



**PROTECT**



Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

# **TAXONOMY OF BENEFIT-RISK ASSESSMENT METHODOLOGIES, AND BENEFIT-RISK METRICS**

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IMI-PROTECT Symposium

Benefit-Risk Integration and Representation Workshop

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Shahrul Mt-Isa, PhD

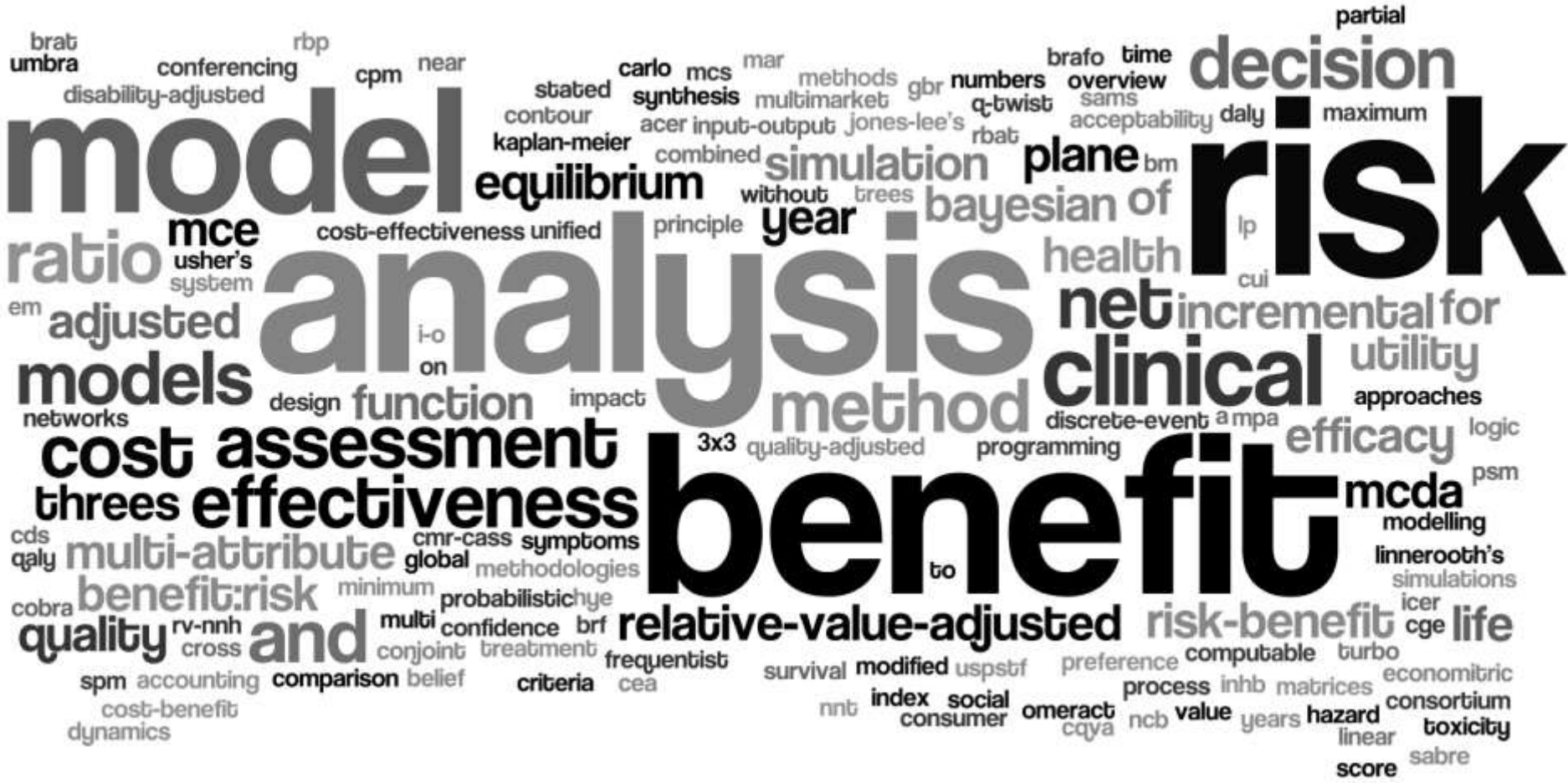
# Disclaimer

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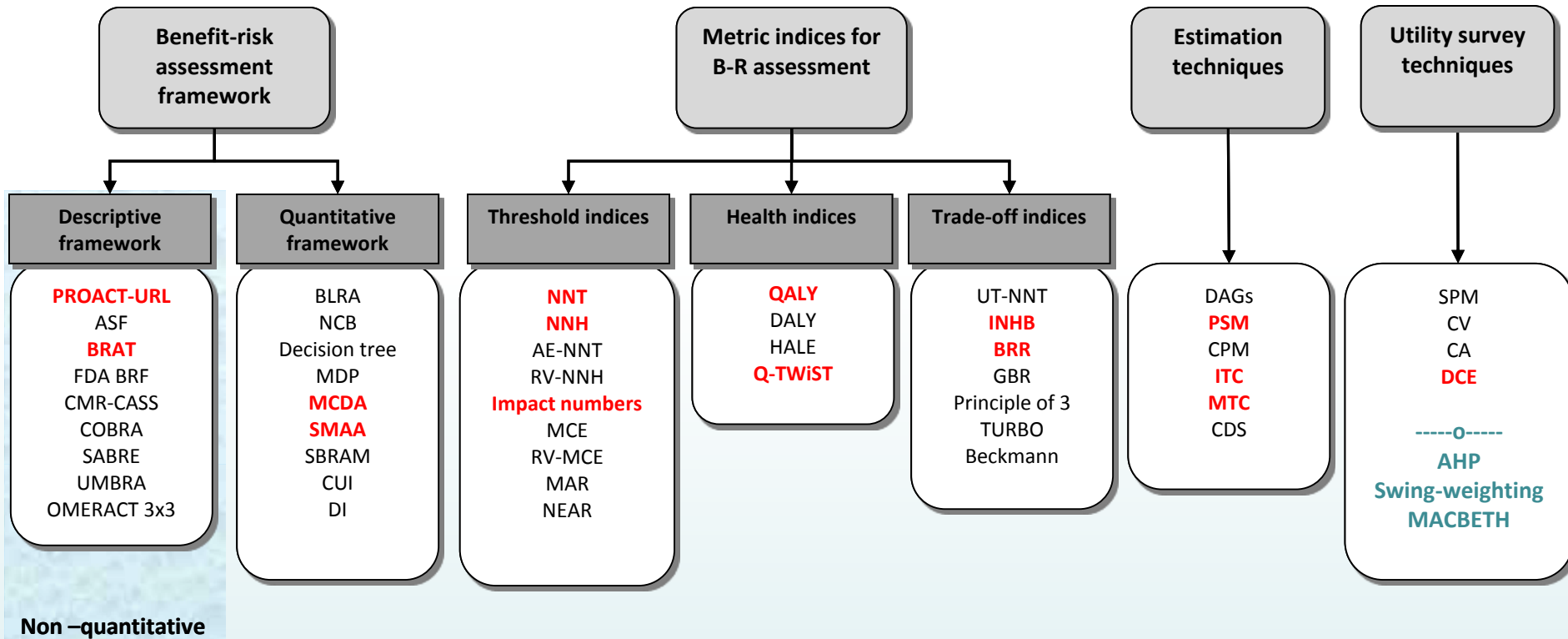
“The processes described and conclusions drawn from the work presented herein relate solely to the testing of methodologies and representations for the evaluation of benefit and risk of medicines.

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.”

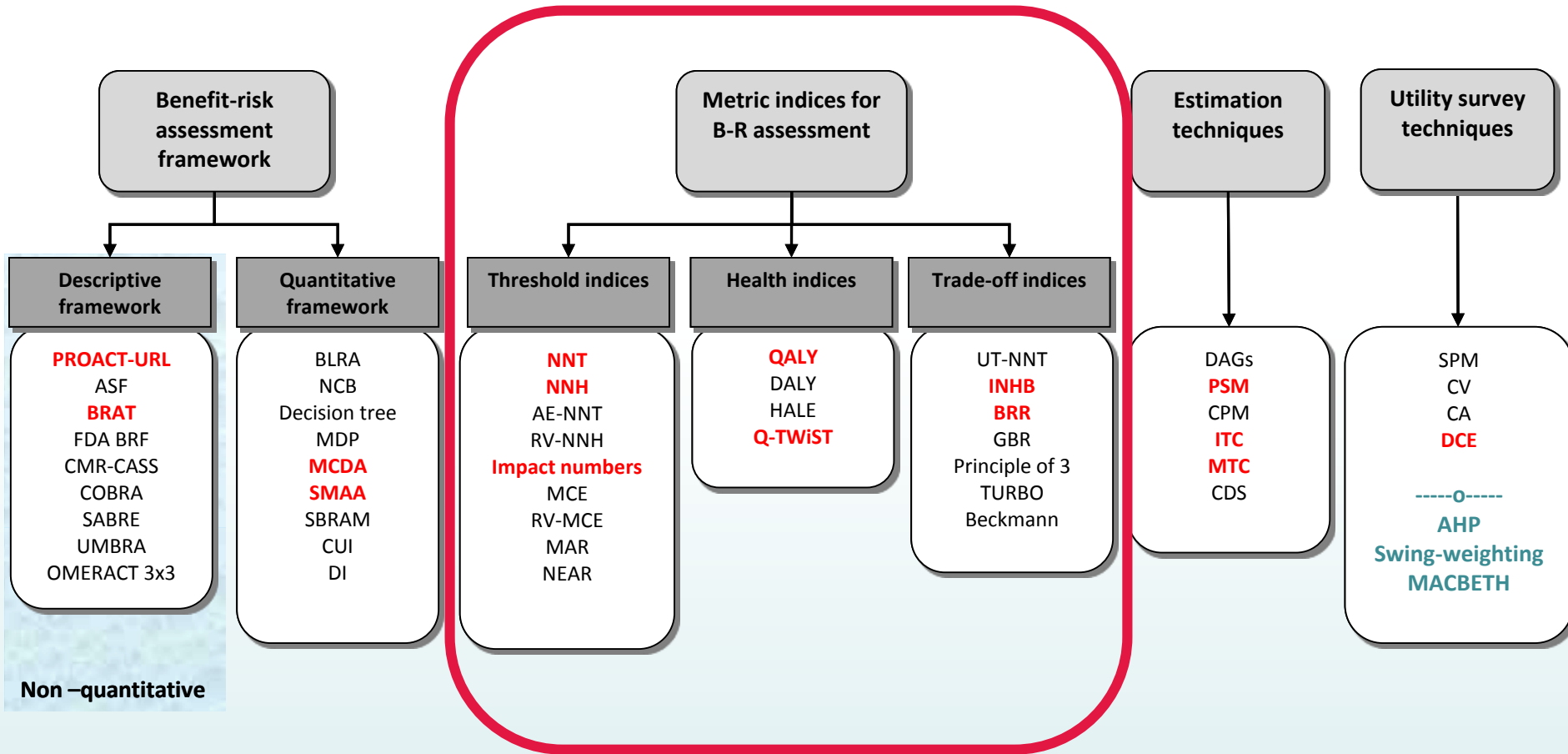
# Which benefit-risk methodology?



# Methodologies available



# Methodologies available



# Metric indices

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- To quantitatively describe and communicate benefit-risk assessment results:

~~1. Number Needed to Treat / Harm (NNT/H)~~

2. Benefit-Risk Ratios (BRR)

3. Incremental Net Health Benefit (INHB)

4. Impact numbers

~~5. QALY~~

~~6. Q-TWiST~~



## Benefit-risk ratio (BRR)

- Benefit divided by risk
- Benefit is expressed as multiples of risk
- BRR is a simple idea but can be powerful
- In practice, equilibrium in most cases is not 1
  - Region of equivalence must be established *a priori*
  - Trastuzumab example



$$\frac{\text{Benefit}}{\text{Risk}} = \frac{\text{NNT}}{\text{NNH}} = \frac{12.3}{39.8} = 0.3 (< 1)$$



## Incremental net health benefit (INHB)

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- Specifically difference between QALY gained (benefit) and QALY lost (risk)
  - QALY is the quality adjusted life years based on time spent in certain health state e.g. using EQ5D index
  - Q-TWiST proposed health states for cancer therapy
- More generally, not using health index

$$\begin{aligned}\text{INB} &= (\text{incremental benefit}) - (\text{incremental risk}) \\ &= (B_1 - B_0) - (R_1 - R_0)\end{aligned}$$



## Incremental net health benefit (INHB)

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- In the trastuzumab example:

$$\begin{aligned}\text{INB} &= (\text{incremental benefit}) - (\text{incremental risk}) \\ &= (B_1 - B_0) - (R_1 - R_0) \\ &= (0.861 - 0.780) - (0.0304 - 0.0053) \\ &= 0.0559\end{aligned}$$

- So in this case, the incremental net benefit is 0.0559 in favour of trastuzumab

# Impact numbers

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- Extend NNT concept to public health perspective
  - Uses background data from the intended population
- “Population Impact Measures (PIM)”
  - Population attributable risk (PAR)
  - Exposure impact number (EIN)  $\equiv$  NNT
  - Population impact number of eliminating a risk factor over time  $t$  (PIN-ER- $t$ )
  - Number of events prevented in the population (NEPP)
- Descriptive measure

[Verma \*et al.\* Population Impact Analysis: a framework for assessing the population impact of a risk or intervention. J Public Health \(Oxf\). 2012 Mar; 34\(1\):83-9. doi: 10.1093/pubmed/fdr026.](#)

# Impact numbers: trastuzumab example

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- Say we want to know, how many event free survivals (EFS) over one year in 1000 women with breast cancer. 50% of whom already receiving trastuzumab, and we would like to increase the uptake to 75% in the population.
  - attributed to receiving trastuzumab
  - will be prevented by receiving trastuzumab under the new regime
  - Assume baseline EFS rate is 0.780 (rate in control group in e.g.)



# Impact numbers: trastuzumab example

PIM	Calculation	Interpretation
PAR	$= \frac{0.5 \times 0.104}{1 + (0.5 \times 0.104)}$ $= 0.049$	5% EFS are due to trastuzumab in the general population
PIN-ER-t	$= n \times r_u \times \text{PAR}$ $= 1000 \times 0.780 \times 0.049$ $= 38.6$	39 women of the 1000
EIN	$= \frac{1}{0.861 - 0.780}$ $= 12.3$	13 women had to take trastuzumab to see one EFS
NEPP	$= n \times P_e \times r_u \times (\text{RR} - 1)$ $= 1000 \times (0.75 - 0.5) \times 0.780 \times 0.104$ $= 20.3$	20 extra EFS when increase intake from 50% to 75%

## Remarks

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- Recommendations for further testing are toolkit to aid methodology selection
  - Complexity and purpose
- Benefit-risk assessment methodologies are NOT tools that can make choices
- Using metric indices alone does not guarantee structured, transparent and/or robust assessment
- Sufficient for simple decision problems, or as quick initial descriptions
- There is a trade-off between being too simplistic and just being too incomprehensible

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# ACKNOWLEDGEMENT

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## IMI-PROTECT Benefit-Risk Group

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Deborah Ashby, Alain Micallef, Steve Hobbiger, Ioanna Tzoulaki, Diana Hughes, Shahrul Mt-Isa.

Billy Amzal, Simon Ashworth, Alex Asiimwe, Johan Bring, Torbjorn Callreus, Edmond Kakit Chan, Christoph Dierig, Gerald Downey, David Gelb, Georgy Genov, Alesia Goginsky, Christine Hallgreen, Richard Hermann, Ian Hirsch, Kimberley Hockley, Gemma Hodgson, Juhaeri Juhaeri, Silvia Kuhls, Alfons Lieftucht, Alison Lightbourne, Davide Luciani, Marilyn Metcalf, Jeremiah Mwangi, Thai Son Tong Nguyen, Richard Nixon, Rebecca Noel, John Pears, Ruth Peters, Lawrence Phillips, George Quartey, Sinan B. Sarac, Susan Shepherd, Isabelle Stoeckert, Elizabeth J. Swain, Andrew Thomson, Laurence Titeux, Rianne van den Ham, Tjeerd van Staa, Edward Waddingham, Nan Wang, Lesley Wise.

Subhakanta Das, Jane Okwesa, Emily Thompson.