MODELING WITHOUT BORDERS

ACoP 10

Tutorial: The Role of Pharmacometrics in Advancing Quantitative Benefit-Risk Assessments for Drug Review and Approval

Chairs: Arnab Mukherjee and Tim Nicholas

The confluence of Statistical and Pharmacometric Approaches for Benefit Risk Analysis: a case study using Bayesian joint models for safety and efficacy

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Outline

- Case Study
  - Setting the scene
  - Multivariate benefit-risk
  - Bayesian joint dose-response model
  - Using the model to inform decisions
- Multi-criteria decision analysis
  - Concepts & methods
  - Conceptual application to case study

Ladies and gentlemen, the story you are about to see is true.

The names have been changed to protect the innocent.

Background

- A drug was in Phase 2 development for the treatment of a chronic disease affecting over 20 millions adults in the US

- Approved products are efficacious but have potentially life-threatening safety risks

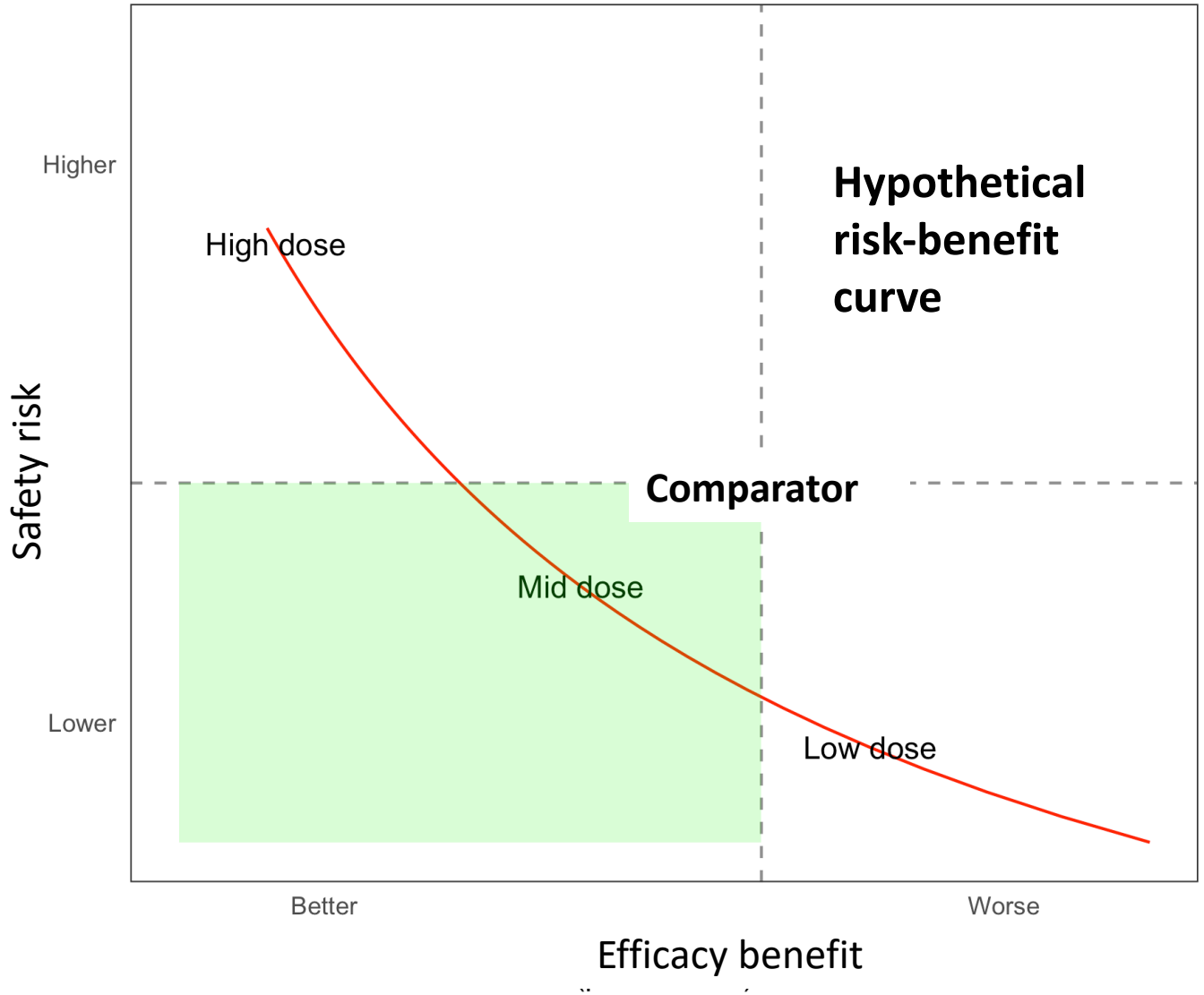
- Based on pre-clinical data, the drug was predicted to have fewer safety concerns while achieving equivalent efficacy as the marketed products.

Key drug development decision

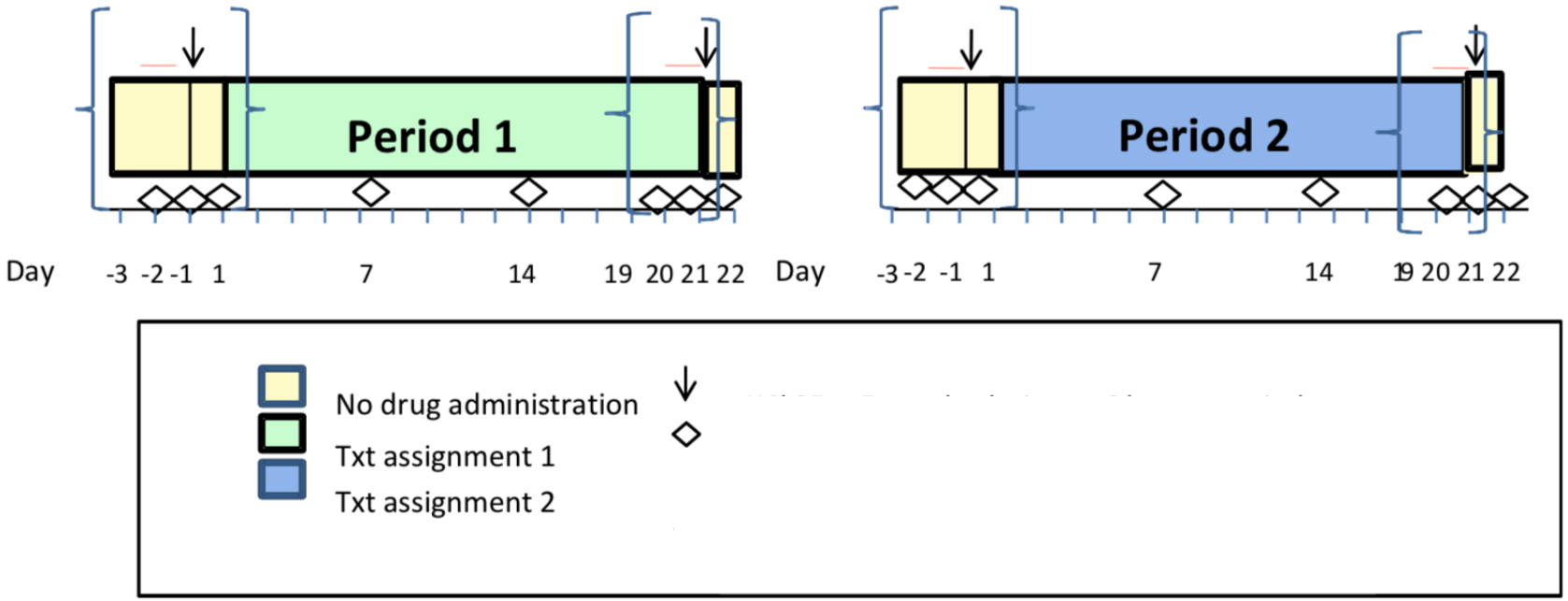
Is there a dose of with desired risk-benefit profile?

- Lower safety risk and equivalent (or better) efficacy
- More improvement in efficacy and equivalent (or better) safety

Risk-benefit is *with respect to marketed treatment*, not absolute



A dose-ranging, positive control, 2-period crossover trial informed the decision



Efficacy:

- **One PD Biomarker**

Safety:

- **Two mechanism-related biomarkers**

Incomplete block design

- **Three dose levels: Low, middle, high**
- **Comparator**

To address the risk-benefit question, we fit (Bayesian) joint models to the three endpoints

Baseline in period 1

Period effect

Counterfactual Placebo response

$$\log(Y_{E,ij}) = \text{BSL}_{E,i} + \text{PRD2}_{E,i} \cdot \text{I}(\text{Period } 2_{ij}) + \gamma_{E,i} \cdot \text{I}(\text{post-baseline}_{ij}) +$$
$$\text{Slope}_E \cdot dose_{ij} + \delta_E \cdot Comp_{ij} + \epsilon_{E,ij}$$

Dose-response

Effect of Comparator

$$Y_{S1,ij} = \text{BSL}_{S1,i} + \text{PRD2}_{S1,i} \cdot \text{I}(\text{Period } 2_{ij}) + \gamma_{S1,i} \cdot \text{I}(\text{post-baseline}_{ij}) +$$
$$\text{Slope}_{S1} \cdot dose_{ij}^{\alpha_{S1}} + \delta_{S1} \cdot Comp_{ij} + \epsilon_{S1,ij}$$

$$Y_{S2,ij} = \text{BSL}_{S2,i} + \text{PRD2}_{S2,i} \cdot \text{I}(\text{Period } 2_{ij}) + \gamma_{S2,i} \cdot \text{I}(\text{post-baseline}_{ij}) +$$
$$\text{Slope}_{S2} \cdot dose_{ij} + \delta_{S2} \cdot Comp_{ij} + \epsilon_{S2,ij}$$

Endpoint association modeled through correlated random effects

Subject-specific Baseline, Period and (counterfactual) placebo effects:

$$BSL_{E,i} = \theta_1 + \eta_{1,i} \qquad BSL_{S1,i} = \theta_4 + \eta_{2,i} \qquad BSL_{S2,i} = \theta_7 + \eta_{7,i}$$
$$\mathrm{PRD2}_{E,i} = \theta_2 + \eta_{3,i} \qquad \mathrm{PRD2}_{S1,i} = \theta_5 + \eta_{4,i} \qquad \mathrm{PRD2}_{S2,i} = \theta_8 + \eta_{8,i}$$
$$\gamma_{E,i} = \theta_3 + \eta_{5,i} \qquad \gamma_{S1,i} = \theta_6 + \eta_{6,i} \qquad \gamma_{S2,i} = \theta_9 + \eta_{9,i}$$

Subject-specific random effects modeled with full-block variance matrix:

$$\eta_i = (\eta_{1,i}, \ldots, \eta_{9,i})^T \sim N(0, \Omega).$$

Bayesian framework provided benefits

- Readily answer key questions in a ***probabilistic framework***.

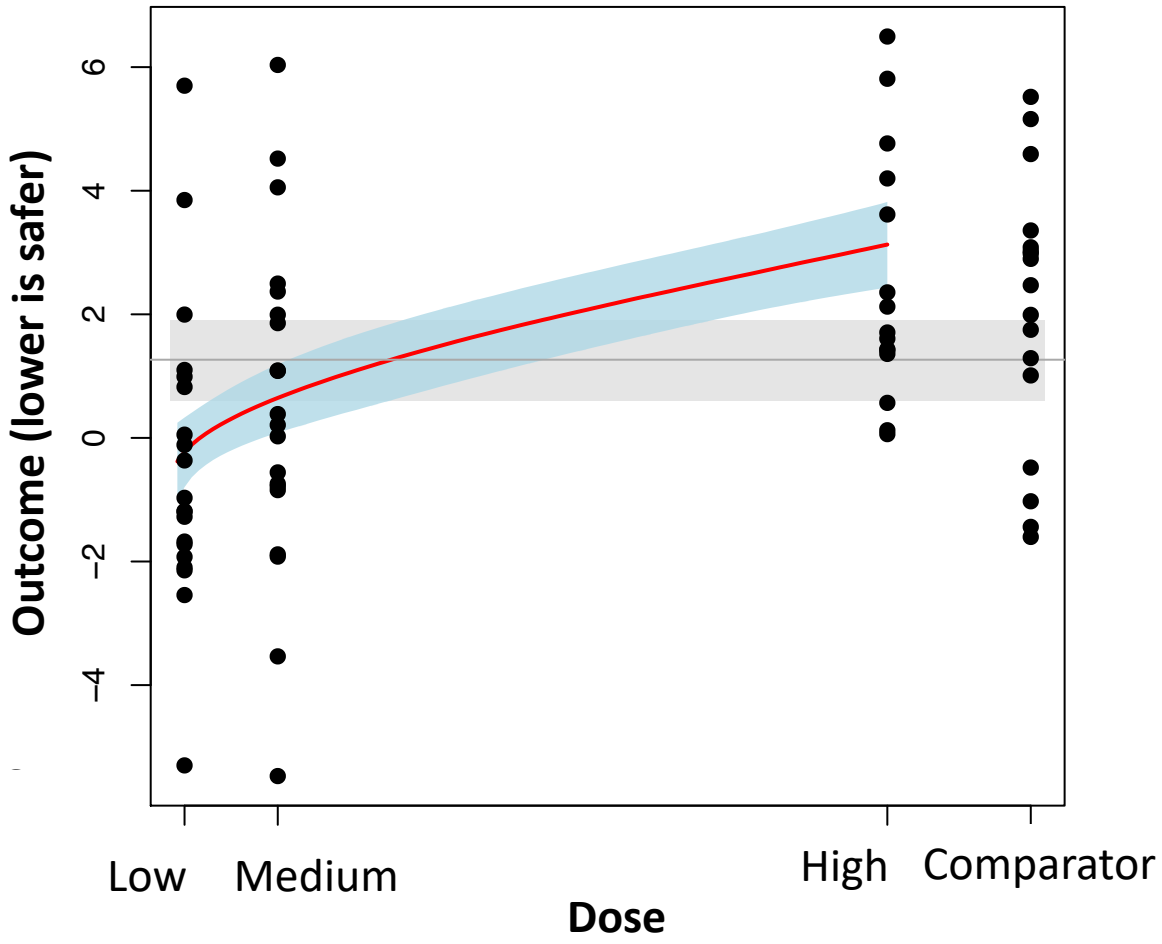
- Allows us to include moderately informative prior distributions on the population-level (counterfactual) placebo response
  - Weakly informative prior distributions on other parts of the model

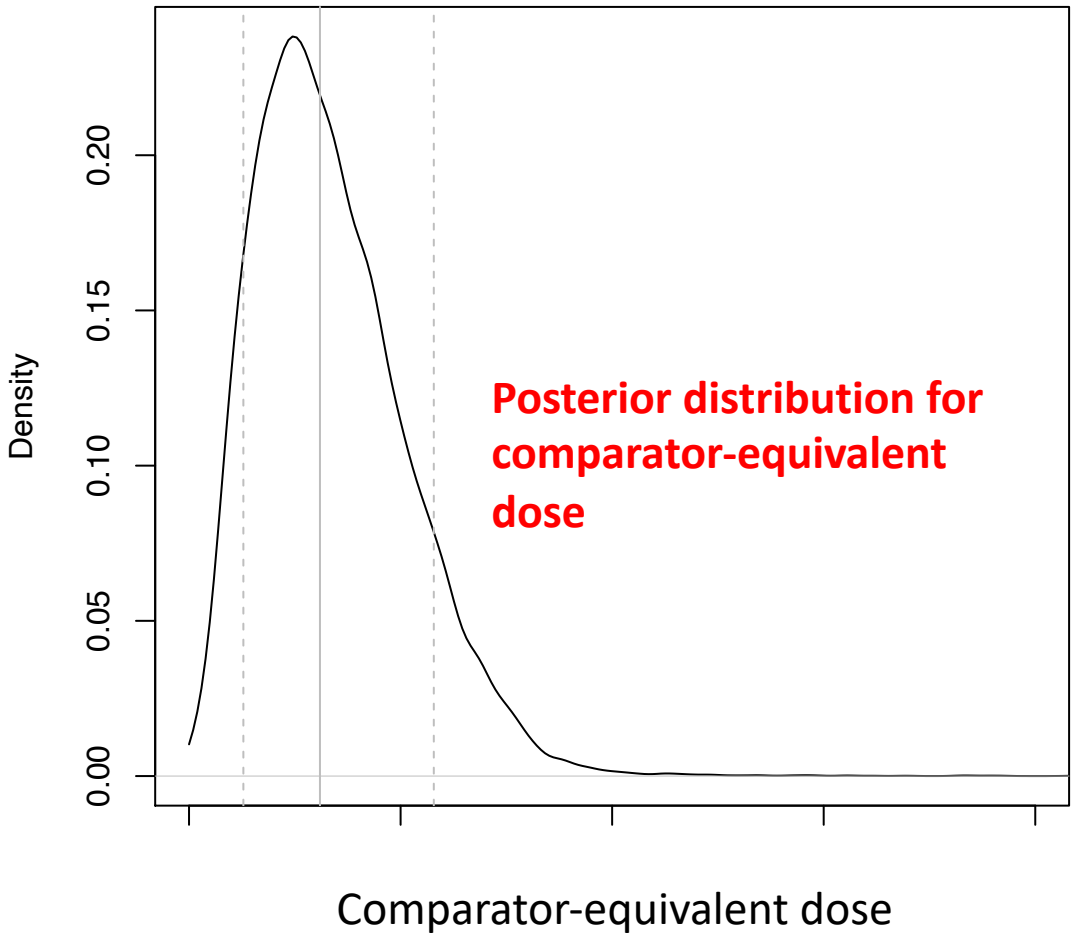
- No need to rely on asymptotic theory to obtain uncertainty in estimates and predictions

Two key metrics were used to inform the decision-making process

- Bi-variate (safety + efficacy) dose-response
- Posterior probability of dose achieving safety and efficacy targets

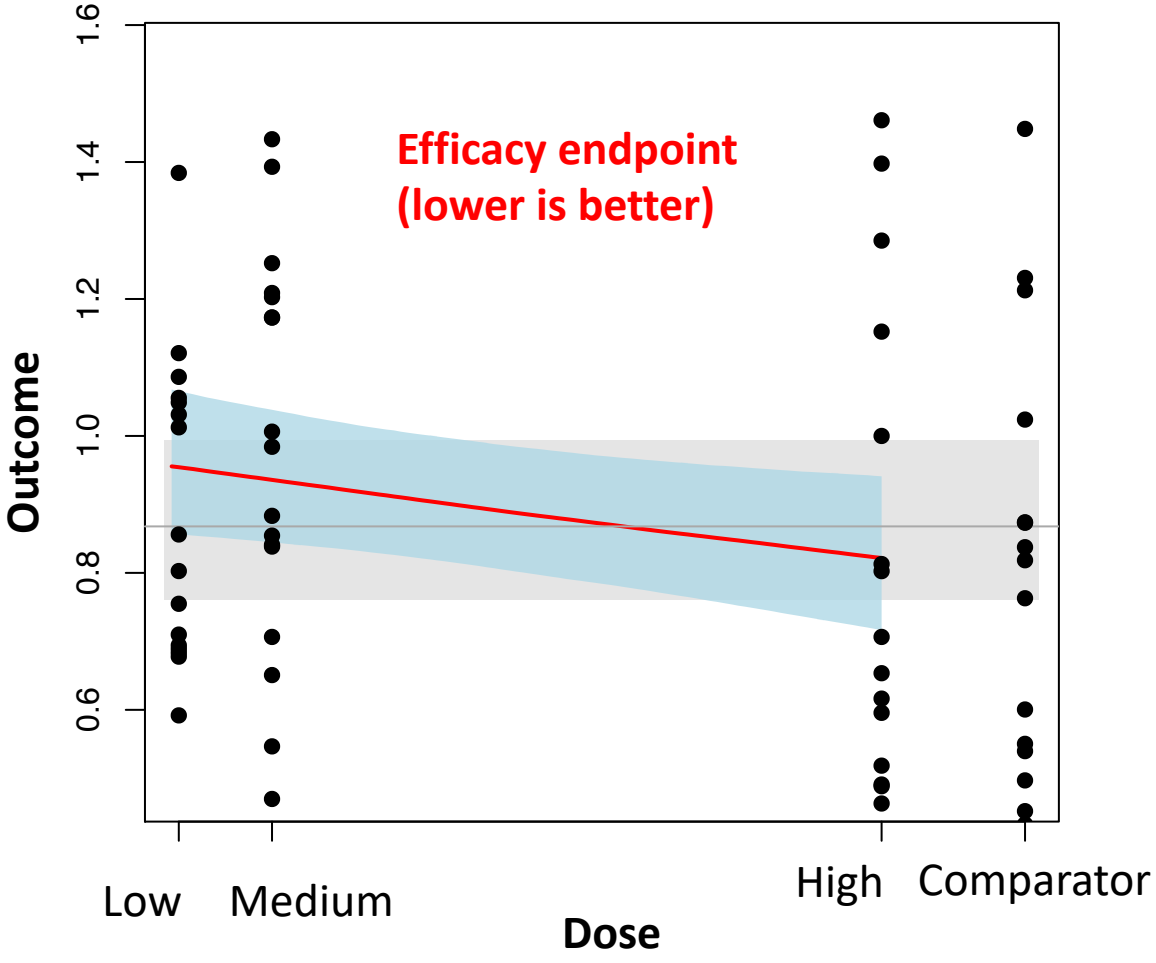
Clear dose-response for safety endpoint 1

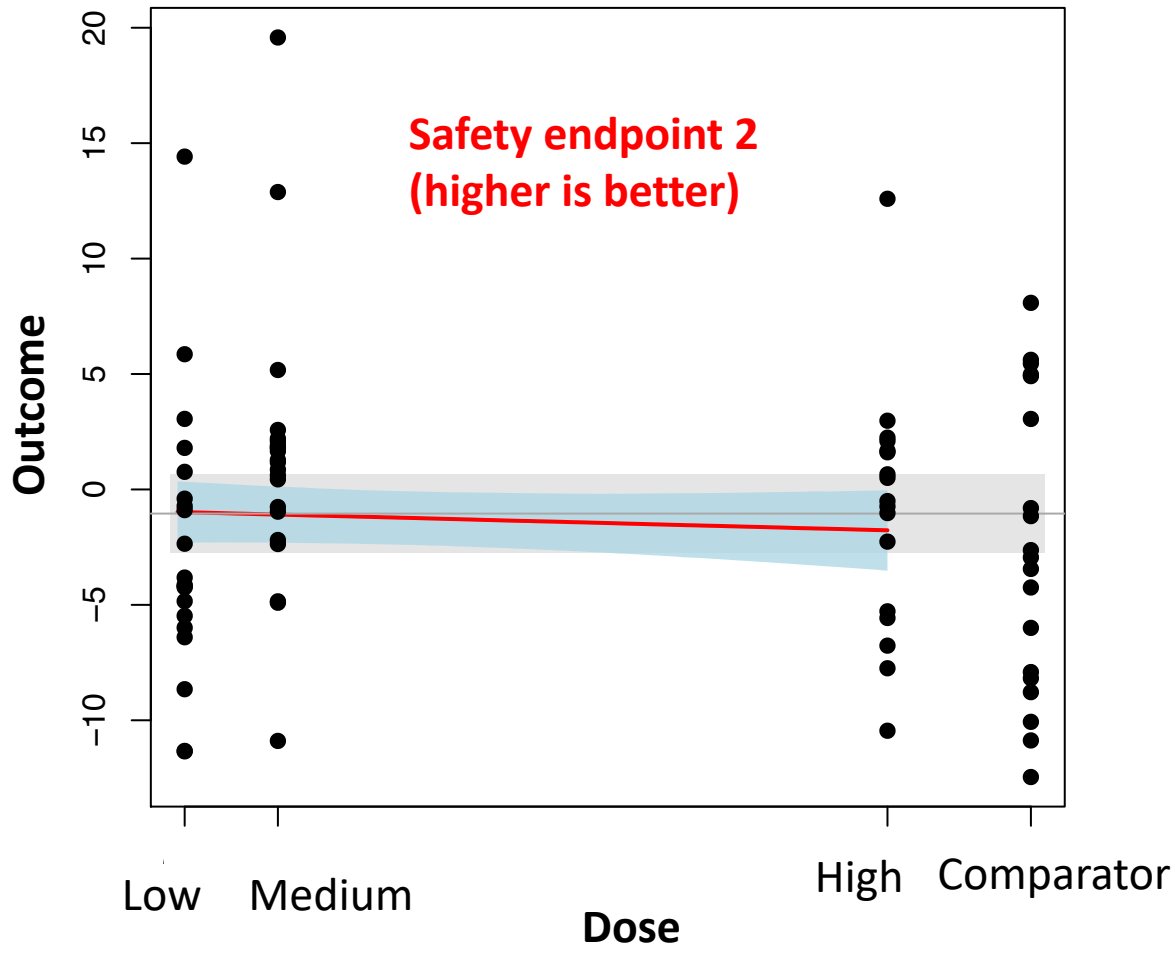




Shaded areas represent 80% credible intervals

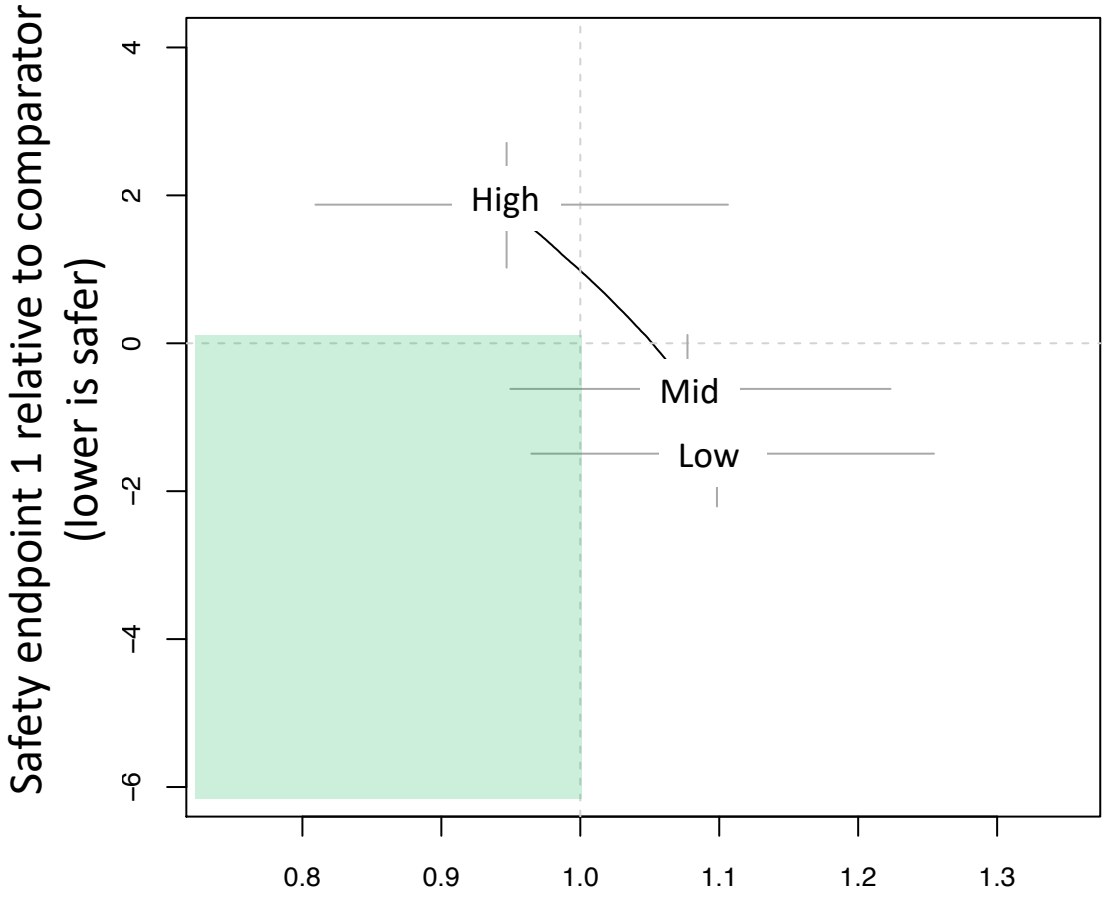
However, shallower dose-response for efficacy and safety endpoint 2

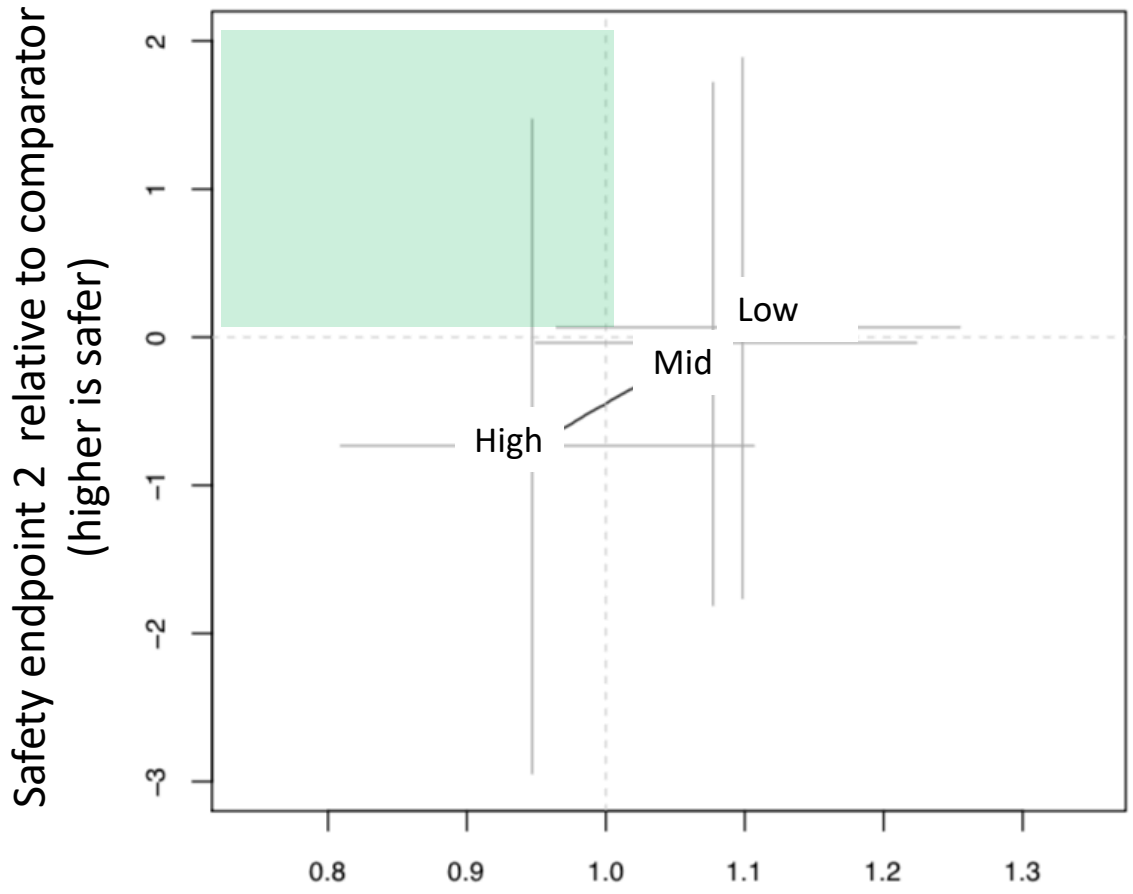




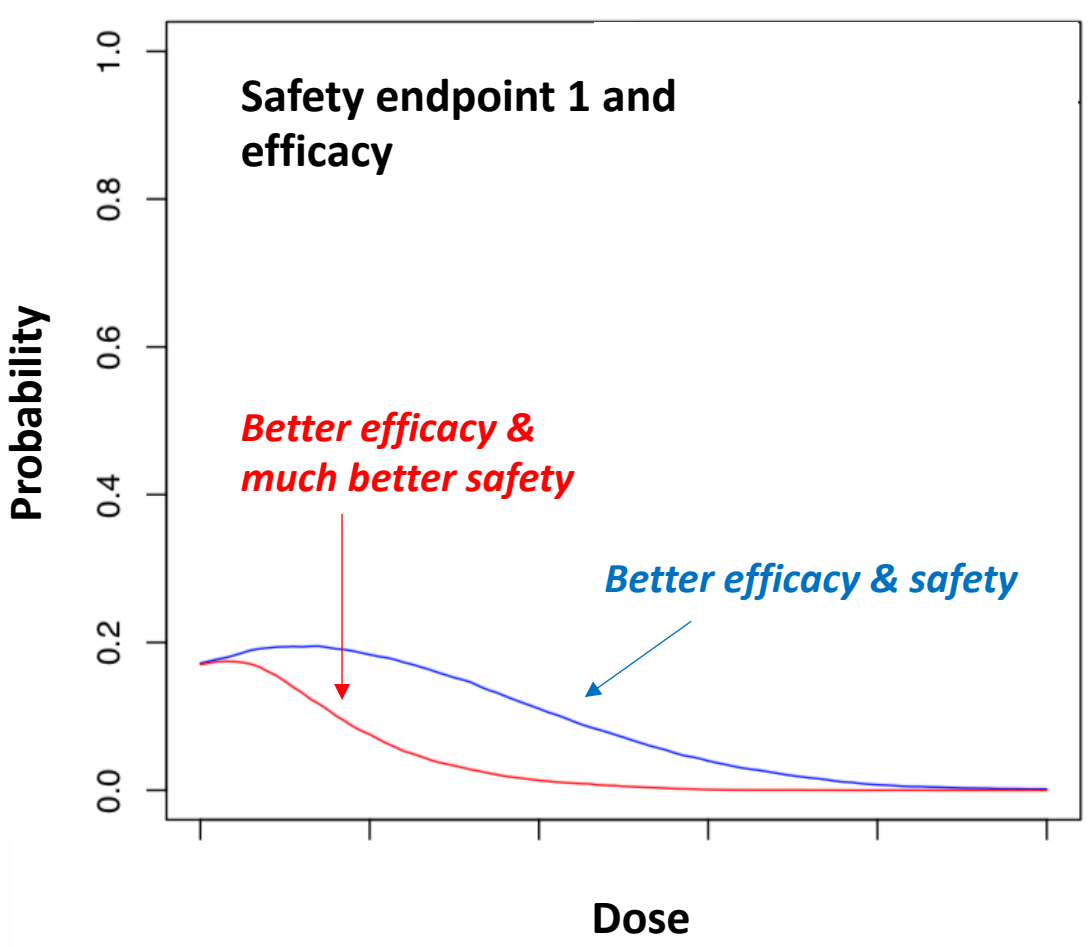
Shaded areas represent 80% credible intervals

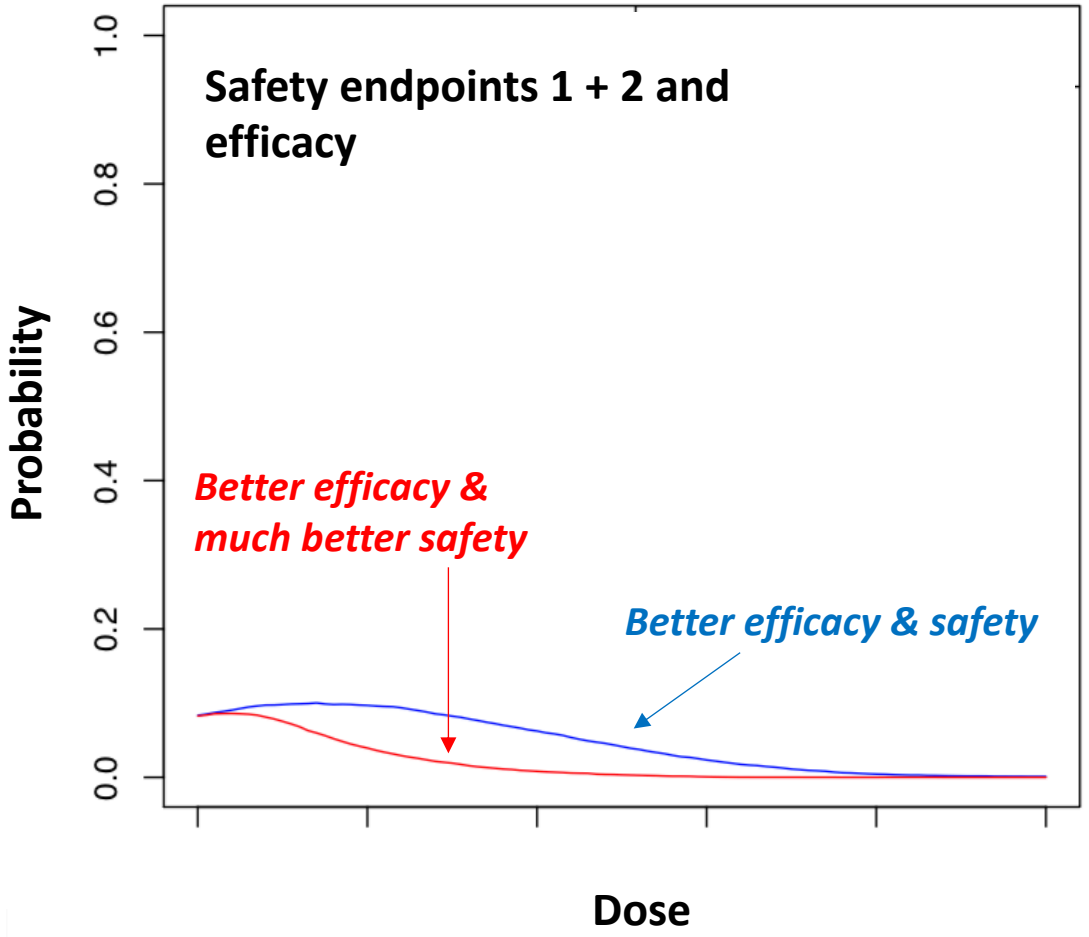
Bivariate efficacy-safety dose-response shows unlikely to achieve desired risk-benefit profile



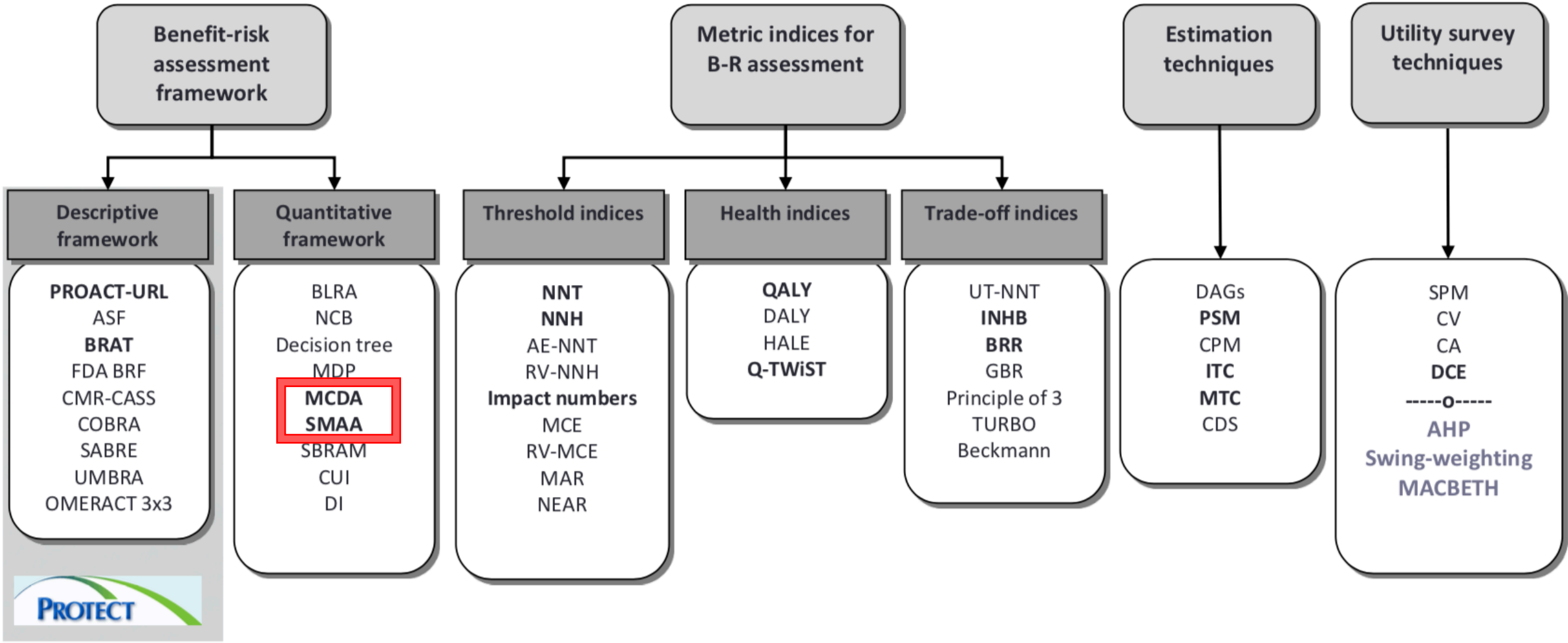


The probability of achieving the target is low at all doses studied





Alternatives / extensions to our approach



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/

Multi-Criteria Decision Analysis

- “A methodology for appraising alternatives on individual, often conflicting criteria, and combining them into one overall appraisal” (Keeney and Raiffa, 1993)

- Explicitly states
  - which criteria are relevant
  - the importance attached to each
  - how to use this information to assess competing products

- Discussion of using PK/PD models as input to MCDA (Bellanti et al., 2015)

MCDA is used to support health care decisions across a wide variety of areas

Decision maker	Example decision	Example criteria	Examples of stakeholders providing preferences
Life sciences companies	Portfolio decision analysis	Relevant aspects of benefits and risk, probability of success	Therapeutic area team; board of directors
Regulators	Benefit-risk assessment	Aspects of benefits and risks	Regulatory committees and/or patients
HTA bodies	Health technology assessment (HTA)	Effectiveness, patient need, burden of disease	HTA committees or general public
Prioritization of patients for health care services	Prioritizing patients' access to health care	Measures of patient "need"; ability to benefit	Patient groups; health professionals;

Adapted from Thokala P, et al. Multiple Criteria Decision Analysis for Health Care Decision Making—An Introduction: Report 1 of the ISPOR MCDA Emerging Good Practices Task Force. Value Health. 2016; 19: 1-13.

Six steps to MCDA

MCDA Step	Description
Define the decision problem	Objectives, type of decision, alternatives
Select criteria on which to base assessment	Identify endpoints / measures relevant to the decision
Measure performance on the criteria	Quantify (expected) effects on criteria of interest. If no data, may be elicited.
Define 'scoring'	Translate effects to a 'utility' scale (delineates preferences ***within*** criteria).
Elicit weighting criteria	Weights delineates preferences ***between*** criteria. Will depend on stakeholder

Adapted from Thokala P, et al. Multiple Criteria Decision Analysis for Health Care Decision Making—An Introduction: Report 1 of the ISPOR MCDA Emerging Good Practices Task Force. Value Health. 2016; 19: 1-13.

Step 6: Aggregate score

$$\text{Aggregate Score} = \sum_{j=1}^{C} w_j \times s_j(\text{performance}_j)$$

Scoring function

Weight

Performance assessment

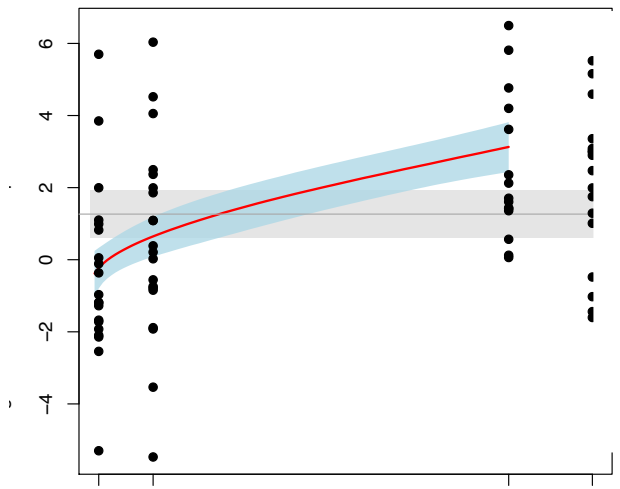
Accounting for uncertainty / variability

MCDA Step	Uncertainty evaluation
Performance measurement	Formal Bayesian modeling to fixed sensitivity analyses
Scoring function	Sensitivity analyses
Weighting criteria	Sensitivity analyses or distributions (SMAA; Tervonen et al, 2011)

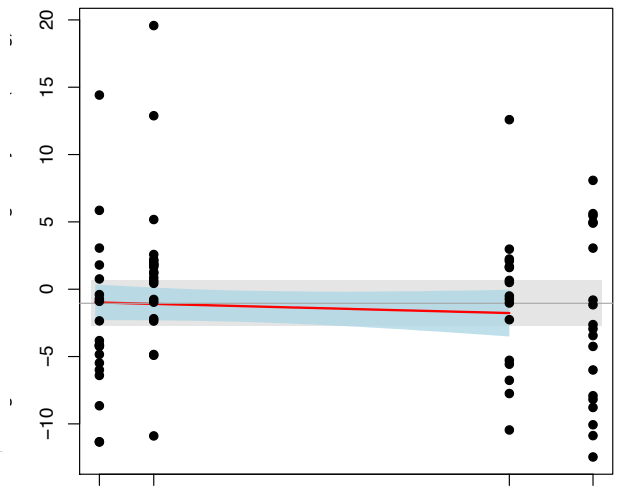
Hypothetical application to case study

Performance Measures

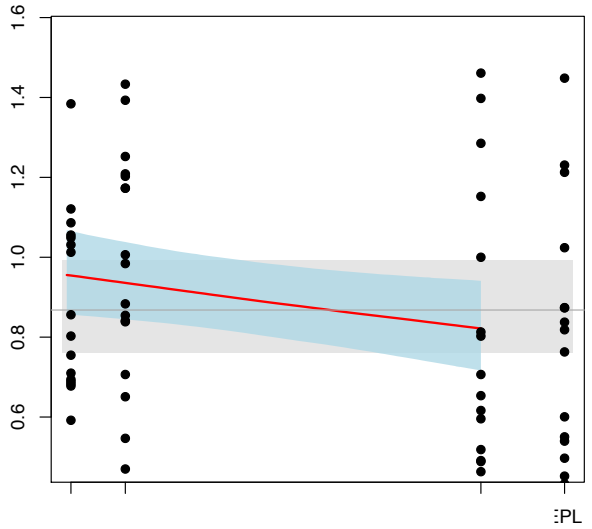
Safety endpoint 1



Safety endpoint 2

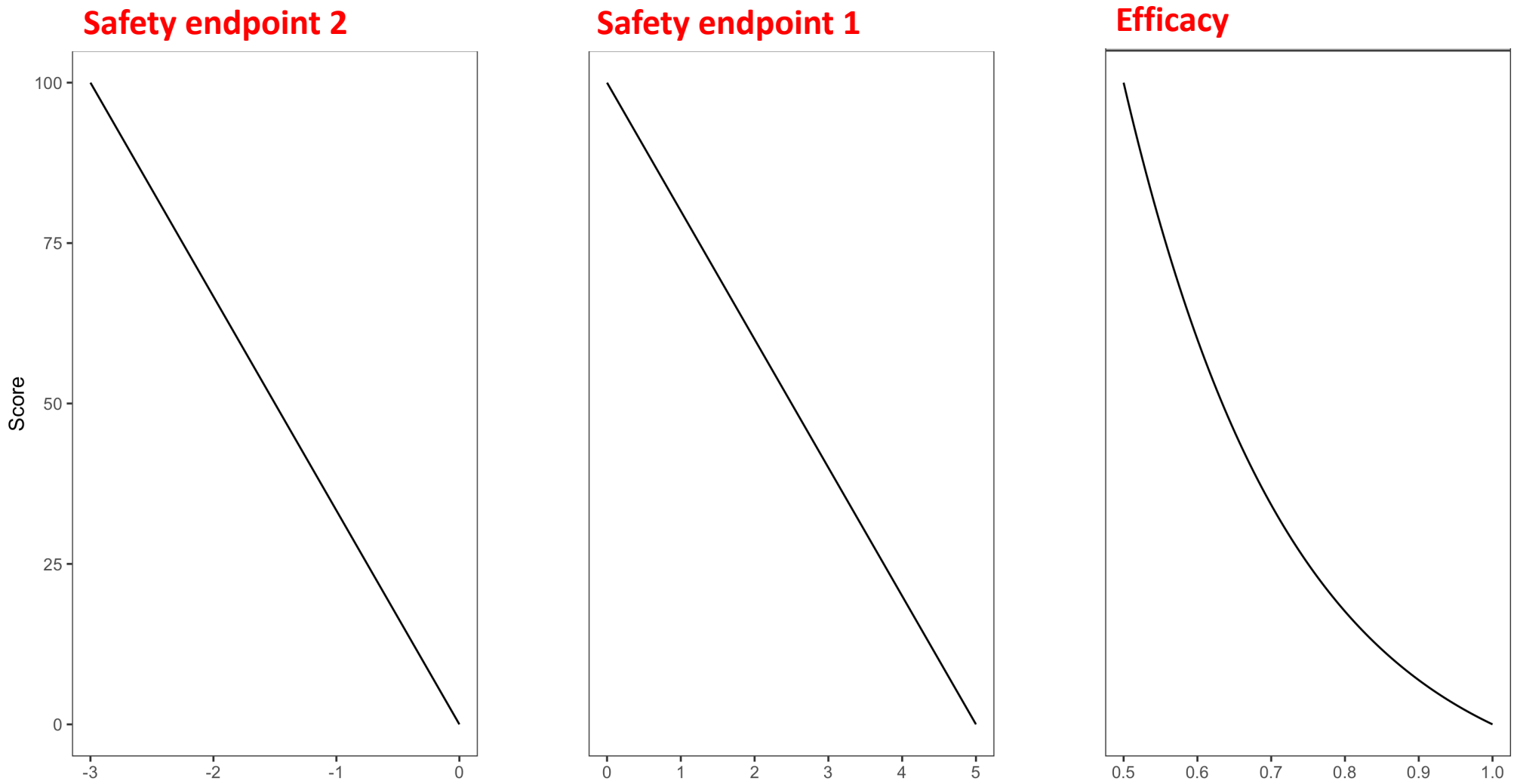


Efficacy



Hypothetical application to case study

Scoring Functions



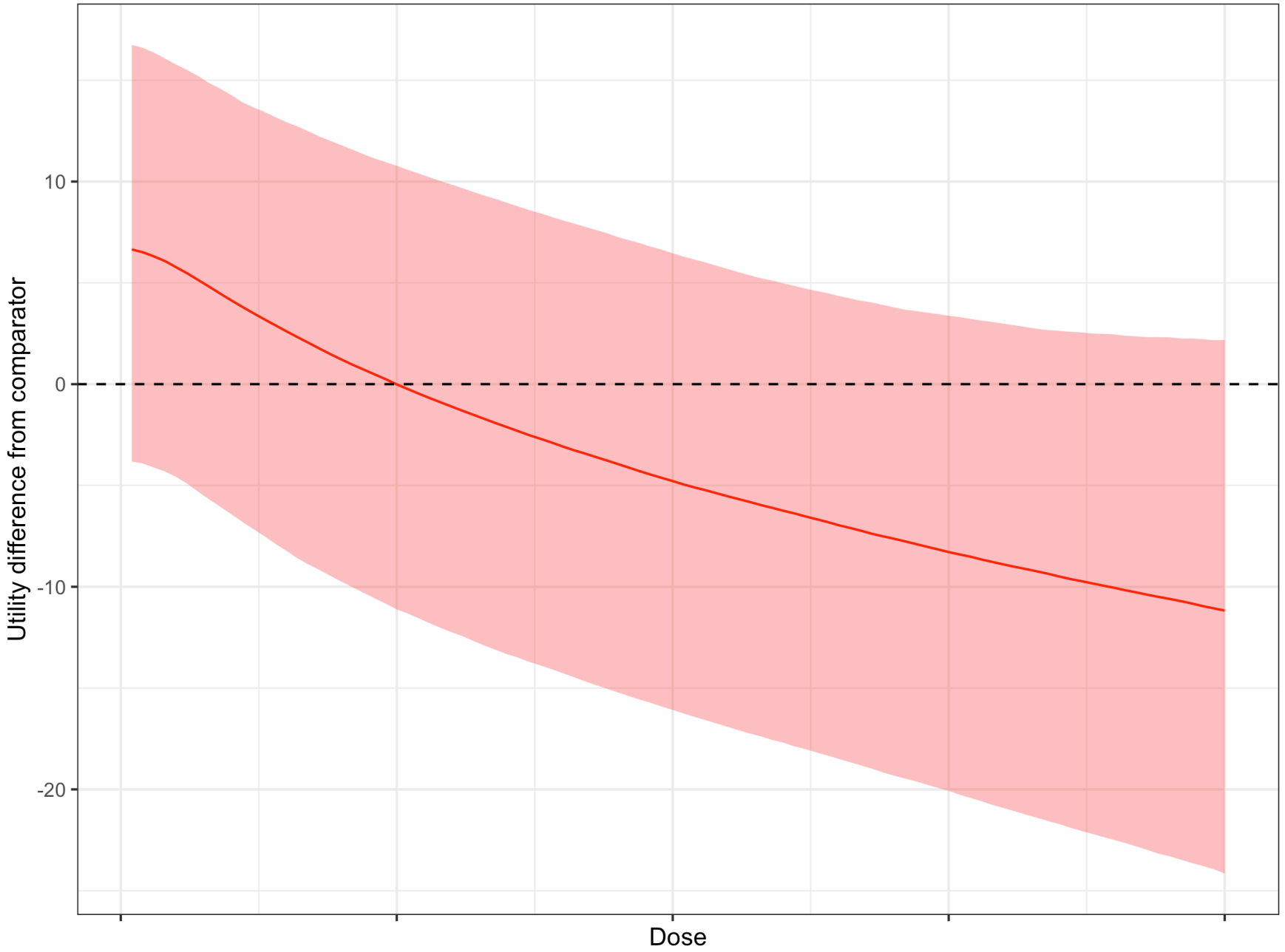
Hypothetical scales for discussion only. Scales were not assessed for the actual analysis.

Hypothetical application to case study

Weighting Functions

Endpoint	Drug Developer	Regulator	A Specific Patient
Safety endpoint 1	0.40	0.55	0.33
Safety endpoint 2	0.20	0.10	0.33
Efficacy	0.40	0.35	0.33

Hypothetical weights for discussion only. Weights were not assessed for the actual analysis.



Difference in utility from comparator.

Median and 90% credible interval, using hypothetical Drug Developer weights.

Key points

- Joint modeling
  - allows modeling of correlations of safety and efficacy measures at the subject- and population levels
  - Intuitive
- Bayesian framework
  - Enables ‘proper’ accounting for uncertainty in decision-making process
  - Formal use of prior information – including formally updating benefit-risk assessment as the drug advances through development
- MCDA
  - Potentially useful approach to integrate efficacy and safety outcomes into a single measure
  - Explicitly models different weights given to outcomes by different stakeholders

Acknowledgements

- Marc Gastonguay
- Arnab Mukherjee, Tim Nicholas
- Other speakers in the session

References

- Bellanti F, van Wijk RC, Danhof M, Della Pasqua O. Integration of PKPD relationships into benefit-risk analysis. Br J Clin Pharmacol. 2015 Nov;80(5):979–91.
- Keeney RL, Raiffa H. Decisions with Multiple Objectives: Preferences and Value Trade-Offs. Cambridge University Press, Cambridge, UK, 1993.
- Thokala P, et al. Multiple Criteria Decision Analysis for Health Care Decision Making—An Introduction: Report 1 of the ISPOR MCDA Emerging Good Practices Task Force. Value Health. 2016; 19: 1-13.
- 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