Use of Patient Preferences Data Regarding Multiple Risks to Inform Regulatory Decisions

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Introduction and Motivation

- Assessing whether treatment benefits outweigh risk of potential adverse events is central to regulatory and clinical decisions in healthcare.
- Discrete-choice experiments (DCEs): Patients' responses to DCEs are often used to quantify tradeoffs across features of medical interventions, and these features often include adverse-event risks expressed as probabilities.
- **Maximum-acceptable risk (MAR):** Tradeoffs from DCEs are used to estimate the maximum increase of single adverse-event risk that would be acceptable given a specified level of benefit. Limitations:
  - Adverse-event considered one at a time.
  - Assumes that all other risks are unchanged.
  - Does not account for correlated adverse-event risks.
- MARs do not make full use of the robust experimental data from stated-preference surveys and has very strong assumptions.
- **SMART (Simultaneous maximum-acceptable risk threshold):** estimates combinations of probabilistic risks of different adverse events that would be acceptable given a specified benefit.
- OBJECTIVE:
  - To estimate MARs and SMARTs for 3 published patient preference studies to demonstrate when the approaches may result in qualitatively different interpretations of risk acceptance.

QUICK FACTS

> Estimates of maximum-acceptable risk (MAR) of an adverse event for a defined treatment benefit can be useful to inform regulatory decisions; however, the conventional metric considers one adverse event at a time.

> This manuscript applies a new approach known as SMART that accounts for multiple adverse events to three published patient preference studies.

> Findings reveal that conventional MARs could lead decision makers to accept a treatment based on individual risk that would not be acceptable if multiple risks are considered simultaneously.

METHODS

- For each study, we extract the raw (i.e., log odds) preference weight.
- We used these preference weights to replicate the reported MAR estimates.
- We estimated SMARTs as follows:
  - Risk A: X^A (levels of risk), ϕ^A (maps risk levels to utilities).
  - Risk B: X^B (levels of risk), ϕ^B (maps risk levels to utilities).
  - Expected Benefit/Baseline Utility:

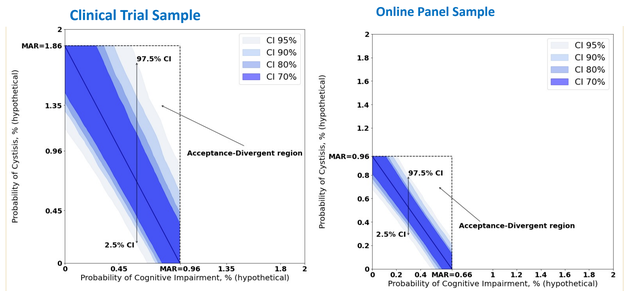
$$X^A = \emptyset^{A(INV)}(benefit + \emptyset^B(X^B))$$

- Result: A combination of $\{x^A, x^B\}$ that offsets the expected benefit.
- We produced confidence intervals of the SMART curves using the variance-covariance matrix, using the Krinsky and Robb method outlined in Cooper in order to account for the uncertainty of the DCE-Preference Weights.
  - We simulate 1000 preference weights and we estimate a SMART function for each of the simulations.
  - From those 1000 simulations we calculated the 95th percentile.

RESULTS

Study 1: Treatment- Resistant Major Depressive Disorder

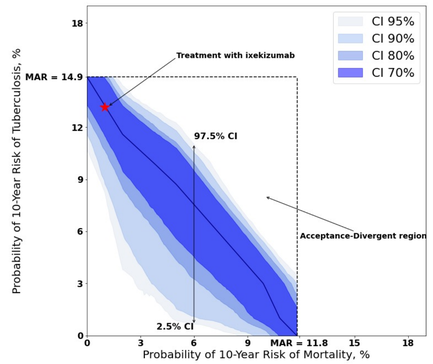
- Patient preference study eliciting benefit-risk tradeoff preferences among adults with treatment-resistant major depressive disorder.
- Participants were recruited from both an online sample of respondents who self-report to the condition and from two clinical trials of a novel ketamine-based therapy, esketamine.
- Two (hypothetical) adverse events: cognitive impairment and ulcerative cystitis.



SMART for esketamine-induced MADRS improvement of 4.1

Study 2: Biologics for Psoriasis

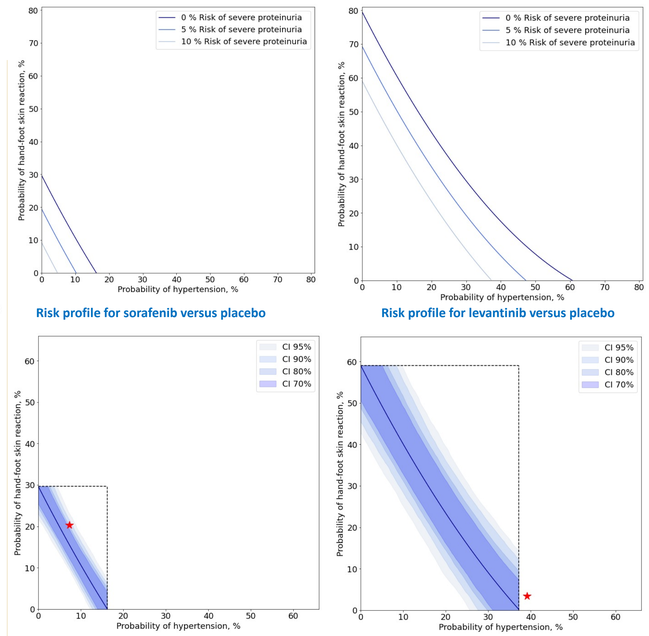
- Patient preference study eliciting benefit-risk tradeoff preferences among adults with varying reductions of plaque psoriasis on the face, body, and hands.
- Two possible adverse events: sever tuberculosis infection and mortality.



SMART for a reduction from 25% to 0% area of hands with moderate plaque psoriasis

Study 3: Radioactive Iodine for Refractory Differentiated Thyroid Cancer

- The study focused on key treatment features that differentiate two treatments indicated for this cancer, sorafenib and Lenvatinib.
- The adverse events included hand-foot skin reaction, hypertension, and proteinuria.



Risk profile for sorafenib versus placebo

Risk profile for levantinib versus placebo

Risk profile for sorafenib versus placebo: PFS gain= 5 months with risk of severe proteinuria of 0%

Risk profile for lenvatinib versus placebo: PFS gain= 14.7 months with risk of severe proteinuria of 10%

- The combined risk profile associated to sorafenib is in the Acceptance-Divergent region. Not for the lenvantinib.

Conclusions

- We identified cases where generation of SMART curves could lead to qualitatively different regulatory conclusions compared to use of single-event MARs.
- We recommend the SMART approach should be used at any time when stated-preference data are considered for regulatory decision making and multiple adverse-event risks are relevant.

References

- Fairchild AO, Reed SD, Gonzalez JM. Methods for calculating the Simultaneous Maximum Acceptable Risk Threshold (SMART). Manuscript under review at *Med Decis Making*.
- Cooper, J. A Comparison of approaches to calculating confidence intervals for benefit measures from dichotomous choice contingent valuation surveys. *Land Economics* 1994; 70(1): 111-122.