Maximum Acceptable Risk: Alternative Measures for Quantifying Patients’ Tolerance for Therapeutic Risks

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Benefit-Risk Tradeoff Preferences

Patient Rankings for Statins

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<thead>
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<th>Risk of kidney failure per 1,000 patients</th>
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Constant-Utility Benefit-Risk Tradeoff Curves
Four Preference-Based Benefit-Risk Measures

Three Approaches to Weighting

• Three approaches to estimating benefit-risk preferences have been offered:
  – Discrete-choice experiments (conjoint analysis)
  – Health-state utilities
    • Standard gamble
    • Time tradeoff
  – Contingent valuation
    • Open-ended questions
    • Closed-ended questions

Discrete-Choice Experiments

Discrete-Choice Experiments

• Alternatives consist of combinations of features
• Preferences among alternatives depend on the relative importance of features
• Subjects state preferences for series of hypothetical alternatives
• Choice tasks identify tradeoff relationships
• Statistical model predicts choice probabilities

Discrete-Choice Experiments

Renal Cell Carcinoma

Example DCE Question

Discrete-Choice Experiments

Renal Cell Carcinoma

Maximum Acceptable Risk of Liver Failure

Discrete-Choice Experiments

Renal Cell Carcinoma

Maximum Acceptable Risk of Liver Failure

Improvements in Progression Free Survival

Hauber et al., ISPOR 15th Annual International Meeting. (2010)
Contingent Valuation

Individuals risk assessment

• The Contingent Valuation (CV) approach elicits directly, through surveys, responses to valuation questions about the value that a patient, health professional or other stakeholder places on the side effects of adverse events in order to compare these effects to the expected benefit of an intervention.

• The goal of a contingent valuation survey is to measure either the compensating variation (CV) or equivalent variation (EV) for the health care intervention in question.

Compensating Variation & Equivalent Variation

• Compensating variation is generally used, if an individual is deciding about the consumption or purchase of the good or service: if patients seek treatments offering potentially significant therapeutic benefits, the maximum the patient will risk serious and life-threatening adverse events is based on the expected benefit of the drug.
• The patient wants to keep his utility at least constant.
  – The gain in benefit is known
  – Maximal Acceptable Risk is measured through CV

• Equivalent variation (EV) is used in general, if an individual owns a good that may be taken away from him.
• The equivalent variation measures the minimum compensation in benefits the patients requires to keep his utility at its original level when he risks his health through side effects and adverse events.
  – Increase in risk is known (fix)
  – Necessary benefit to compensate is measured through EV

MAR & MAB

• Maximum Acceptable Risk (MAR) = Willingness to accept risk, to gain benefit
  - (2) \( MAR = R(A, q, D, U) - R(A, q, D, U_0) \)

• Minimum Acceptable Benefit (MAB) = Willingness to forego benefit, to avoid risk
  - (3) \( MAB = R(A, q, D, U) - R(A, q, D, U_1) \)

• The two measures may yield very different values for the same change in drug consumption, hence it is important to determine which valuation concept is the appropriate one.

Private Decision vs. Regulation

• If an individual has the power to decide about the consumption or purchase of the health care good or service (analog the case of a private good), it must be clearly specified how the intervention must be consumed and on what terms (cost or risk).
• If an individual owns a certain health state that may be taken away from him (analog the case of a public good) it is common to frame the survey as a referendum. That is, the respondent is asked whether he would vote in favor of a proposition that, if approved by the majority of voters, would provide the clinical intervention at a given risk to the population.
Choice of Technique

- In constructing the contingent valuation survey a researcher must also decide what technique to use to elicit Maximum Acceptable Risk (MAR).

  **Open-ended elicitation methods**, which include bidding games and risk cards, provide a point estimate of the respondent’s maximum acceptable risk for the intervention or drug in question.

  **Closed-ended methods**, which ask the respondent whether he would risk at least a stated amount, provide intervals in which the respondent’s maximum acceptable risk lies.

Open-ended elicitation methods: Direct Questioning

- Among open-ended approaches the simplest is to ask the respondent “What is the most you would risk...?” for a specified benefit (endpoint or symptom) in question.

  - This does not provide the respondent with implied value cues, but may be a difficult question to answer, especially if the specified benefit is an unfamiliar one.
  - For this reason gross outliers, or refusal to answer the question might characterize collected MAR data using this approach.

Open-ended elicitation methods: Risk cards

- An alternative is to allow the respondent to choose his maximum acceptable risk from a card that lists possible probabilities of adverse events (risk values).

  - This is likely to be an easier task, but may encourage the respondent to limit his announced MAR to the values on the card.

Open-ended elicitation methods: Bidding Game

- MAR amounts were sometimes elicited using iterative bidding protocols. In a bidding game respondents were queried about a certain risk figure:

  - Those who agreed to risk the adverse events (given a certain probability) were offered higher and higher risks, until they finally switched to a “no” answer.
  - Respondents who declined to risk the initially offered probability of an adverse event were offered lower risks, until they said “yes.”
  - The starting point of the question could bias MAR estimate: This approach has been questioned in WTP, because it was found to produce starting point biases. The final MAR amount could be significantly related to the choice of the initial figure.

Closed-ended methods

- Closed-ended approaches, which ask respondents whether they would risk a stated amount for the specified benefit in question, require only a yes-no answer.

  - Their take-it-or-leave-it format mimics the choice facing patients in real health care decision-making, or, in the case of a public good, the choice facing citizens in a referendum.

Closed-ended methods

- The simplest dichotomous choice question asks each respondent whether he would risk at least the probability r*x for the benefit in question, where r is varied randomly across respondents from a list of values chosen by the researcher.

  - An affirmative answer to this question, however, indicates only that the respondent’s MAR lies in the open interval (r, ∞). For this reason, an initial closed-ended question is often followed by a question designed to more narrowly bracket the respondent’s MAR.
Analysis of CV Responses

- This is the (weighted) frequency distribution of responses when the MAR question is open-ended.
  - Mean of MAR
  - Median of MAR
  - Trimmed mean
- In the case of a closed-ended question one can compute the percent of the sample that is willing to risk at least a given value, which provides an estimate of one minus the cumulative distribution of MAR.
  - Probit model

Crohn’s Disease
Example Stated-Choice Question

<table>
<thead>
<tr>
<th>Attributes</th>
<th>Treatment A</th>
<th>Treatment B</th>
</tr>
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<tbody>
<tr>
<td>Severity of Crohn’s symptoms during treatment</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Effect on serious complications</td>
<td>Prevents</td>
<td>Prevents</td>
</tr>
<tr>
<td>Time between flares</td>
<td>1 year</td>
<td>2 years</td>
</tr>
<tr>
<td>Treatment requires oral steroids</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Chance of dying from a serious infection within 10 years</td>
<td>None would die</td>
<td>None would die</td>
</tr>
<tr>
<td>Chance of dying or having severe disability from PML within 10 years</td>
<td>None would die</td>
<td>50 patients out of 1,000 (2%) would die</td>
</tr>
<tr>
<td>Which would you choose if these were the only options available?</td>
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Hypothetical Case Study

(Discussion of participant survey results)
### Preference Data

<table>
<thead>
<tr>
<th>QUESTION</th>
<th>ANSWER</th>
<th>N</th>
<th>ANSWER</th>
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- **Risk Tolerant**
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