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Current practices and gaps in benefit-risk assessment: Opportunities for combining MCDA with model-based approaches

Kevin Marsh, PhD

Presenter

Kevin Marsh, PhD

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- Director of patient preference and multi-criteria decision analysis (MCDA) teams
- Co-chair of International Society for Pharmacoeconomics and Outcomes Research (ISPOR) MCDA Good Practices Task Force

Objectives

- Illustrate how quantitative BRA is undertaken by industry to demonstrate the value of technologies.
- Illustrate how quantitative BRA can be incorporated into model-based approaches to trial design.
- Identify the challenges, and potential solutions to using quantitative BRA to inform trial design.

Clarification on terminology

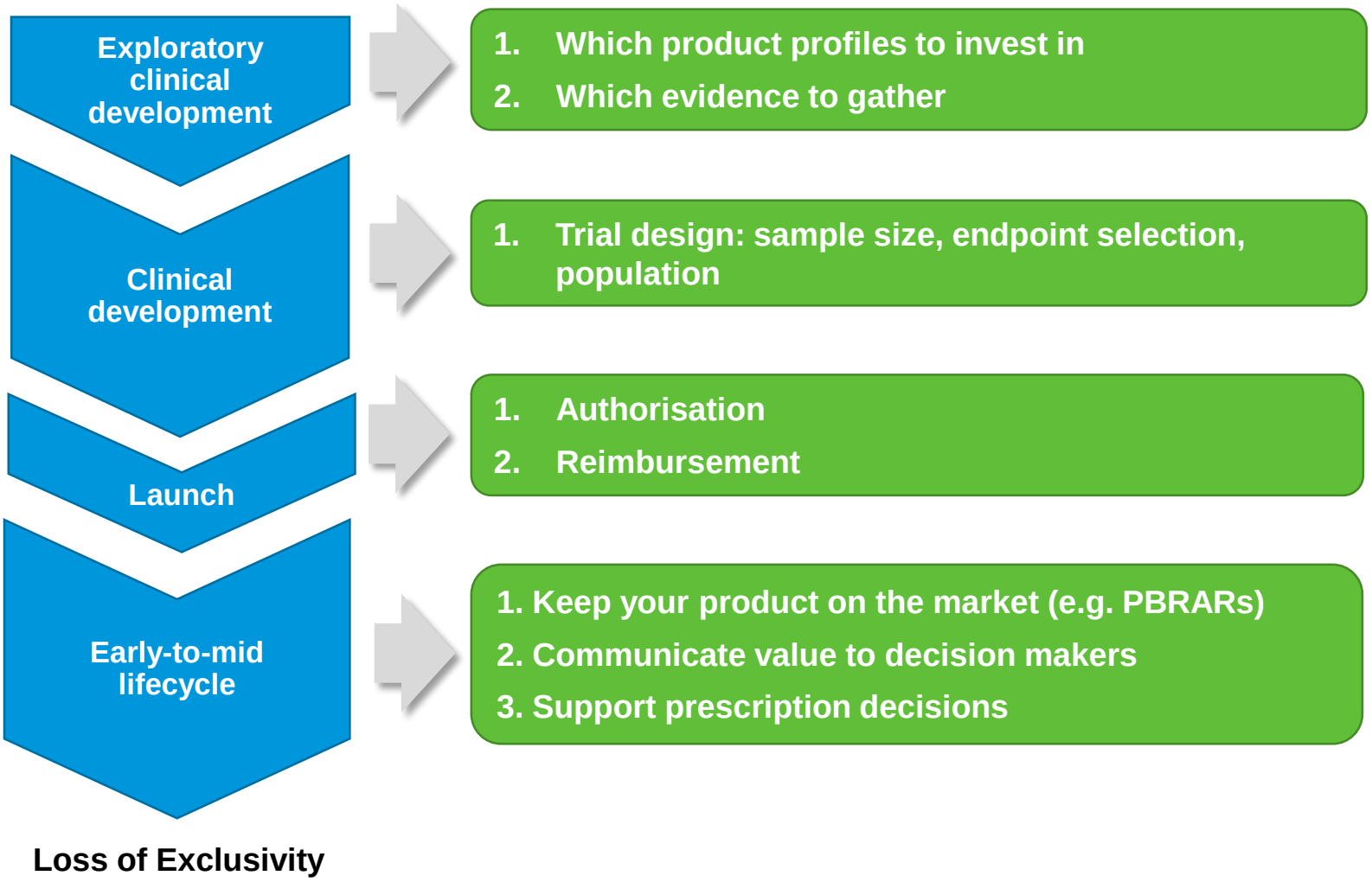
- **Quantitative BRA = MCDA with preferences elicited by any method (that correspond with the axioms of utility theory)**
  - Direct methods e.g. swing weighting
  - Indirect methods ('stated preference') e.g. discrete choice experiment

Web-Based Discrete Choice Experiment

Attribute	Option A	Option B
Clinical Benefit	5 out of 100 patients achieve a clinical improvement	20 out of 100 patients achieve a clinical improvement
Adverse Event	2 out of 100 patients have an adverse reaction	10 out of 100 patients have an adverse reaction
Convenience	No impact on daily life	Significant impact on daily life
Which treatment would you choose?	☐	☒

When is quantitative BRA useful?

BRA Throughout the Drug Lifecycle



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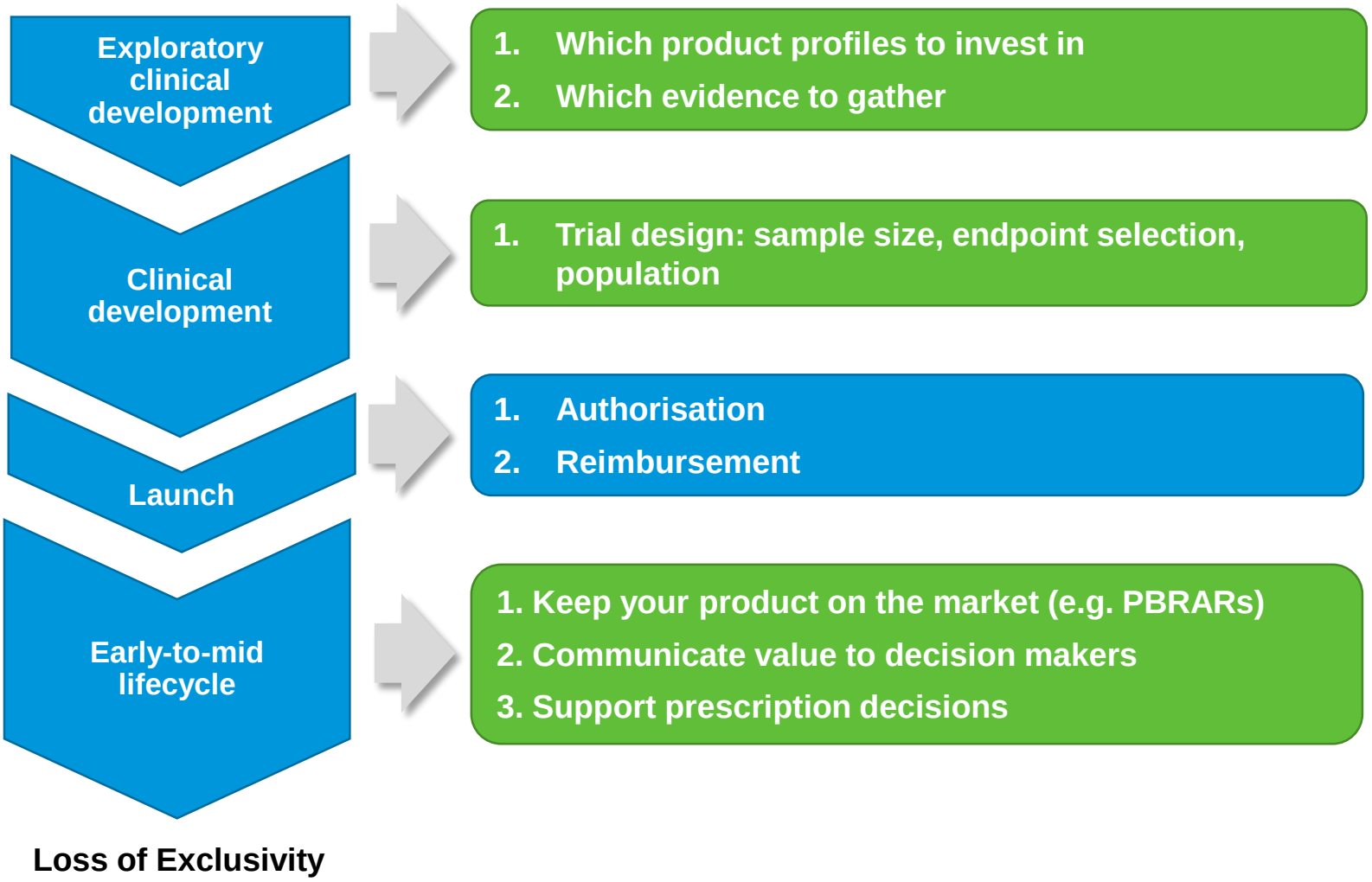

Quantitative BRA

Current Regulatory Opinion – FDA (CDRH)

- **Approved a weight-loss device with an increased r**
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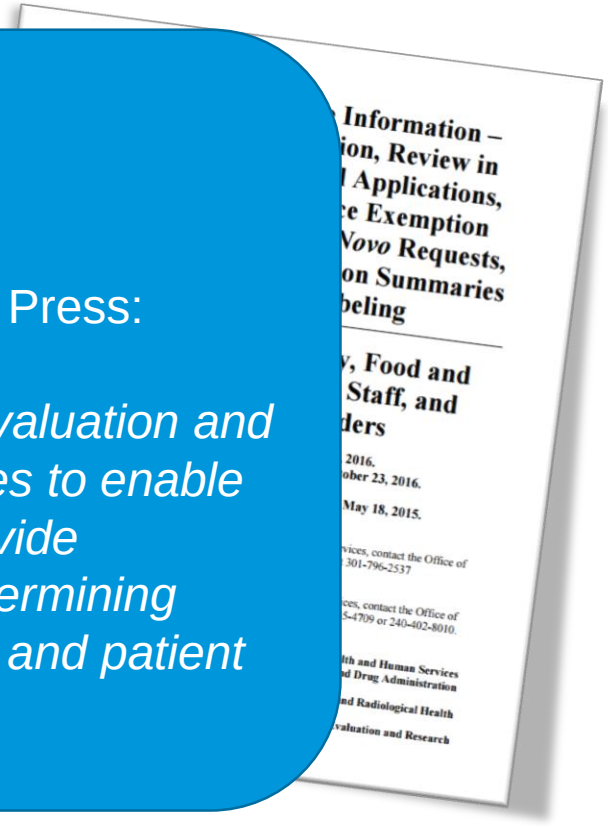
Similar signals from CDER teams

e.g. Miller and Woodcock, Value in Health, In Press:

"In the near future, CDER [Centre for Drug Evaluation and Research] plans to issue a series of guidances to enable patient groups, and others, to collect and provide structured input on patient preferences in determining benefit-risk trade-offs, the burden of disease, and patient assessment of present treatments…."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Quantitative BRA

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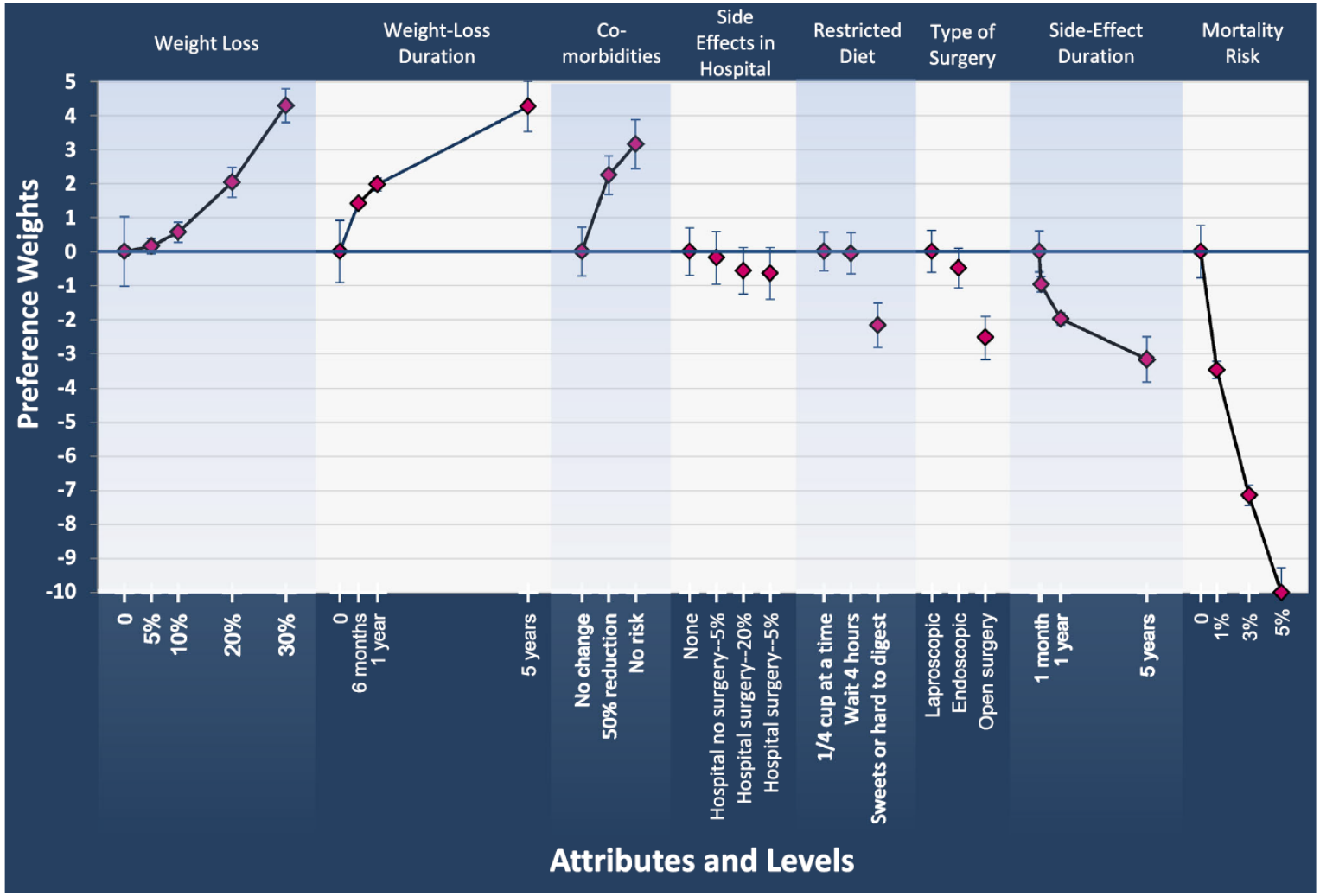
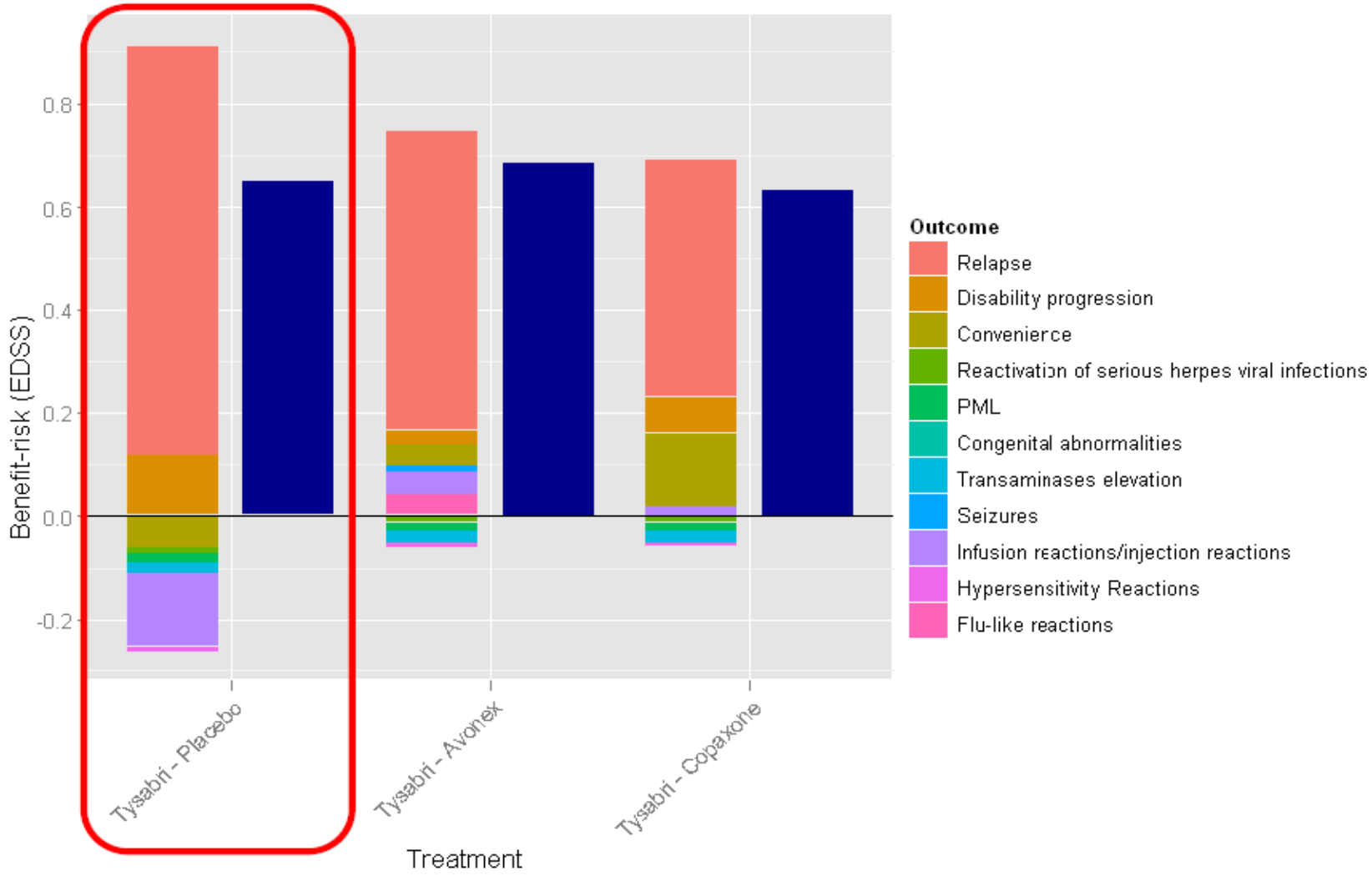


Source: Ho, et al. *Surg Endosc* 2015

Does a treatment have a positive BR balance?

Benefit-risk MCDA of Tysabri versus Comparators



What is the probability that a treatment has a positive BR balance?

Stochastic Multi-criteria Acceptability Analysis

$$v(x) = \sum_{k=1}^{n} w_k \cdot v_k(x_k)$$

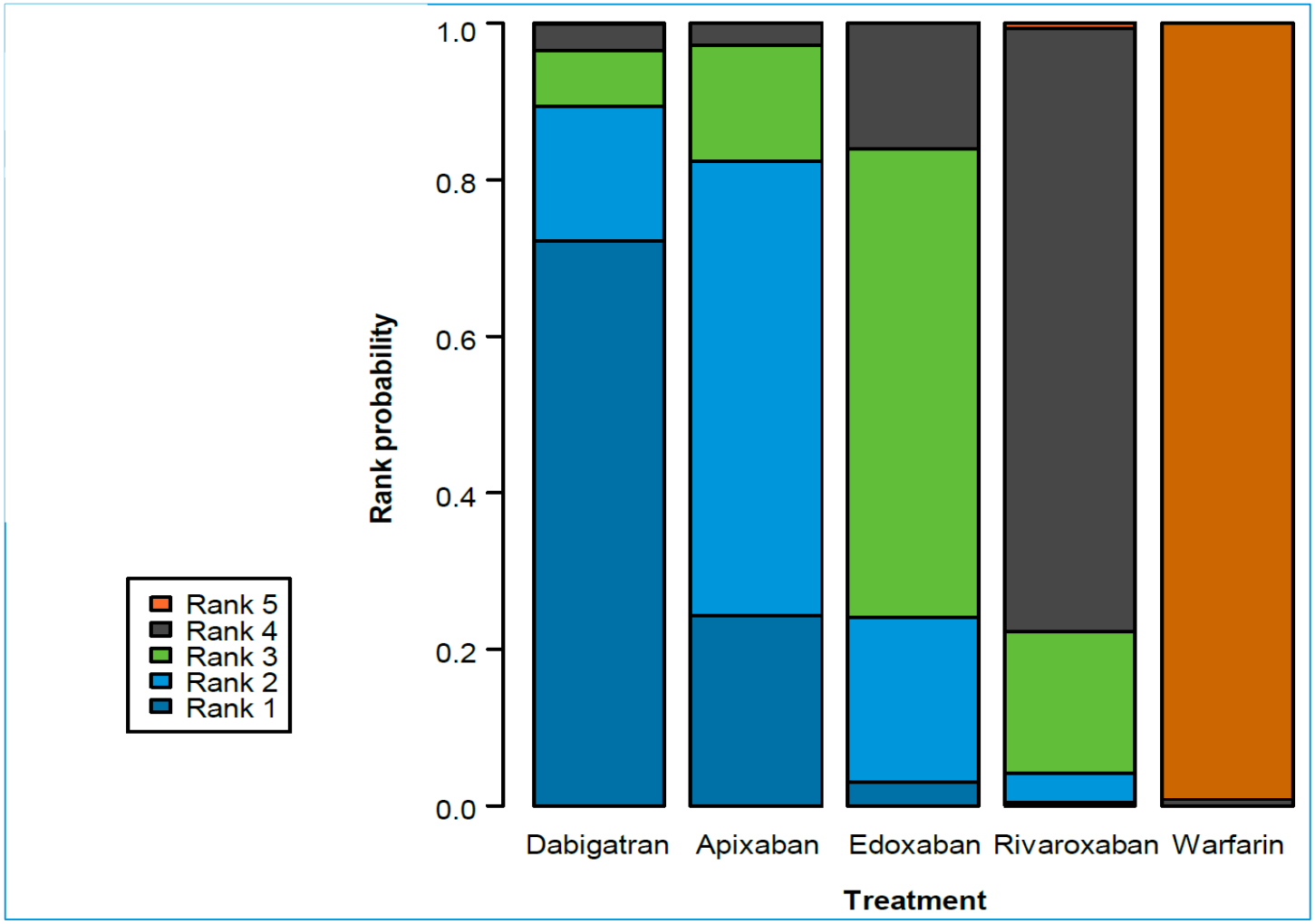
Sample x 10,000

Sample x 10,000

- **Draw weight and performance samples, and in each iteration:**
  1. Calculate v(x) for each treatment
  2. Rank treatments in descending order according to v(x)
- **Then, estimate rank probabilities as shares of iterations in which the treatment obtained the rank**

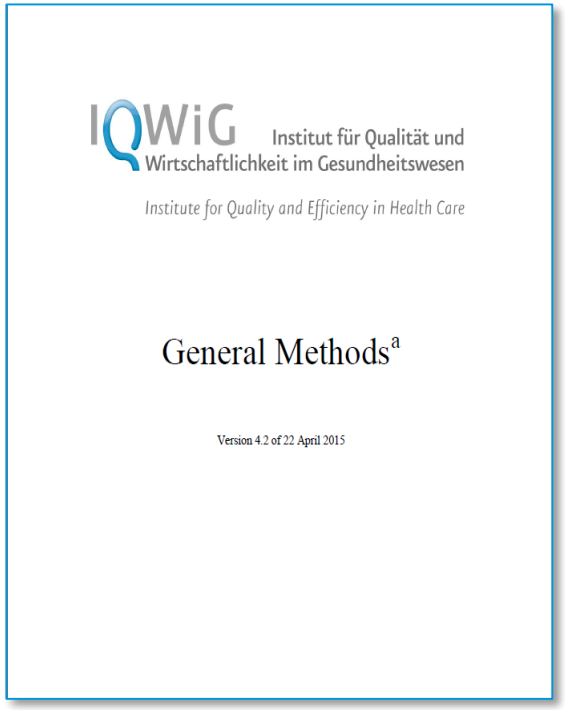
What is the probability that a treatment has a positive BR balance?

Stochastic Multi-criteria Acceptability Analysis



qBRA in HTA

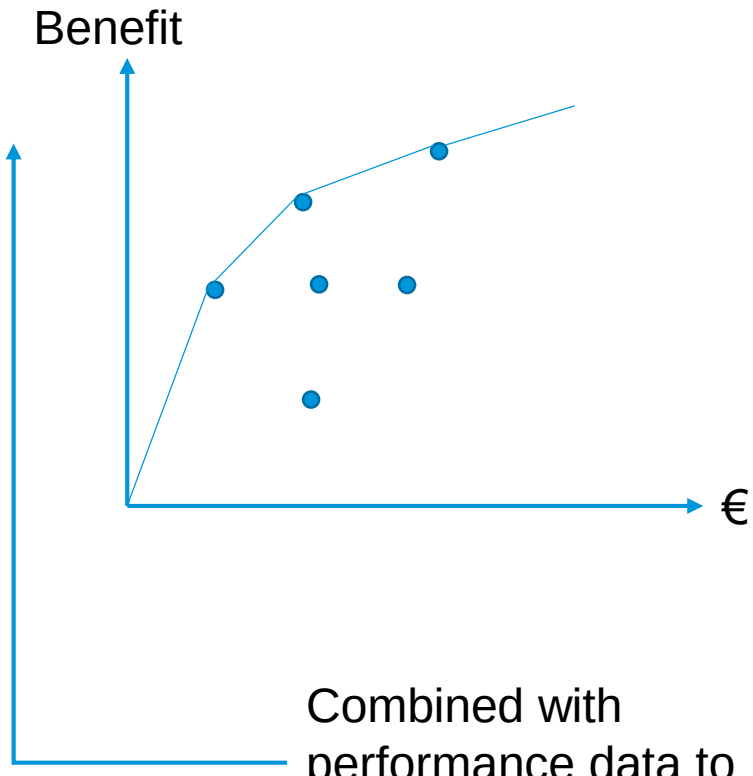
IQWiG General Methods Guide v4.2



- If a measure of overall benefit for the comparison of interventions is to be determined […] *procedures for multi-criteria decision-making or determining preferences can be applied*……the analytic hierarchy process (AHP) and the conjoint analysis (CA)

qBRA in HTA

Is a treatment on the efficiency frontier?

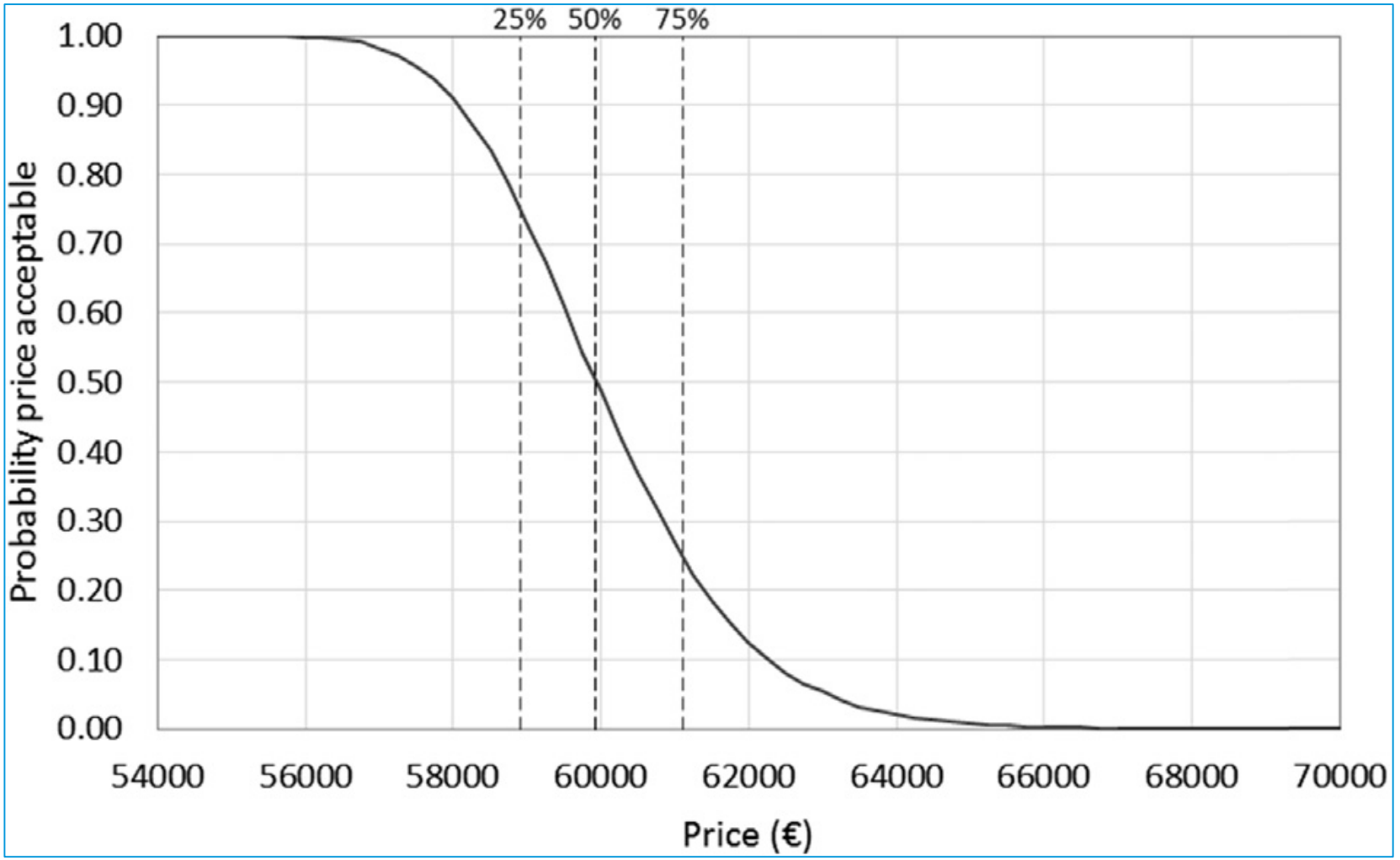


Patient-relevant outcome measure	Group priority Patients	Group priority Professionals (position in rank order)
Response	0.324	0.061 (5)
Improvement of cognitive function	0.125	0.062 (4)
Reduction of anxiety	0.118	0.054 (6)
Improvement of social function	0.107	0.090 (3)
Avoidance of relapse	0.091	0.144 (2)
Remission	0.085	0.475 (1)
Reduction of pain	0.054	0.033 (7)
No other serious adverse events	0.039	0.029 (8)
No (attempted) suicide	0.026	0.022 (9)
No other adverse events	0.023	0.020 (10)
No sexual dysfunction	0.007	0.007 (11)

Combined with performance data to estimate aggregate benefit

qBRA in HTA

What is the probability that a treatment is on the efficiency frontier?



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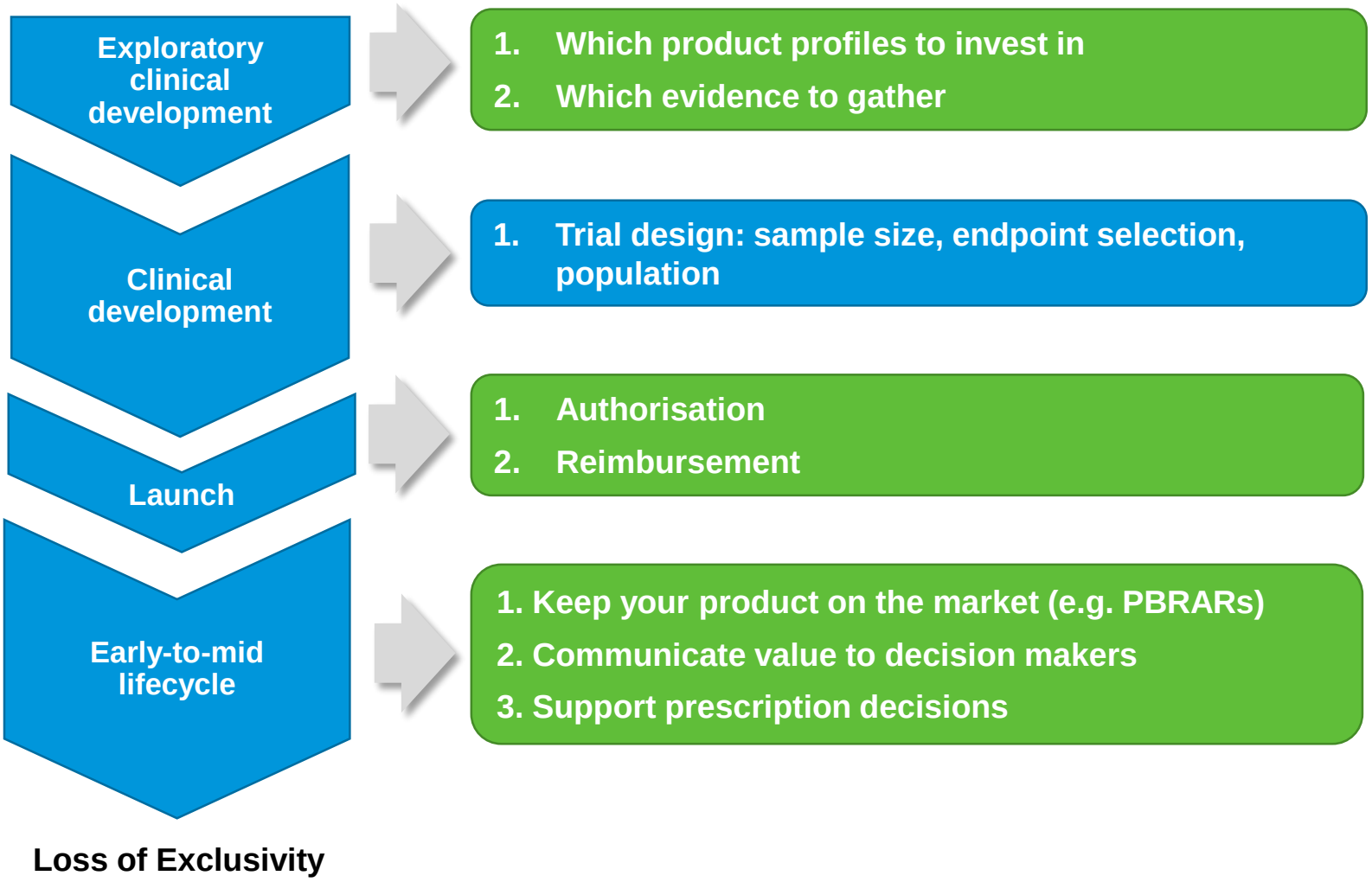


qBRA to support trial design

An input into trial simulation

- Objective:
  - Understand the likely impact of trial design scenarios
  - Lower development costs, improve the chance of ‘success’

	Sample size	Dose	Population	Etc….
Strategy A				
Strategy B				
Strategy C				

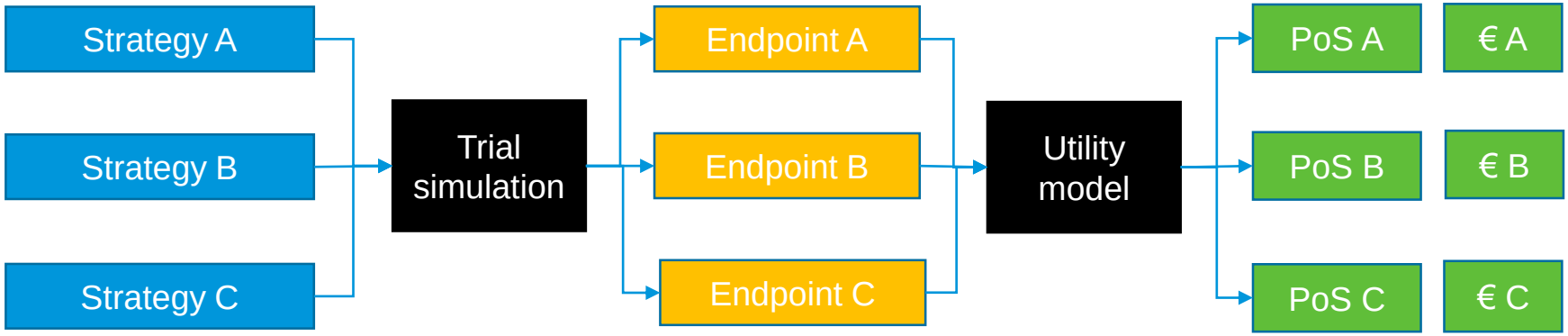
qBRA to support trial design

An input into trial simulation

Strategy

Trial outputs

Evaluation criteria



qBRA to support trial design

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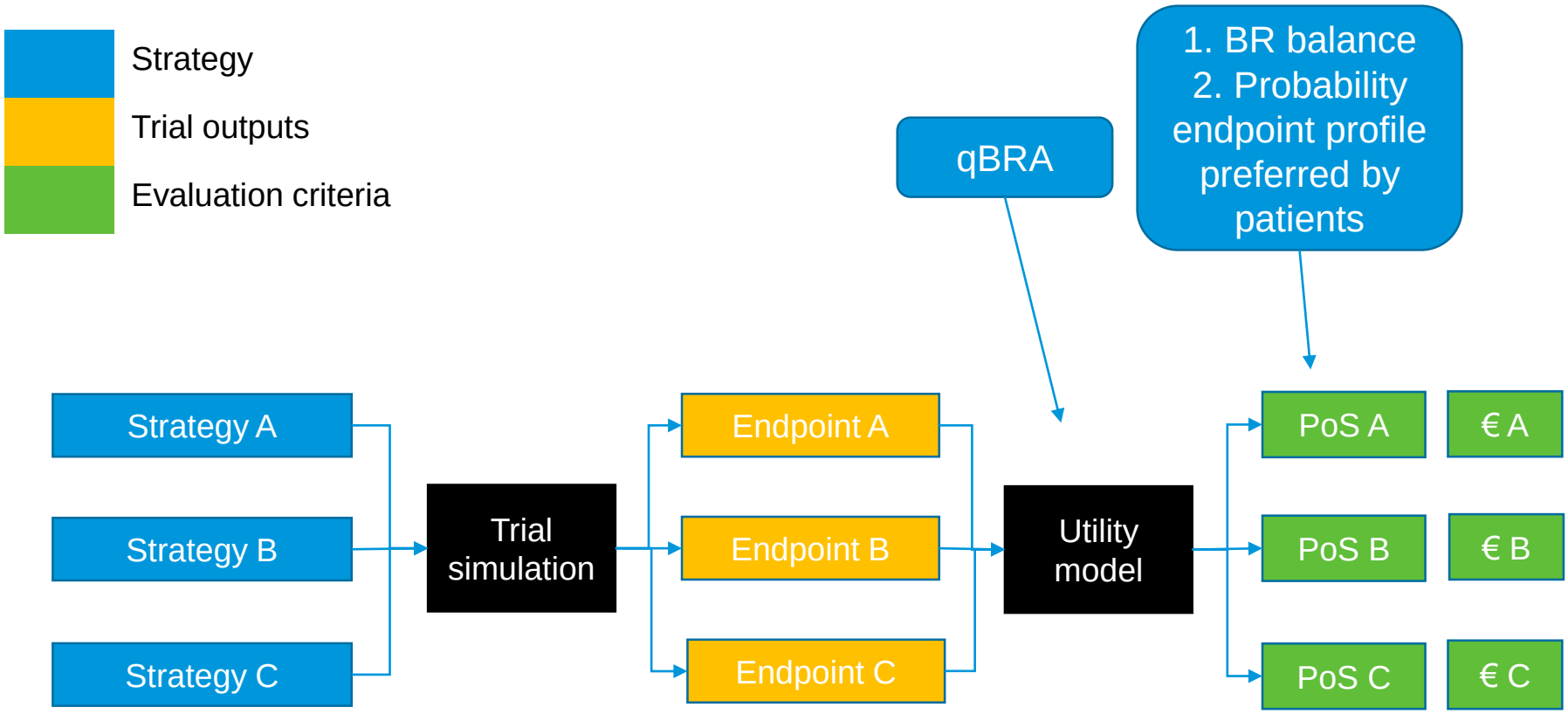
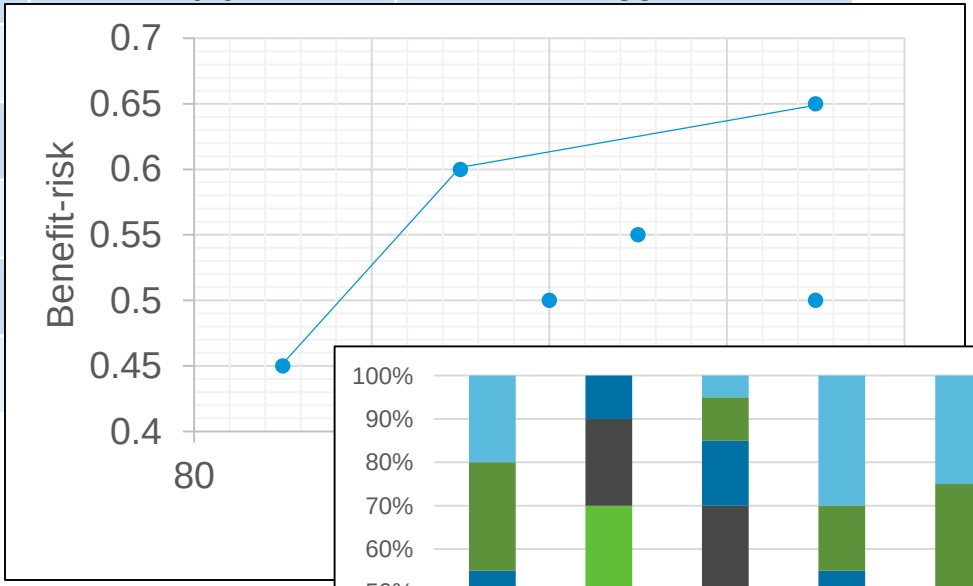
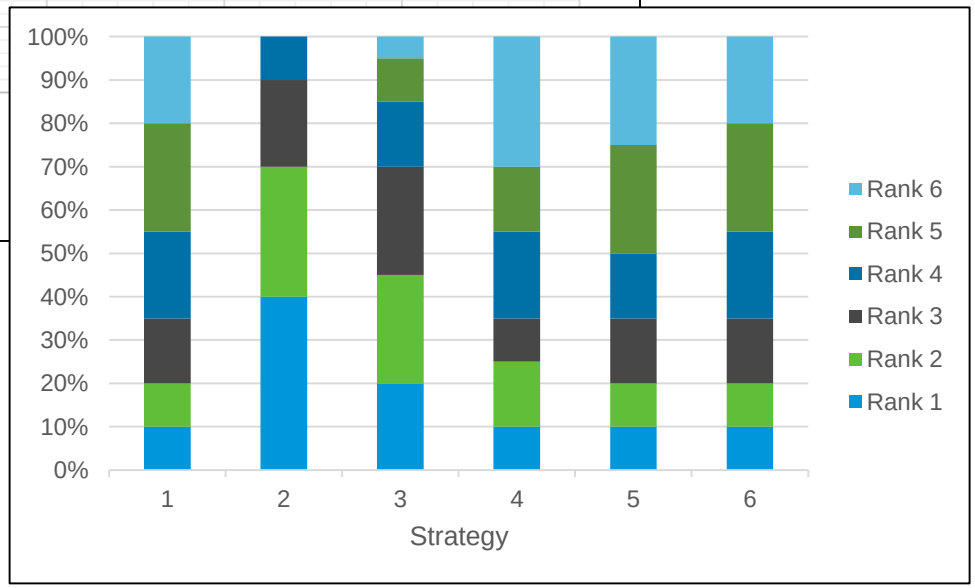


qBRA to support trial design

Illustrative outputs

Strategy	€m	Benefit-risk (BR)	Value for money (£/BR)
1	110	0.6	183
2	90		
3	150		
4	130		
5	120		
6	150		





qBRA to support trial design

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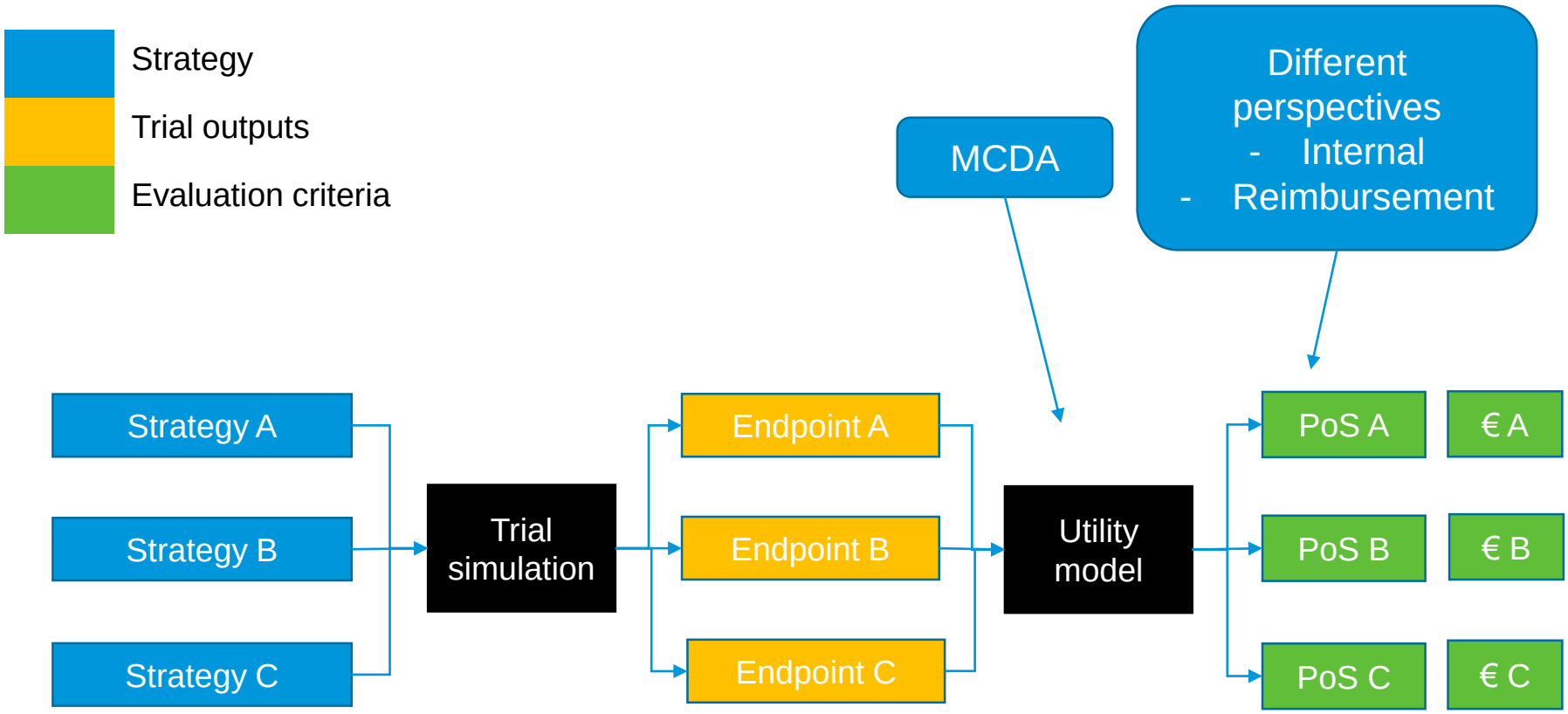


qBRA to support trial design

An input into trial simulation – FDA's view

Miller and Woodcock (CDER staff), Value in Health, In Press:

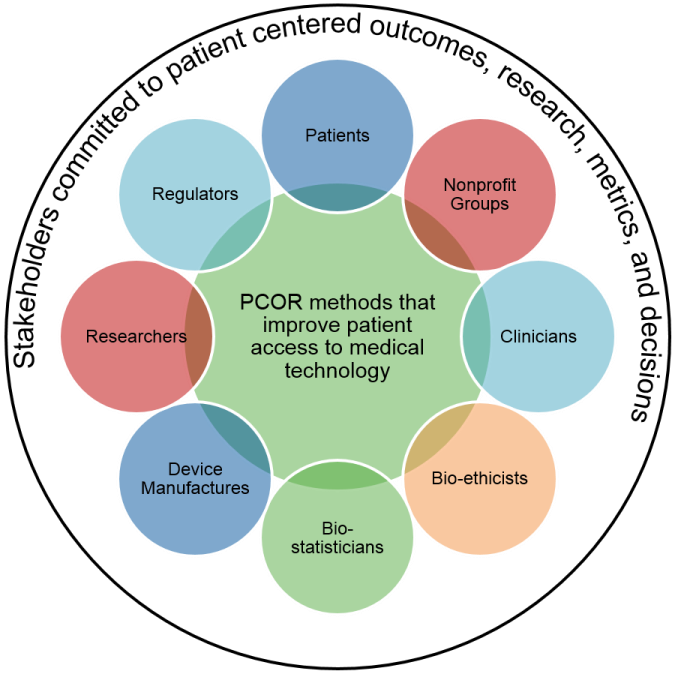
"In the near future, CDER plans to issue a series of guidances to enable patient groups, and others, to collect and provide structured input on patient preferences in determining benefit-risk trade-offs, the burden of disease, and patient assessment of present treatments. This input will be used to inform subsequent CDER guidances on ensuring that the structure and assessment of clinical trials are meaningful to patients..."

qBRA to support trial design

An input into trial simulation – FDA's view

FDA with (i) Medical Devices Innovation Consortium, and (ii) Michael J Fox Foundation

"Collaboration to Move Clinical Trials from Generic p-value of 0.05 to Therapy-Specific Patient Values"



Demonstrate "methods to use Patient Preference Research as an explicit means to set significance levels in clinical trial design can transform the way FDA approves medical devices".

Challenges implementing qBRA earlier

Challenge	Implication
Uncertainty in performance ranges	Use experts to specify likely ranges
Longer list of attributes	Elicitation method (e.g. swing weighting)
Preference method	Good practice is still a work in progress E.g. IMI PREFER
Recruitment	Depends on the disease area/ perspective

Thank you

Questions?

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