MSR127

Implementing Simultaneous Maximum Acceptable Risk Thresholds (SMARTs) in Discrete Choice Experiments (DCE): A Feasible Approach to Quantify Tolerance for Multiple Risks

L. Panattoni[1], J. Coulter[2], G. Gahlon[1], B. Hauber[2], N. Land[1], A.H. Nguyen[1], T. Flottemesch[1], M. Maravic[1], P. Hur[2]

[1]Precision AQ, New York, NY, USA; [2]Pfizer Inc., New York, NY, USA

INTRODUCTION

- Quantifying patient preferences for treatment benefits and risks is critical for informing regulatory decisions, clinical guidelines, and shared decision-making.
- Maximum acceptable risk (MAR) is a widely used metric that estimates the highest level of a single risk patients are willing to accept for a given benefit, assuming all other risks remain constant.
- However, real-world treatment decisions often involve multiple risks occurring simultaneously, so considering tolerance for multiple risks jointly may provide important information.
- To address this complexity, simultaneous maximum acceptable risk thresholds (SMARTs) have been proposed as an extension of MAR to capture trade-offs across multiple risks in combination.[1]

Objective

- To demonstrate the feasibility of estimating SMARTs and compare SMARTs to individual MAR estimates within and across regions.

METHODS

Discrete Choice Experiment

- A DCE was utilized to capture the trade-offs patients make between efficacy (benefits) and adverse events (risks) when choosing between potential treatment options.
- A total of N=177 patients in the United Kingdom (UK) and N=246 patients in the EU (France, Germany, Italy, and Spain) were included in the analysis.
- Preference weights were estimated using random parameters logit models and effects coding to obtain a preference weight for each level of the attributes tested.

Benefit-Risk Trade-Off Measures

- Benefit-risk trade-offs (MARs and SMARTs) were computed for three risks: Risk A, Risk B, and Risk C. A treatment benefit was selected from one of the efficacy attributes tested.
- **MARs** were calculated as the percentage-point change in a risk that exactly offsets the utility gained by a given increase in benefit.[2]
  - A MAR was calculated for all levels of treatment benefit and risk attributes.
  - Each estimated MAR assumes other risks are constant at their lowest level.
- The **SMART** of Risks A, B, and C was estimated and identified jointly acceptable risk combinations assuming a specified improvement in the efficacy attribute is achieved.
  - The SMART (Fairchild et al 2023)[1] is calculated as:

$$SMART = p^1_{j=1} = l^{-1}\left(\frac{g(H^1)-g(H^0)-\sum_{j=2}^{J}[l_j(p^1_j)-l_j(p^0_j)]*[-k_j(AE_j)]}{-k_{j=1}(AE_j)} - l(p^0_{j=1})\right)$$

Where:

- H^i is a vector of *i* treatment benefits, and $g(H^1)-g(H^0)$ is the utility change from changing from vector H^1 to H^0.
- $k(AE_j)$ is the risk of adverse event *j*.
- *l*(.) are weighted probabilities to allow non-linear preferences.

- Confidence bands for the MARs and SMARTs were computed using the Krinsky-Robb method (1986).[3]
- The MARs, SMARTs, and their respective confidence bands were compared across regional subgroups.

Implementation of SMARTs

Step 1) Select a benefit and at least two risks.

- Scale the preference weights from 0-10 in reference to the benefit, most preferred level is 10 and the least preferred level is 0.
- Set all risk preference weights to the same scale (**Table 1**).

Benefit of interest = 10% increase in efficacy

$$\textbf{Benefit quantity} = \left(\frac{10}{45-20}\right) * 10 = 4 = S$$

Step 2) Calculate the total disutility at each incremental unit in each risk attribute.

- Assume the lowest level of risk yields 0 disutility.
- For each incremental increase in risk, calculate the slope between risk and utilities.
- Using the slopes, calculate the cumulative utility for each incremental increase in risk (**Table 2**).

Step 3) For each level of calculated utility, calculate the total disutility of the combined risks for every risk combination.

Step 4) Identify risk thresholds in one of two ways:

i. Find max(*j*) for each level *i* such that $a_i + b_j \leq S$.
ii. Calculate total disutility [Step 2] for all but 1 risk. Then, subtract the disutility from the benefit to find the maximum threshold with the last risk.

Step 5) Using the thresholds identified in Step 4, plot the results using a smoothing function or fit a functional form.

- For each level *i*, we have the maximum *j* and can plot level *i* vs. *j*.

Table 1. *Re-scaling of preference weights (Example)*

Attribute-Attribute Level	Weights	Re-scaled values
Efficacy Attribute (Higher level = greater utility)		
20%	-1.94	0
35%	0.26	6.07
45%	1.68	10
Risk A (Higher level = lower utility or *greater disutility*)		
1%	1.66	0
4%	0.07	-4.37
7%	-1.73	-9.33
Risk B (Higher level = lower utility or *greater disutility*)		
0.1%	0.46	0
0.3%	-0.14	-1.66
0.5%	-0.32	-2.17

Table 2. *Calculating total disutility at each incremental unit (Example)*

Incremental level of Risk A	Utility	Slope
0.01000	0.00000	-145.766
0.01005	-0.00729	-145.766
0.01010	-0.01458	-145.766
0.01015	-0.02186	-145.766
0.01020	-0.02915	-145.766
…		
0.03995	-4.36569	-145.766
0.04000	-4.37298	-165.082
0.04005	-4.38123	-165.082
0.04010	-4.38949	-165.082
…		

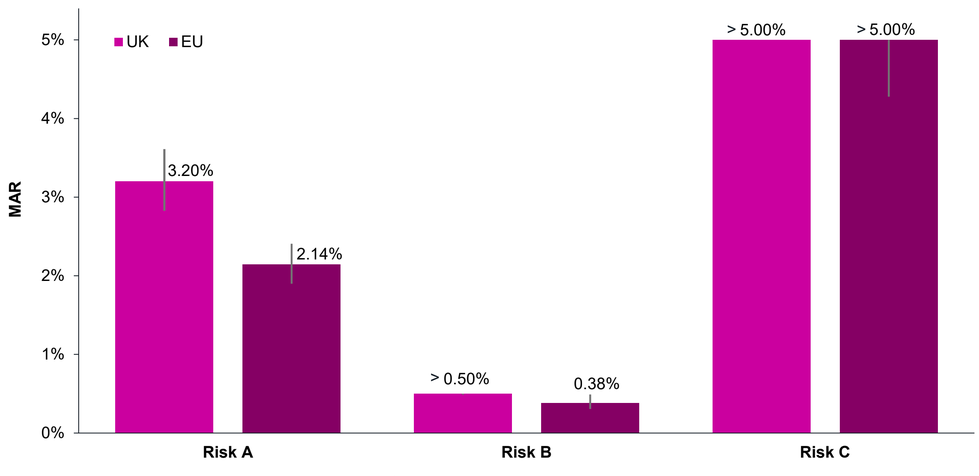
Confidence Intervals

- Using the preference weights as the mean vector, μ, and the variance-covariance matrix from the model as matrix Σ, sample a sufficient number of replicates, *B*, from a multivariate Gaussian distribution using mean μ and variance Σ.
- Iterate Steps 1-4 *B* times. For each level of one risk, compute the 2.5th percentile value and the 97.5th percentile value for the lower and upper threshold values.

RESULTS

- Tolerance for any individual risk was lower when considered in combination with other risks (SMART) versus when considered alone (MAR).
- Across regions, the MAR of Risk A in exchange for the treatment benefit was higher for patients in the UK than in the EU (3.2% [CI=2.8%-3.6% vs. 2.1% [CI=1.9%-2.4%]) (**Figure 1**).
- The MARs for Risk B and Risk C were close to or above their respective maximum levels tested in the DCE (0.5% and 5%, respectively).

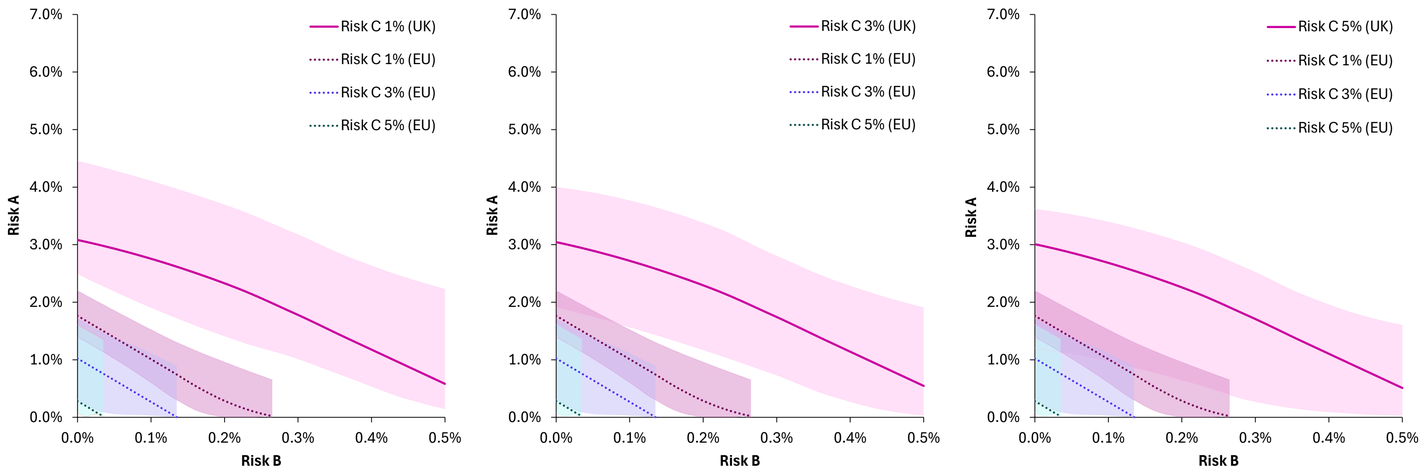
Figure 1. *MARs in exchange for the specified treatment benefit by region*



Risk attributes were capped at the highest level of each risk attribute that was shown in the DCE exercise. Error bars indicate 95% CIs. Ranges of risk levels included in the DCE: Risk A 1%-7%; Risk B 0.1%-0.5%; Risk C 1%-5%.

- In exchange for a specified treatment benefit, patients in the UK were willing to accept significantly higher levels of Risk A and Risk B when Risk C was 1% (*Left Panel*, **Figure 2**) – and when Risk C was 3% when Risk B exceeded approximately 0.1% (*Center Panel* , **Figure 2**) – than every risk combination for patients in the EU.
  - That is, when Risks A and B were considered jointly, the SMART demonstrated patients in the UK were willing to accept significantly higher levels of each risk than patients in the EU if Risk C was below 3%.
- However, when Risk C was 5%, there were no statistically significant differences between any risk combination for patients in the UK and EU (*Right Panel*, **Figure 2**).

Figure 2. *SMARTs for three risks in exchange for the specified treatment benefit by region*



Graph axes represent the tested ranges in the DCE; a LOESS smoother was applied to each curve. Shaded areas represent 95% CIs. The areas where the confidence bands do not overlap indicate areas where there are statistically significant differences in risk tolerance between regions.

CONCLUSIONS

- Calculating SMARTs is feasible and may provide a more nuanced understanding of benefit-risk trade-offs than traditional MAR estimates.
- In addition to exhibiting variation across countries in benefit-risk trade-offs, our findings show patients' tolerance for individual risks decreases when multiple risks are considered jointly, highlighting the importance of accounting for real-world complexity in preference studies.
- Incorporating SMARTs into benefit-risk assessments may improve the accuracy of patient-centered evaluations and can enhance shared decision-making by reflecting the simultaneous nature of treatment risks.

PRECISION AQ™

Booth #1003

Pfizer

REFERENCES

1. Fairchild AO, Reed SD, Gonzalez JM. Method for calculating the simultaneous maximum acceptable risk threshold (SMART) from discrete-choice experiment benefit-risk studies. Med Decis Making. 2023;43(2):227-238.
2. Hauber AB, González JM, Groothuis-Oudshoorn CG, et al. Statistical methods for the analysis of discrete choice experiments: a report of the ISPOR conjoint analysis good research practices task force. Value Health. 2016;19(4):300-315.
3. Cooper JC. A comparison of approaches to calculating confidence intervals for benefit measures from dichotomous choice contingent valuation surveys. Land Economics. 1994:111-122

ACKNOWLEDGMENTS

Funding for early conceptual research for this study was provided by Pfizer, Inc.

Abbreviations:
CI, confidence interval; **DCE**, discrete choice experiment; **EU**, European Union countries included in study (France, Germany, Italy, and Spain); **MAR**, maximum acceptable risk; **SMART**, simultaneous maximum acceptable risk thresholds; **UK**, United Kingdom

Presented at the 2025 ISPOR Europe Annual Meeting in Glasgow, Scotland 9-12 November 2025.