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Benefit-Risk Assessment Using Bayesian Choice-Based Conjoint: An Example

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Panel Session: Bayesian Methods in Assessing Benefit-Risk Preference in a Structured Framework

Report on work performed with Saurabh Mukhopadhyay, Jeremy Jokinen and Anthony Oladipo

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Summary

Increasing demand for evidence-based value judgments, particularly those incorporating the patient viewpoint, in pharmaceutical development, regulatory decision-making and marketing has led to guidance about how to incorporate such evidence but optimal methodology is still under study and may vary depending on decision type

Hierarchical Bayesian methodology used with partial panel discrete choice experiment (AKA choice-based conjoint) sampling from stakeholders has the potential to minimize cognitive burden for respondents and minimize sample size needed

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Benefit-risk Planning and Assessment

Where might quantitative analysis fit?

Multiple Criteria Decision Analysis – A Framework

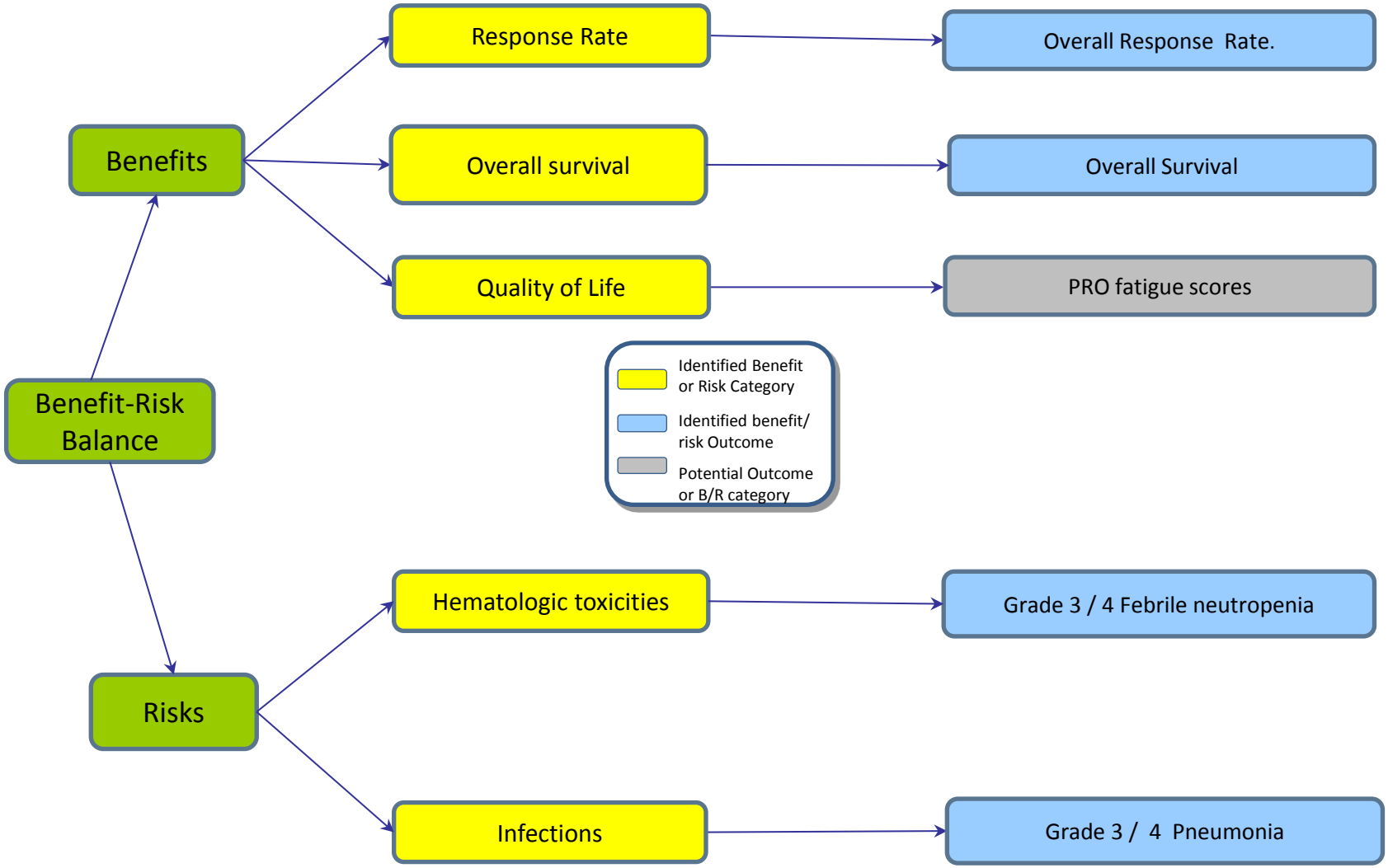
Step	Description
Defining the decision problem	Identify objectives, type of decision, alternatives, stakeholders, and output required
Selecting and structuring criteria	Identify criteria relevant for evaluating alternatives
Measuring performance	Gather data about the alternatives' performance on the criteria and summarize this in a "performance matrix"
Scoring alternatives	Elicit stakeholders' preferences for changes within criteria
Weighting criteria	Elicit stakeholders' preferences between criteria
Calculating aggregate scores	Use the alternatives' scores on the criteria and the weights for the criteria to get "total value" by which the alternatives are ranked
Dealing with uncertainty	Perform uncertainty analysis to understand the level of robustness of the MCDA results
Reporting and examination of findings	Interpret the MCDA outputs, including uncertainty analysis, to support decision making

MCDA, multiple criteria decision analysis.

International Society for Pharmacoeconomics and Outcomes Research MCDA Emerging Good Practices Task Force

Value in Health 19(2016)1-13.

Benefit-risk value tree example - oncology



Methodologic Approaches

- Healthcare MCDA approaches most commonly use a value measurement model
  - To what degree is one alternative preferred over another?
  - Additive models combine criteria (features) to get total score for each alternative considered
- Scoring methods fall into decompositional versus compositional
  - Compositional looks at each criterion separately
  - Decompositional has stakeholders rank alternatives based on some or all of the criteria
    - CBC or DCE fall into this category
    - Partial CBC methodology is what we will describe, PAPRIKA (Potentially All Pairwise RanKings of all possible Alternatives) is a partial methodology described by ISPOR

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Pilot project – Incorporating stakeholder preferences

Hierarchical Bayesian analysis of Discrete Choice Experiment

Choice Based Conjoint

- In Choice-Based-Conjoint (CBC), also known as DCE, respondents choose among sets of experimentally controlled profiles
- Even with a moderately large number of attributes (features) present, it becomes more challenging to the respondents to choose by comparing from a set of Full Profiles (FPs).
- A Partial Profile CBC may be more efficient (less cognitive burden) and so recommended to administer and capture true value of individual attributes.

Full

Hoover	Eureka	Panasonic
9 Amps	12 Amps	10 Amps
12 ft cord	16 ft cord	24 ft cord
Dirt sensor	-	-
-	Micron filter	Micron filter
1 yr warranty	2 yr warranty	6 mo warranty
Edge cleaner	Edge cleaner	-
Flex hose	-	Flex hose
-	Height adj.	Height adj.
$249	$199	$299

Partial

Hoover	Eureka	Panasonic
9 Amps	12 Amps	10 Amps
Edge cleaner	Edge cleaner	-

Bayesian Solution

Hierarchical Bayes (HB) approach provides a method of recovering utilities from a relatively small number of subjects, each evaluating only a small (random) subset of all possible combinations.

By using an extended model, HB allows us to estimate the effect of respondents' characteristics on their part-worth utility values

- For example, in case of patients it may be age, gender, disease severity, etc. For investigators, it may vary based on experience, patient's condition, etc.

Even within the same set of characteristics, those values may also differ from one respondent to another.

- We model this through hierarchical specification of the priors on part-worth utilities.

Bayesian Solution

The Hierarchical Bayes benefit risk (HBBR) model we propose here is developed for a CBC experiment with partial profiles.

We use a utility model to estimate the benefit-risk of a treatment. In this process, we first estimate *implicit* part-worth utility values of each attribute and then combine them to recover the overall B-R.

Specifically, a multivariate statistical model is used for this purpose:

$$u = x'\beta$$

where u is the overall B-R utility of a treatment, part-worth utility parameters β is associated to various attribute levels x which is a vector of 1's and 0's indicating whether or not the corresponding attribute levels are present in a treatment profile.

An important feature of the Bayesian modeling known as borrowing strength will be leveraged here to estimate all attribute level utilities.

Bayesian Solution

- These overall B-R utilities (u) are not explicitly observables but we can observe them implicitly from responders' choices. We utilize a logit model to *link* the overall B-R utility of h-th respondent with the preference for k-th choice alternative:

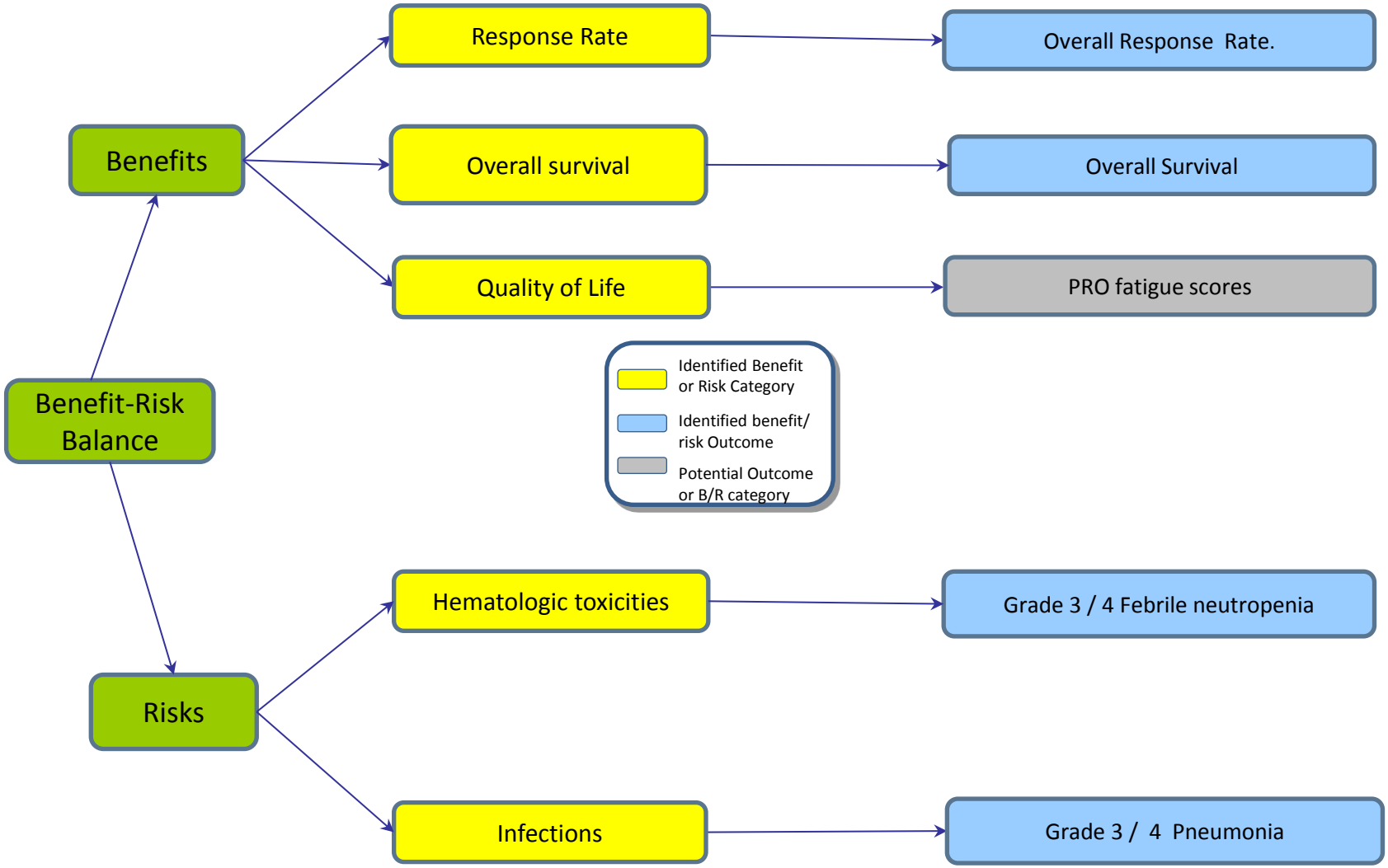
$$p_{\{h,k\}} = \text{logit}(u_{h,k}) = \frac{\exp(x_k'\beta_h)}{\sum_l \exp(x_l'\beta_h)}$$

  We then specify a conjugate Hierarchical priors for β_h using a normal and inverse-Wishart priors.

- Full methodologic details will be shared in an upcoming manuscript.

- We propose estimating the model using a simple choice based conjoint (CBC) experiment where respondents will make a series of choices and it is expected that the preferred options will have higher utility as compared to the non-preferred options.

Benefit-risk value tree example - oncology



Example tradeoff questions based on the value tree

1) [A] High (~20 months) OS and High (~60%) chance of febrile neutropenia vs.

[B] Moderate (~15 months) OS and Low (~20%) chance of febrile neutropenia

2) [A] Very High (~30 months) OS and Moderate (~40%) chance of febrile neutropenia vs.

[B] High (~20 months) OS and Low (~20%) chance of febrile neutropenia

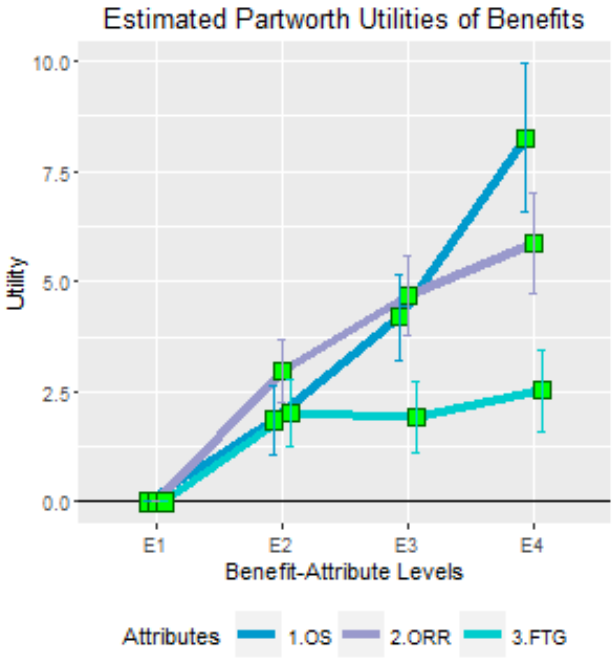
3) [A] Low (~12 months) OS and Low (~5%) chance of severe pneumonia vs.

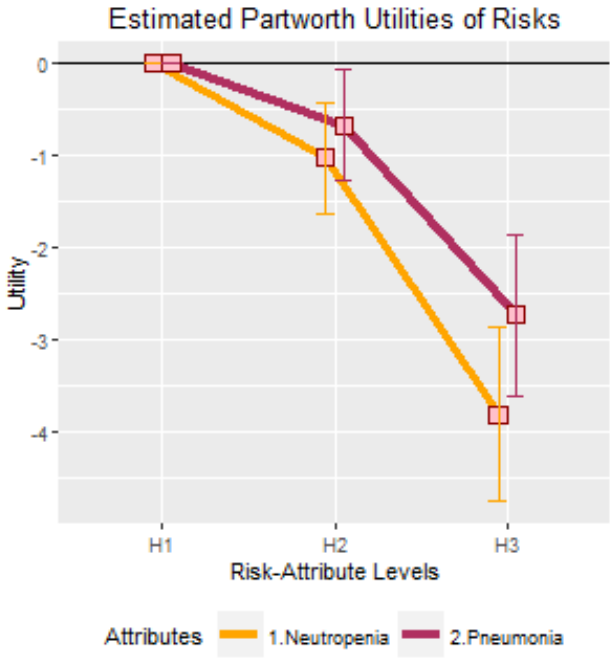
[B] High (~20 months) OS and High (~20%) chance of severe pneumonia

Implementing HBBR Model

- In our example the treatment under consideration has 3 benefit attributes (B1, B2 and B3) and 2 risk attributes (R1 and R2).
- Each of the benefit attributes has 4 levels and each risk attribute has 3 levels
- We construct all distinct choice pairs where respondents would need to make tradeoff between one benefit and one risk attribute levels to make the choice.
- In our example, there are 108 such choice pairs for which respondents would need to make a tradeoff to indicate their preferences.
- We aimed for a sample size of 40 where each respondent randomly received a 'deck' of 18 different pairs to rank. Decks were created to lead to a total of 8 or more responses per pair of criteria across the 40 respondents.
- Internal experts used for the pilot, designed to ultimately sample patients. Data represent 23 respondents to date.

Estimated Part-worth Utilities





Overall Survival (OS): 12, 15, 20, 30 months
Objective Response Rate (ORR): 45, 60, 75, 85%
Fatigue Improvement (FTG): 20, 25, 35, 45% chance

Febrile neutropenia: 20, 40, 60% chance
Pneumonia: 5, 10, 20% chance

Some conclusions according to these preferences of respondent stakeholders (internal SMEs):

1. **If OS is high (30 months) then average B-R is positive regardless of risk**
2. **If risk of febrile neutropenia is high, OS and/or ORR must be high or very high for positive B-R**
3. **Utility for fatigue improvement plateaus at 25% chance**

Conclusions

- Although DCE is increasingly used in health outcome research, its usage in benefit-risk assessment so far is fairly limited, but the proposed HBBR model drastically reduces hindrances that contributed to this under-utilization.
- This model is expected to produce very high quality preference data with small number of respondents.
- Proper calibration of various attribute levels is needed – which should be done in collaboration with the experts in the therapeutic area and also through pilot experiments.
- Uncertainty assessment methodologies are in progress, with deterministic and probabilistic approaches being explored.
- While there are not always quantitative answers to benefit-risk assessment and related decision makings, when quantitation is desired this method represents a promising approach for drug development.

Additional References and Acknowledgments

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Thanks to Madeline Michael for her work to create the online discrete choice survey tool.


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[Backup slide] Fitting HBBR to the Choice Data

- The HBBR model was fitted to the data using MCMC method (Gibbs sampler)
  - After the iterations converge to a posterior distribution, parameter estimates are obtained using draws from their joint posterior distribution.
  - The 1st plot shows traces of actual draws of the various part-worth utilities from the MCMC simulation.
  - The 2nd plot shows the trace of log-likelihood function to ensure that the MCMC reached a stationary state