Enhancing Medical Product Development and Review with Bayesian Quantitative Benefit Risk Methods

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October 24, 2024

Disclaimer

The views and opinions expressed in this presentation are solely my own. They do not represent the official stance or viewpoints of Sarepta or any other agency or organization with which the ASA BSWG Benefit-Risk Subteam members are employed or affiliated with.

Who Are We?

- We are a group of individuals from pharma companies, regulatory agencies, and academia, within the American Statistical Association Biopharmaceutical Section (ASA BIOP) Bayesian Scientific Working Group (BSWG), with a special interest in benefit risk

ASA Bayesian Statistics Working Group – Benefit Risk Team

Members

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Our Aims

- To understand how best to apply benefit-risk methodologies across the pharmaceutical industry
- To discuss and make recommendations on key methodological issues
- To share examples of how benefit-risk has been used within pharmaceutical companies
- To share external information including new developments around benefit-risk
- To publish research in journals and books regarding these methodologies.
- To disseminate information on research and best practices to broader scientific community as well as to engage in education efforts through conferences, workshops and seminars.

How Long Have We Been Around

- Started in 2014
- Early publications include:
  - Costa M, He W, Jemiai Y, Zhao Y, Di Casoli C, **The Case for a Bayesian Approach to Benefit-Risk Assessment: Overview and Future Directions, Therapeutic Innovation and Regulatory Science,** Vol 51, Issue 5, 2017**,** journals.sagepub.com/doi/abs/10.1177/2168479017698190
  - Book chapter entitled "Risk Benefit" for the book *Bayesian Methods in Pharmaceutical Research* published by CRC press. Editors: Emmanuel Lesaffre, KULeuven, Belgium, Gianluca Baio, University College, London, UK, Bruno Boulanger, Arlenda, Belgium.
- Re-started in 2021, been meeting at least monthly since, added new members

Why Use Bayesian Methods: A Case Study

Treatment for PAD – VOYAGER Study

Treatment for Symptomatic PAD	**Benefits** *(reduced risk of events)*	All-cause mortality Non-fatal ischemic stroke[1] Non-fatal myocardial infarction[1] Non-fatal acute limb ischemia[1] Non-fatal major amputation of vascular etiology[1] Need for revascularization procedure after randomization
	Risks *(increased risk of events)*	Non-fatal TIMI intracranial bleed[2] Non-fatal, non-intracranial TIMI major bleed[2] Non-fatal TIMI minor bleed Non-fatal TIMI bleed requiring medical attention Non-fatal TIMI minimal bleed

[1] Together with CV death, components of the pre-specified primary efficacy endpoint
[2] Together with fatal bleeds, components of the pre-specified primary safety endpoint

Review Documentation:
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/202439Orig1s035.pdf

MCDA and SMAA

- MCDA calculates overall utility in each treatment group i as:

$$U_i = w_1 u_1(\xi_{i1}) + \cdots + w_n u_n(\xi_{in})$$

  - ξ_{ij} - Performance of treatment i on criterion j
  - $u_j(.)$- Linear value function that maps the performance on criterion j to [0,1] scale
  - w_j - Weight (relative importance) given to criterion j
- Probabilistic MCDA (pMCDA) accounts for uncertainty in ξ_{ij} values by:
  - Drawing from the posterior distribution of these values
  - Calculating a posterior $Prob(U_i > U_{i'})$
- SMAA builds on pMCDA by accounting for uncertainty in weights, drawing w_j from a simplex such that:
  - $a < \frac{w_j}{w_{j'}} < b$, where $w_{j'}$ is the weight for most important criterion, a , b specified and $\sum_j w_j = 1$

MCDA, SMAA Stakeholder Preferences

- Preference was elicited from 7 reviewers
- All reviewers indicate all cause mortality most important
  - Specified tradeoffs for other outcomes with a range expressing uncertainty
- As an example, we'll focus on Reviewer E
  - Preferences from other reviewers led to similar conclusion

Table 4. Tradeoffs against all-cause mortality. Tradeoffs were provided by each respondent as an individual response and a plausible range.

	Respondents familiar with sNDA					Other FDA	
Outcome	**A**	**B**	**C**	**D**	**E**	**F**	**G**
Ischemic stroke	1	3	7	5	3	5	5
	0.5-2	2-5	3-15	1-30	2-4	5-7	3-20
Myocardial infarction	5	3	4	5	4	8	8
	2-10	2-4	2.5-7.5	2-30	3-5	7-10	5-20
Acute limb ischemia	20	5	15	20	6	5	7
	5-20	3-10	10-20	5-50	5-7	5-7	3-15
Major amputation of	10	2	7.5	20	5	8	5
vascular etiology	2-10	2-3	5-15	5-50	4-6	7-10	2-20
Revascularization	40	5	25	75	9	9	15
procedure	5-50	3-10	20-40	50-200	8-12	8-9	12-40
TIMI intracranial bleed	1	1	8	2	2	4	5
	0.5-2	1-1	10-20	1-10	2-3	4-6	2-10
Non-intracranial TIMI	40	10	15	30	7	7	7
major bleed	540	5-20	10-25	20-100	6-9	6-7	3-15
TIMI minor bleed	50	365	75	100	25	8	15
	5-50	180-∞	50-100	50-300	20-40	7-10	10-40
TIMI bleed requiring	100	365	125	300	9	8	30
medical attention	5-50	180-∞	100-150	100-500	8-20	7-10	20-50
TIMI minimal bleed	∞	∞	150	500	35	10	∞
	10-∞	∞-∞	100-200	300-1000	30-70	9-10	∞-∞

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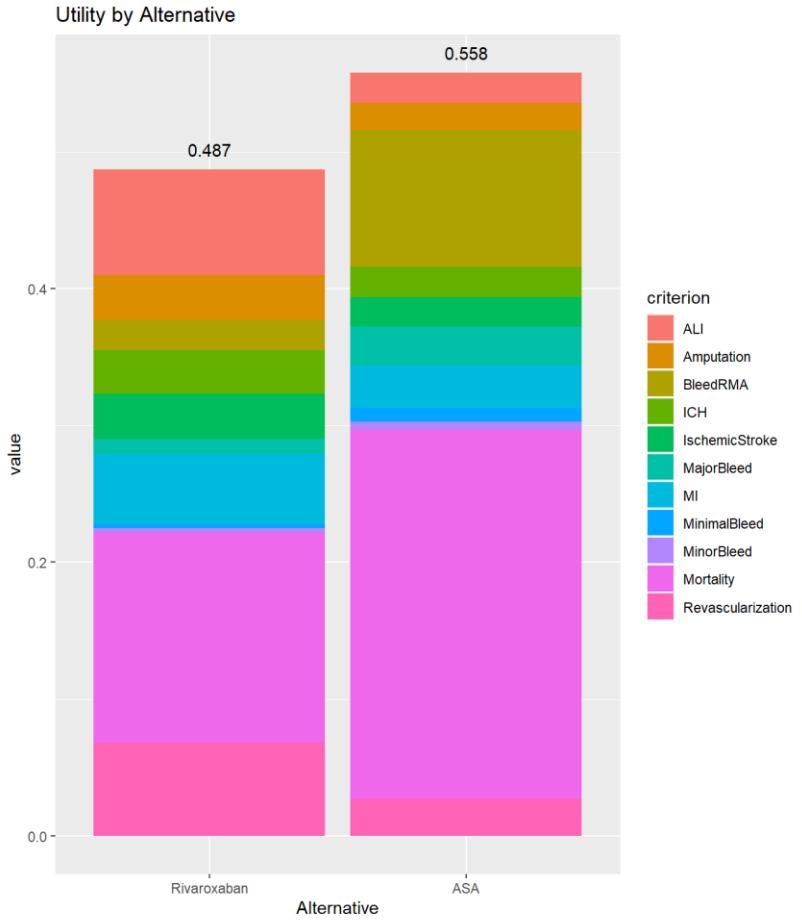
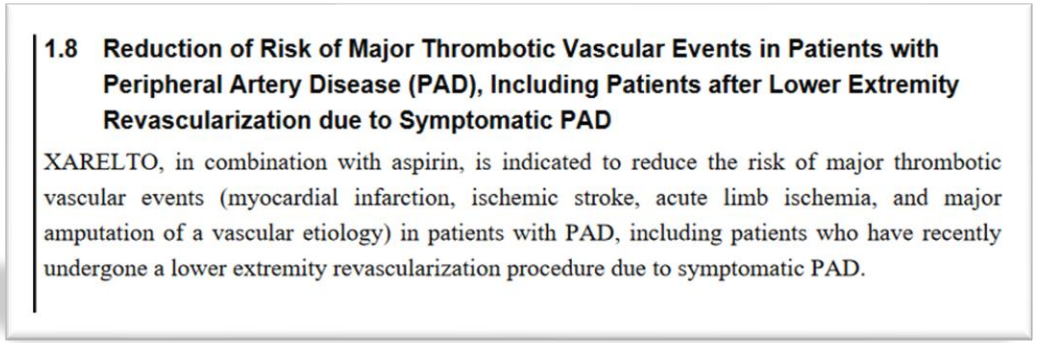
MCDA, SMAA Results – Reviewer E

- MCDA results indicated rivaroxaban slightly less preferred
  - Net Utility for Treatment = 0.49
  - Net Utility for SoC = 0.56
  - Driven by difference in most important criterion of All-cause mortality
- SMAA results similar
  - Probability of treatment preferred = 32.5%
- Only one (of 7) reviewers' weight preferences indicated a preference for treatment in MCDA and SMAA



Regulatory Decision

- Regulatory decision-making process considered (among other things): VOYAGER met the pre-specified primary endpoint, COMPASS mortality results statistically different, heterogeneity in regulator preferences
  - **No quantitative analysis that tried to formally incorporate prior study data**
- Approved on 23 August 2021, creating a combined PAD indication
  - Results of the two trials – COMPASS and VOYAGER – summarized together in labeling
  - Benefit-risk analysis documented alongside clinical and statistical reviews and referenced in regulatory benefit-risk assessment



1.8 Reduction of Risk of Major Thrombotic Vascular Events in Patients with Peripheral Artery Disease (PAD), Including Patients after Lower Extremity Revascularization due to Symptomatic PAD

XARELTO, in combination with aspirin, is indicated to reduce the risk of major thrombotic vascular events (myocardial infarction, ischemic stroke, acute limb ischemia, and major amputation of a vascular etiology) in patients with PAD, including patients who have recently undergone a lower extremity revascularization procedure due to symptomatic PAD.

Review Documentation: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/202439Orig1s035.pdf
Label: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/202439_S035_022406S037lbl.pdf

Prior Study (COMPASS) Data

- "Efficacy endpoints in COMPASS PAD were analysed according to the pre-specified endpoints in VOYAGER when applicable."
- Differences on benefits:
  - Ischemic stroke for VOYAGER included stroke of uncertain/unknown etiology whereas COMPASS only included ischemic stroke
  - Amputation included adjudicated events in VOYAGER and investigator reported events in COMPASS
- Data on risks such as bleeding events reported only in overall population, not available for PAD
- Can justifiably borrow data on All-Cause Mortality, MI and maybe Ischemic Stroke

Table 20: Efficacy Results in VOYAGER (Intent-to-Treat Population) and COMPASS PAD

	VOYAGER			COMPASS PAD		
	XARELTO N=3286	Placebo N=3278	Hazard Ratio (95% CI)* p-value†	XARELTO N=2492	Placebo N=2504	Hazard Ratio (95% CI)*
Outcome Components	Event Rate (%/year)			Event Rate (%/year)		
5-Component Outcome (Major thrombotic vascular events)‡	6.8	8.0	0.85 (0.76, 0.96) p=0.0085	3.4	4.8	0.71 (0.57, 0.87)
MI	1.7	1.9	0.88 (0.70, 1.12)	1.1	1.5	0.76 (0.53, 1.09)
Ischemic Stroke§	0.9	1.0	0.87 (0.63, 1.19)	0.5	0.9	0.55 (0.33, 0.93)
CV death¶	2.5	2.2	1.14 (0.93, 1.40)	1.4	1.7	0.82 (0.59, 1.14)
ALI	2.0	3.0	0.67 (0.55, 0.82)	0.4	0.8	0.56 (0.32, 0.99)
Major amputation of a vascular etiology#	1.3	1.5	0.89 (0.68, 1.16)	0.2	0.6	0.40 (0.20, 0.79)
All-cause mortality	4.0	3.7	1.08 (0.92, 1.27)	2.8	3.1	0.91 (0.72, 1.16)

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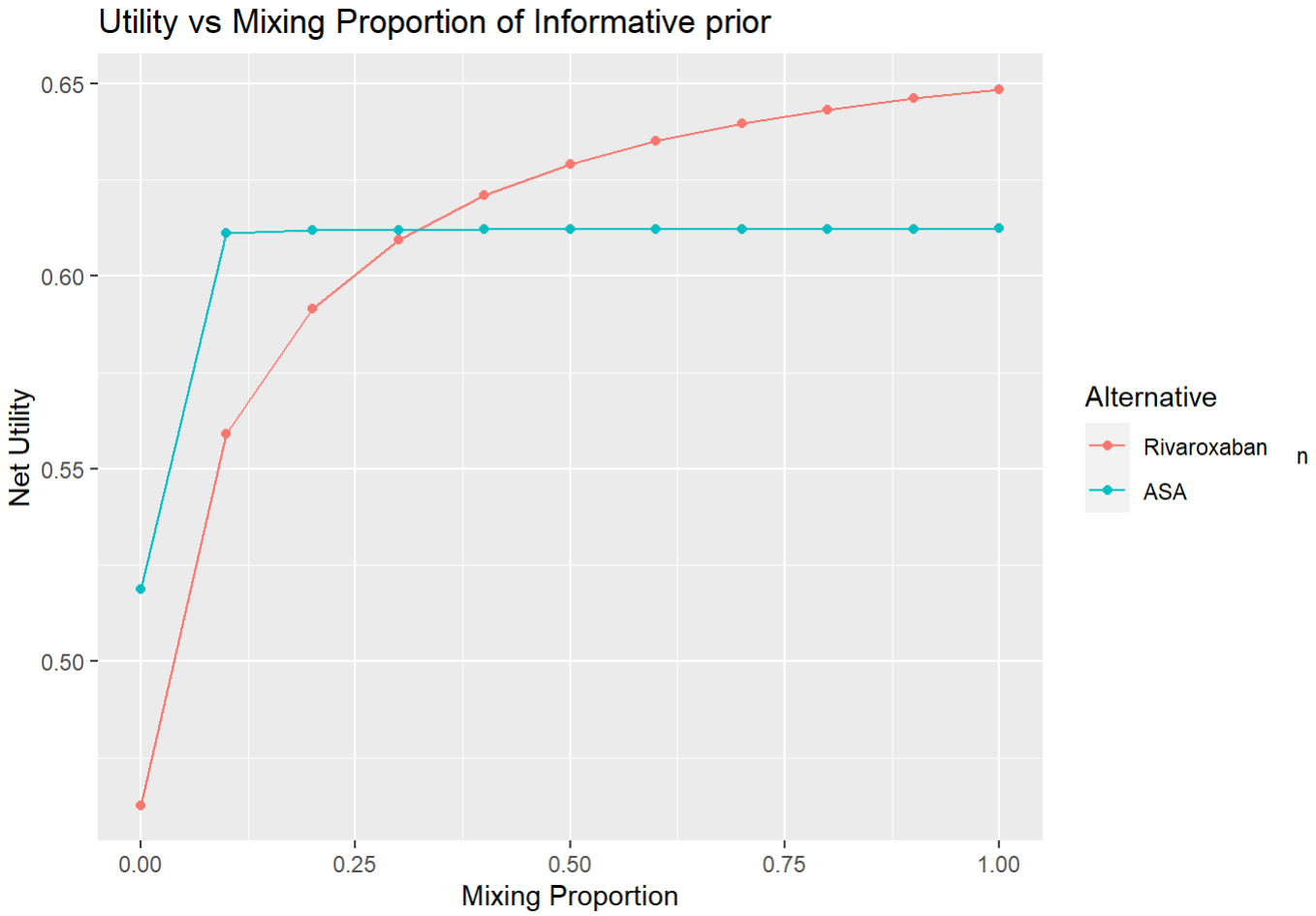
Label: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/202439_S035_022406S037lbl.pdf

Incorporating Prior Study Data: Borrowing through Conjugate Mixture Priors

- Borrow from a prior study data but control amount of information borrowed using a mixture prior
- Imagine a scenario where performances, ξ_{ij}, are rates, we use a conjugate Gamma-Poisson model and specify priors:
  - $\xi_{ij} \sim d * Gamma(a_{ij}, b_{ij}) + (1-d) * Gamma(0.001, 0.001)$
  - d is the weight (between 0 and 1) we want to put on the prior coming from prior study, usually with $a_{ij}, \mathrm{b_{ij}}$ such that a_{ij}/b_{ij} was the rate observed in this prior study
- Similarly for Beta-Binomial (proportions) and Normal-Normal (continuous) models

Effect of Borrowing

- With ~ 30% borrowing from COMPASS study data on three efficacy outcomes: all cause death, MI, ischemic stroke, rivaroxaban becomes preferred alternative
- For SMAA results, using specified range of weights, rivaroxaban became the preferred alternative (Probability > 50%) at 20% borrowing
- Both results indicate similarity / exchangeability with prior study as very little borrowing needed to change results
- Support conclusion reached by structured benefit risk assessment

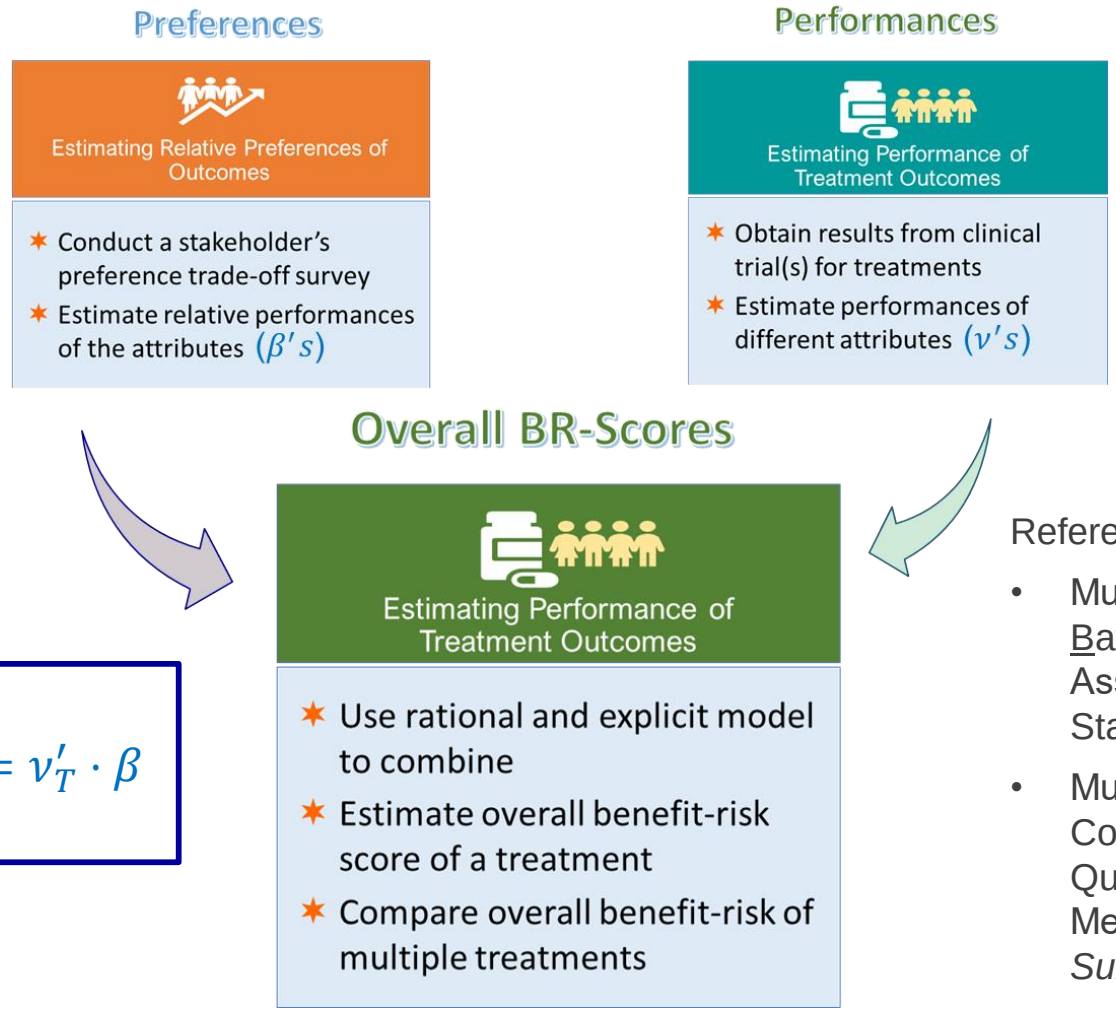


Takeaways

- Bayesian Methods
  - Formally considering prior experience with the compound
    - Amount of borrowing from single prior study could be varied to see sensitivity in findings and / or dynamic borrowing could be used to determine weights
    - Hierarchical models could be used when multiple trials are involved
  - More generally, facilitate computation of probabilities of simultaneous efficacy and safety
- Paper published in TIRS:
  - Dharmarajan, S., et al. Incorporating Prior Data in Quantitative Benefit–Risk Assessments: Case Study of a Bayesian Method. *Ther Innov Regul Sci* 58, 415–422 (2024).
  - Shiny App: Quantitative BR Analysis (shinyapps.io)

What Else Have We Been Up To?

Methods: HBBR



$$U_T = \sum_{j=1}^{m} \sum_{j=1}^{k_j} \nu_{j,l} \cdot \beta_{j,l} = \nu_T' \cdot \beta$$

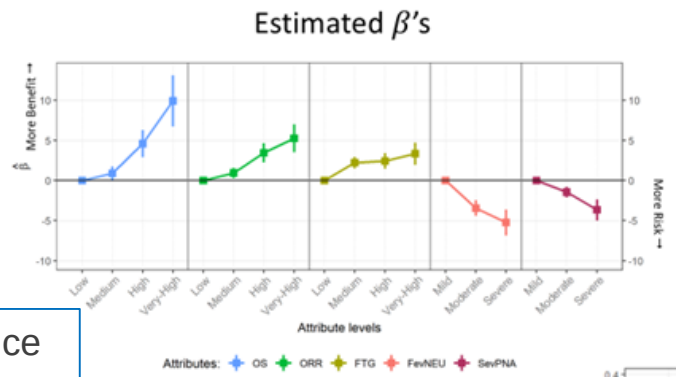
References:

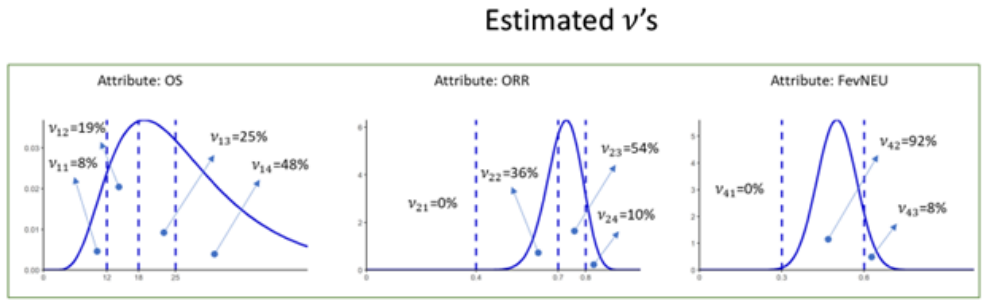
- Mukhopadhyay S, et. al., 2019. "Hierarchical Bayesian Benefit–Risk Modeling and Assessment Using Choice Based Conjoint." Statistics in Biopharmaceutical Research.
- Mukhopadhyay, S., Payne, R., 2024. "A Comprehensive Bayesian Approach to Assess Quantitative Benefit-Risk Assessment of a Medical Product Throughout its Life Cycle". *Submitted*.

Illustration

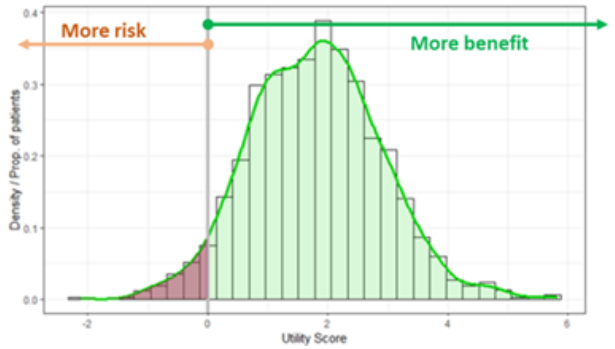
- Illustration of HBBR Using Hematologic Indication

Estimated preference parameters ($\beta's$) from specially designed DCE survey from a small number of responders





Estimated performance parameters ($\nu's$) of a treatment from a clinical trial data



Distribution of Overall BR Utility Score of the Treatment

Note: simulated and mock data were used for illustration

Software

- Bayesian MCDA SMAA Shiny App
- Brisk R package available on CRAN
- ‘hbbr’ R package available on CRAN (R-shiny version in preparation)

Organized Sessions, Talks

- ASA BIOP RISW 2022
  - Session Name: *Recent Developments in Bayesian Benefit Risk Analysis: Methods and Case Studies*
  - Presenters: Saurabh, Zhong, Sai
- JSM 2023
  - Session Name: *Leveraging Innovative Methods and Tools for Interactive Quantitative Safety and Benefit-Risk Assessment*
  - Presenters: Erya Huang (Bayer), Neetu Sangari (Pfizer), Richard, Saurabh, Sai
- ISBS 2024
  - Session Name: *Innovative and Practical Approaches to Quantitative Benefit-Risk Assessment of Medical Products*
  - Presenters: Saurabh, Margaret Gamalo (Pfizer), Zhili, Richard
- MBSW 2024
  - Session Name: *HTA statistics, Benefit-Risk, HEOR*
  - Presenters: Saurabh, Richard, Hongwei Wang (AbbVie)
- R in Pharma (coming up in October 29)
  - Presenters: Saurabh
- Looking For Additional Venues To Outreach

Future Directions

- Landscape paper and short course(s) planned for next year
- Join us!
  - Welcome statisticians, epidemiologists, clinical scientists, psychometricians, data scientists
  - Email Madhurima at Madhurima.Majumder@bayer.com
- Collaborate
  - Share your experience with us, we geek out on a monthly basis and love guest speakers!

Thank You!