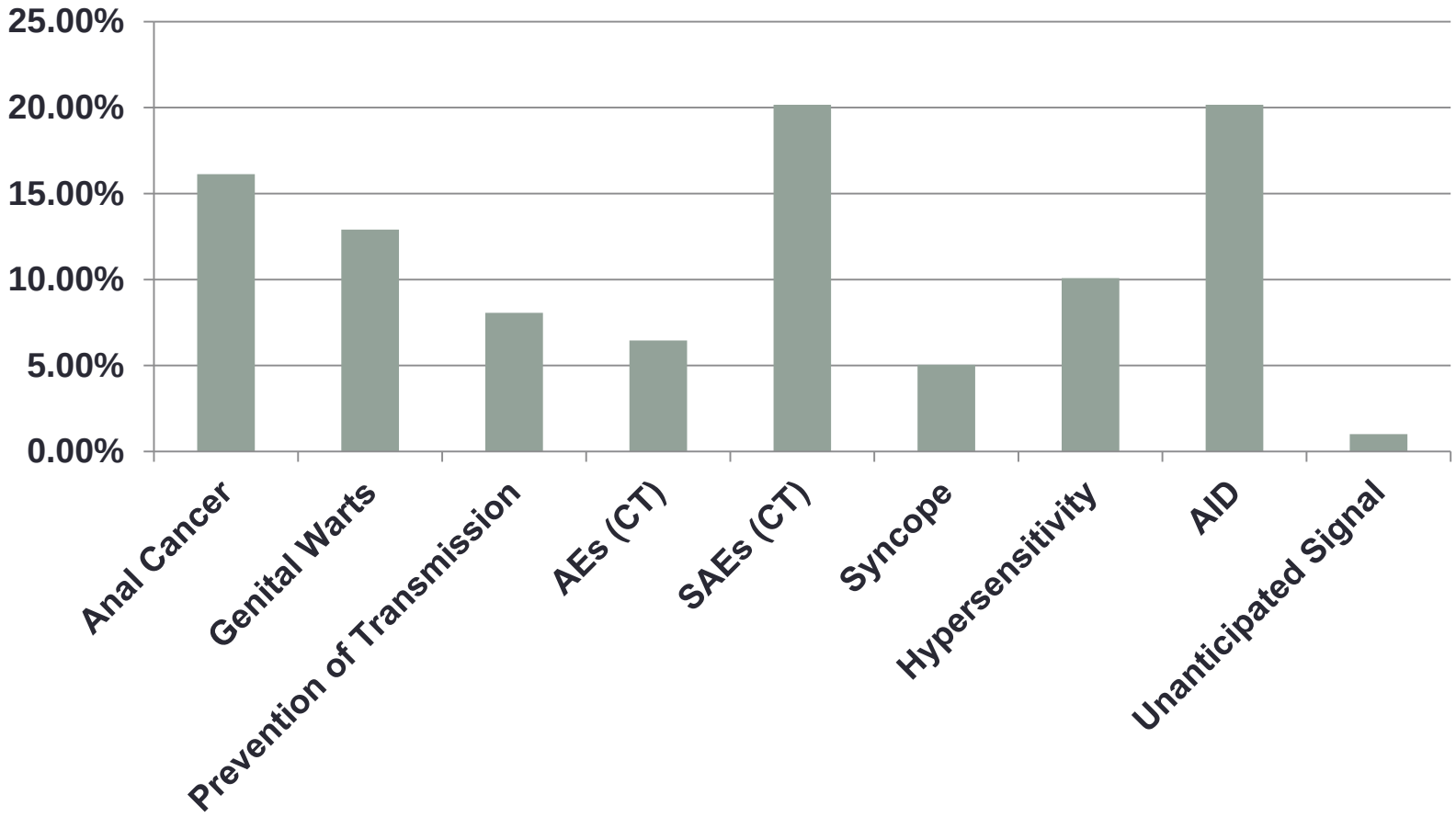
EMA Assessments

2011: "The CHMP concluded that the expected very limited benefit in the general population with respect to prevention of anal cancer is not expected to outweigh potential safety issues, therefore the extension of the indication to include premalignant anal lesions and anal cancer was not considered as approvable."

2014: "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. It was noted that subjective assessments are also needed."…"Overall, the MCDA analysis was considered of interest. The model has been discussed in the Benefit-risk methodology project Work package 2 report, issued by EMA. The results appear to be consistently in favour of qHPV vaccine over no vaccination using several different sensitivity analyses."

EMA assessment report EMA/653012/2011, EMA assessment Report EMA/415775/2014

What Do Giving Preference Weights Really Mean?



Ex 2: Natalizumab

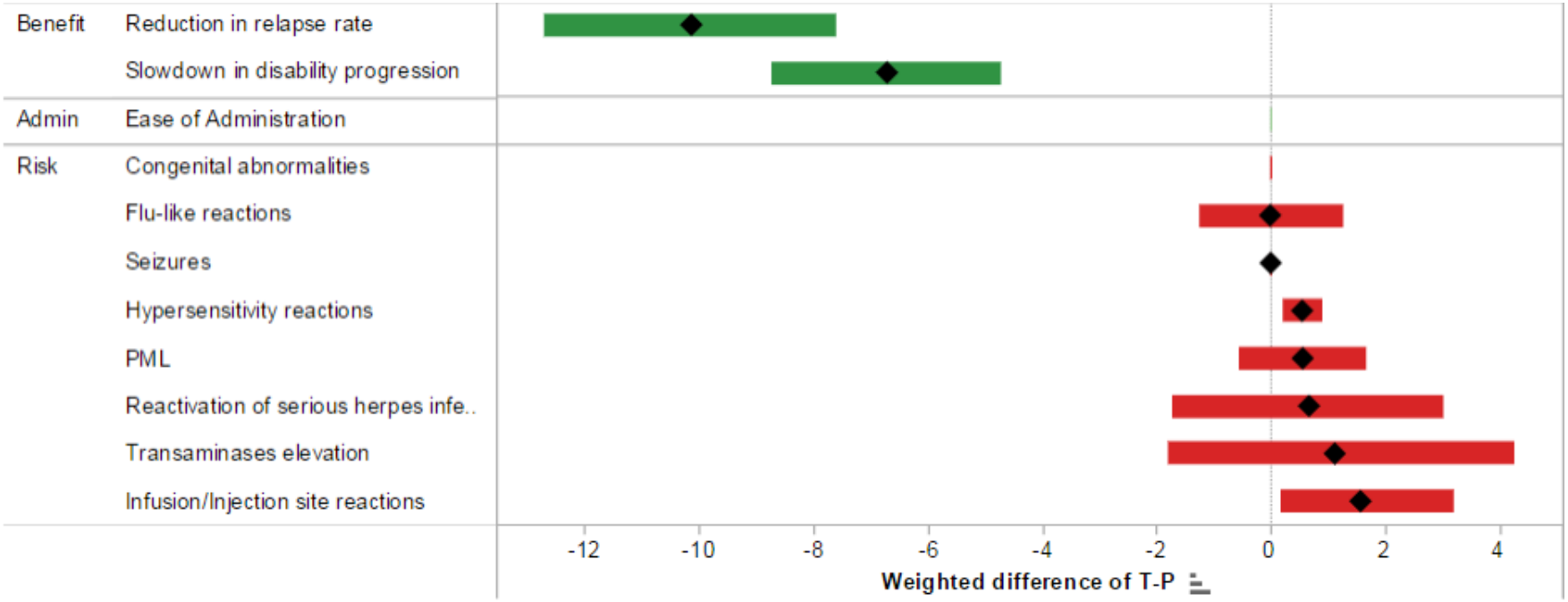
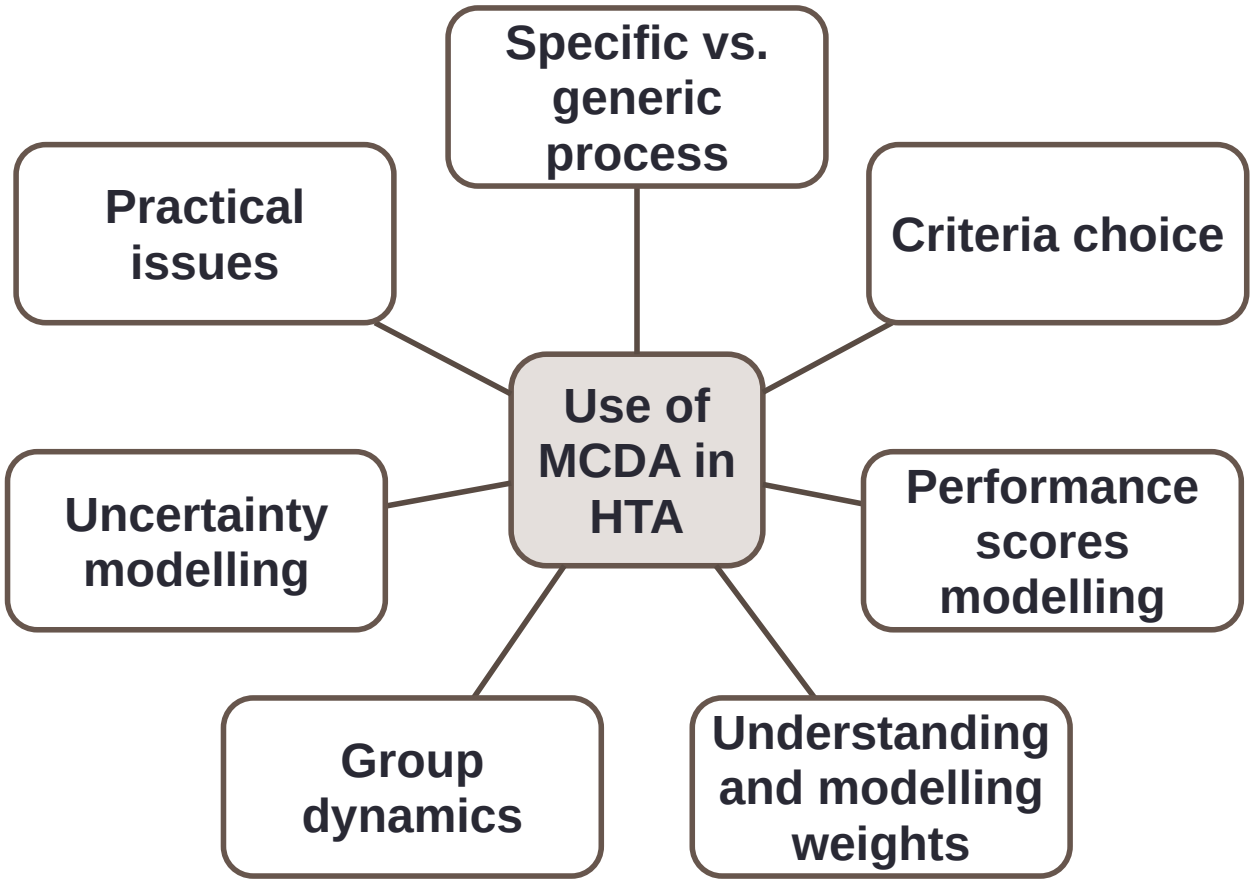


Table: Weighted rates difference

Generic issues with using MCDA

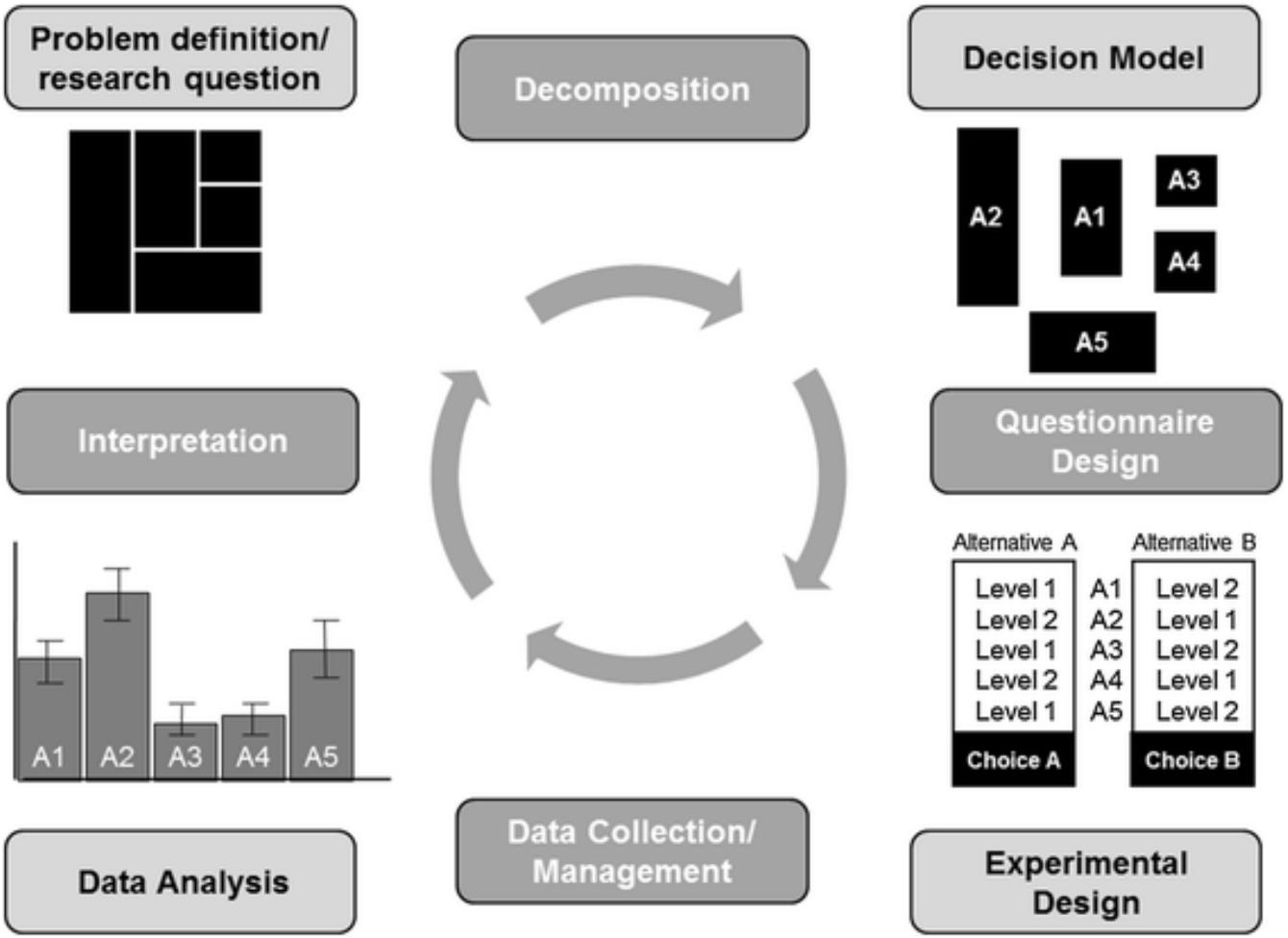


Thokala, P. NICE Decision Support Group (DSU). Multiple Criteria Decision Analysis for Health Technology Assessment. http://www.nicedsu.org.uk/MCDA%20for%20HTA%20DSU.pdf

Thoughts on Swing-Weighting

- Easy to implement
- Ensure consistency by design
- May not be very easy to understand
- May require facilitation and/or very clear instructions
  - EMA conducted swing-weighting online and regarded it as feasible and a success
- Other methods are available…

Discrete Choice Experiment

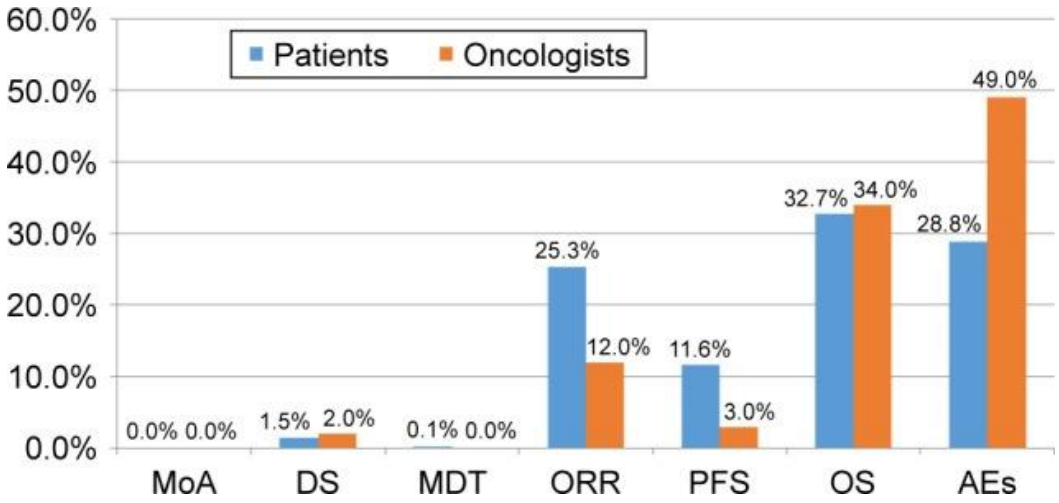


Mühlbacher, A. & Johnson, F.R. Appl Health Econ Health Policy (2016) 14: 253. https://doi.org/10.1007/s40258-016-0232-7

Ex 3: DCE in Advance Melanoma

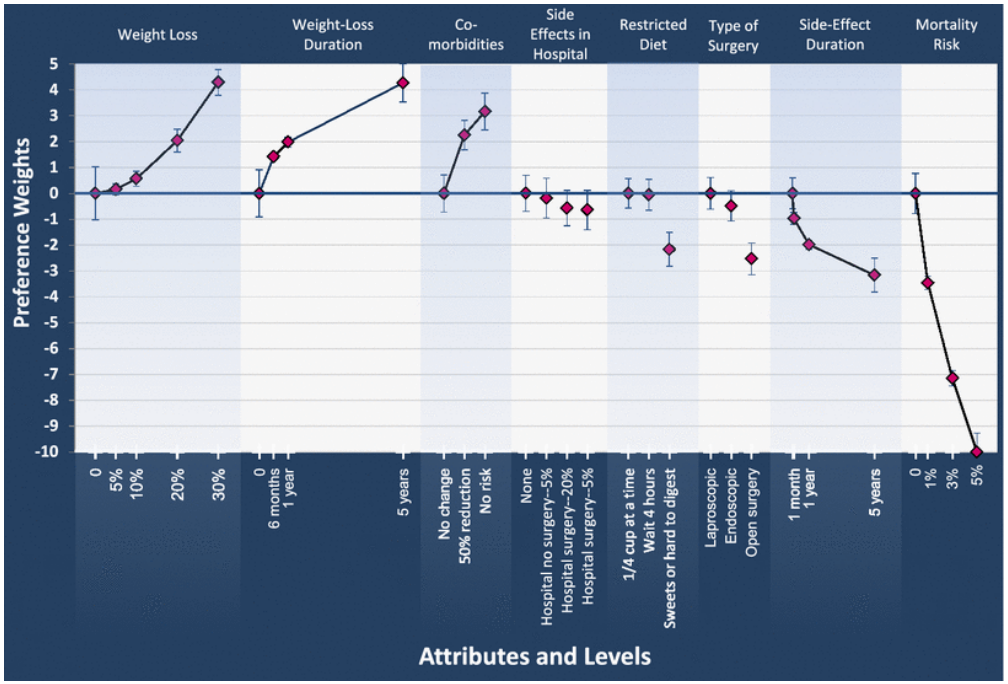
Patient profile
Under 65 years of age
ECOG PS 2
Few manageable co-morbidities (eg, hypertension)
BRAF wild-type
LDH level normal
Low tumor burden
Patient seeks aggressive treatment, able to accept/deal with side effects

Attribute	Medicine A	Medicine B
Mode of administration	IV	IV
Dosing schedule	One medicine taken by 30-minute infusion every 3 weeks	One medicine taken by 60-minute infusion every 2 weeks
Median duration of therapy	3 months	8 months
Objective response rate (ORR)	15%	33%
Progression free survival (PFS)	3 months	5 months
Overall survival (OS)	45% of patients survive to 12 months	55% of patients survive to 12 months
Grade 3/4 toxicities/adverse events	10%	55%
Select only one	**Medicine A**	**Medicine B**
If these were the only medications available to you for **first line** prescribing for this patients with advanced (unresectable/metastatic) melanoma, which **one** would you choose?	❑	❑



Liu, Frank Xiaoqing et al. "Patient and Oncologist Preferences for Attributes of Treatments in Advanced Melanoma: A Discrete Choice Experiment." *Patient preference and adherence* 11 (2017): 1389–1399. *PMC*. Web. 10 Nov. 2017.

Ex 4: DCE in Weight-Loss Devices in Obese Respondents



- In early 2015, FDA CDRH approved a device to treat obesity that had missed one its co-primary efficacy endpoints
- The approval was in part based on an obesity device patient preference study CDRH had conducted
- Minimum acceptable benefit (MinB) vs. Maximum acceptable risk (MaxR)

Ho, M.P., Gonzalez, J.M., Lerner, H.P. et al. Surg Endosc (2015) 29: 2984.
https://doi.org/10.1007/s00464-014-4044-2

DCE in Weight-Loss Devices in Obese Respondents Example 2

Ho, M.P., Gonzalez, J.M., Lerner, H.P. et al. Surg Endosc (2015) 29: 2984.
https://doi.org/10.1007/s00464-014-4044-2

ISPOR BR Taskforce – Review of BRA

- Good practice guidelines for outcomes research
- Each quantitative method has its unique advantages and disadvantages based on data requirements and statistical properties.
- Methods that incorporate the patient's risk tolerance and preference for health states may represent a promising area
- Limited number of empirical applications of methods
- No consensus for a clear gold standard
- Recommend the use of multiple BR methods across different therapeutic areas and populations

Ref: https://www.ispor.org/workpaper/practices_index.asp
A Review of Quantitative Risk–Benefit Methodologies for Assessing Drug Safety and Efficacy . Report of the ISPOR Risk–Benefit Management Working Group. http://www.ispor.org/workpaper/riskbenefitsmethods/risk_benefit_quantitative_methods.pdf

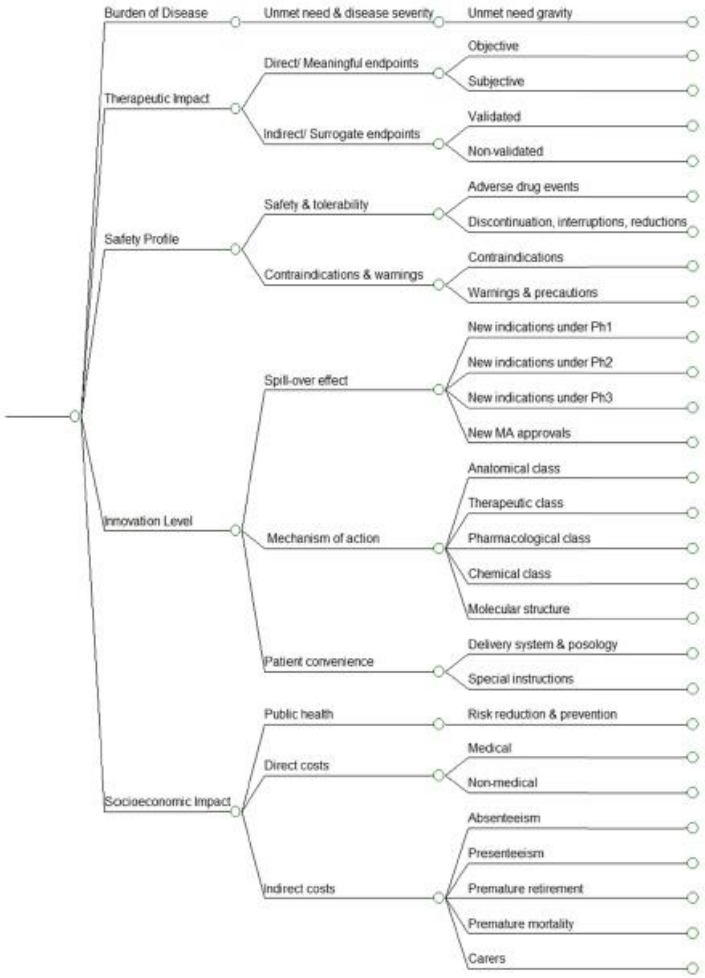
IQWiG

- Institute for Quality and Efficiency on Health Care
- Evaluates BR considering patient relevant endpoints
- Separate efficiency frontiers for each endpoint to be aggregated (by weighting) for evaluation
- Explore methodologies for identification, weighting and prioritisation of multiple patient relevant endpoints
- Pilot multi-attribute stated preference methods Analytic Hierarchy Process (AHP) and Conjoint Analysis (CA) / Discrete Choice Experiment (DCE)
- Currently testing if DCE can be integrated into conventional HTA process

https://www.iqwig.de; https://www.iqwig.de/en/methods/methods-paper.3020.html

The Advance Value Framework

- New value framework for evaluation of new medicines
- Secondary and primary evidence used to identify decision-makers' value concerns
- A generic value tree structured incorporating different evaluation criteria
- MCDA methodology proposed for value judgements and preference elicitation



Aris Angelis, Panos Kanavos, Multiple Criteria Decision Analysis (MCDA) for evaluating new medicines in Health Technology Assessment and beyond: The Advance Value Framework, In Social Science & Medicine, Volume 188, 2017, Pages 137-156, ISSN 0277-9536, https://doi.org/10.1016/j.socscimed.2017.06.024

Industry/Regulatory/HTA Activities

- EMA Effects table and FDA sBR table
- BR methodologies such as MCDA
- Interactive tools for exploring BR balance including visual analytics
- Patient engagement and patient preferences methodologies
- Knowledge generation and transfer
- Monitoring updates on guidance and requirements
- HTA links

Summary

- Methodology selection is not straightforward
- “No one-size-fits-all” method, and no restriction on using only one method per assessment
- The importance is to be transparent
  - Methodologies and evidence used must be defensible
  - Key benefits and key risks considered and why
  - Not just perspective but also appropriate comparators
  - Being quantitative can be more objective
- Methodologies are **tools to support** decision-making

THANKS

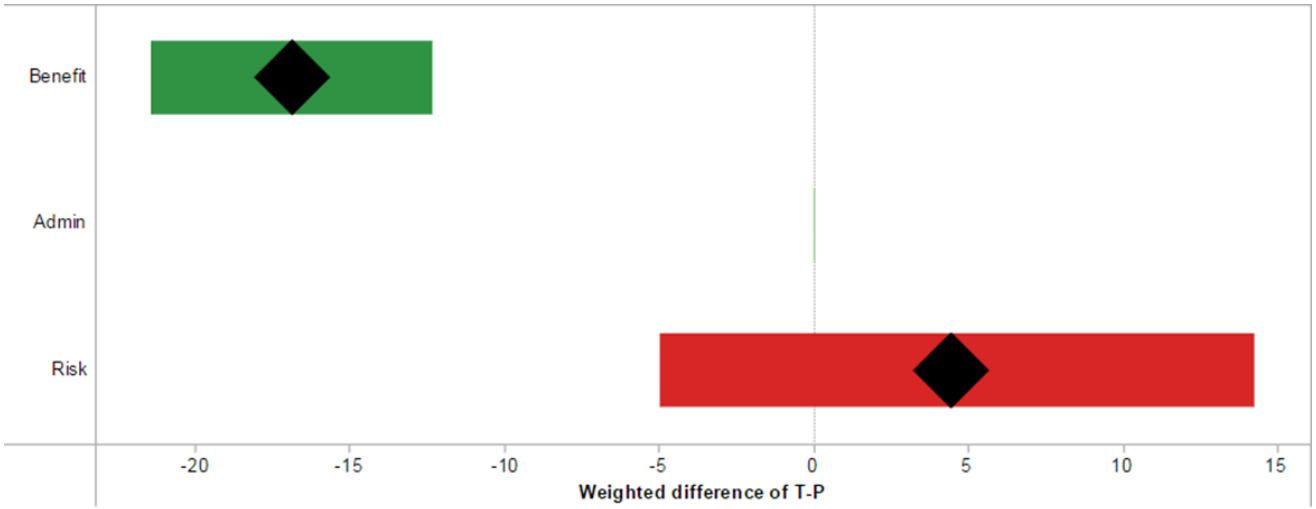
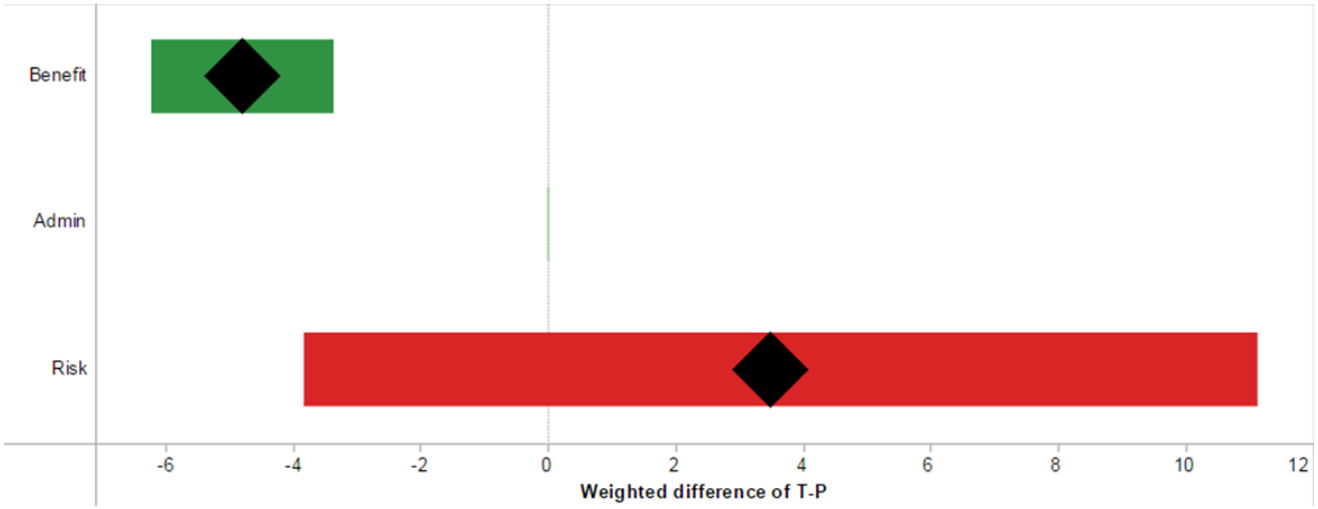


Table: Weighted rates difference



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