

Maximum Acceptable Risk and Healthy -Year Equivalents in AD

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Study Objectives

- **Estimate benefit-risk trade-off preferences for treatments that offer AD progression benefits with mortality risks**
- **Use preference estimates to calculate**
 - Mild-year equivalents for moderate and severe AD
 - Health-state utilities for mild, moderate, and severe AD
 - Maximum acceptable risk for disease-progression benefits

Approaches to Quantifying Risk Tolerance

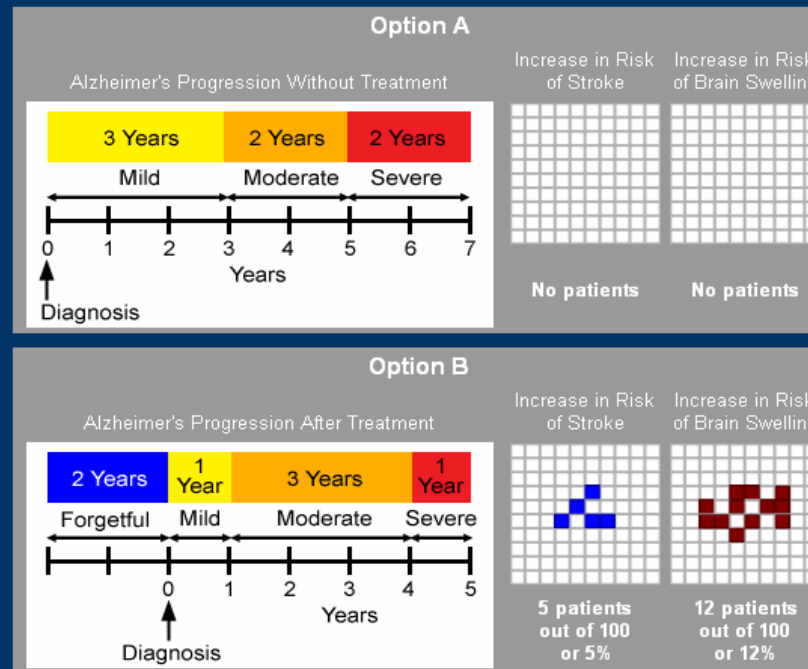
- **Standard Gamble**: Offer respondents a specified condition with certainty or a gamble between death and perfect health

“What probability of death would make you indifferent between the certain outcome and the gamble?”

- **Stated Choice**: Offer patients series of constructed treatment alternatives

“Which treatment would you choose if these were the only alternatives available?”

Example Stated-Choice Question



Which option would you choose if these were the only options available?

Select one answer only

Option A



Option B



Next Question

Inclusion/Exclusion Criteria

- **US general population**
- **Age 60 years and older**
- **No diagnosis of AD, dementia, or memory loss**
- **No prior personal use of prescription AD medications**

Survey Instrument

- **Web-enabled, online survey (N = 2,146)**
- **Subjects chose hypothetical treatment from 10 pairs of alternatives**
- **2 survey versions**
 - Mild reference condition
 - Moderate reference condition

Analysis—Nonlinear Stated-Choice Utility Function

$$\begin{aligned} \text{SC Utility} = & \beta_{\text{mild}} \cdot \text{MILD Years} \\ & + \beta_{\text{mild} \cdot \text{mod}} \cdot (\text{MILD Years} \times \text{MODERATE Years}) \\ & + \beta_{\text{severe}} \cdot \text{SEVERE Years} \\ & + \beta_{\text{srisk}} \cdot \text{STROKE Risk} \\ & + \beta_{\text{erisk}} \cdot \text{ENCEPHALOPATHY Risk} \end{aligned}$$

Mild Year Equivalent

MYE: Fraction of one mild AD year that is equivalent to a moderate or severe year

$$\text{MYE}_{\text{severe}} = \frac{\beta_{\text{severe}}}{\beta_{\text{mild}} + \beta_{\text{mild*mod}} \cdot \text{Moderate Years}}$$

Stated-Choice Utility and Chaining Calculations

- **SC mild-year equivalent**

- Based on clinically relevant tradeoffs
- But—not scaled between instantaneous, painless death and perfect health

- **Chaining to conventional health utilities**

- Adjust MYE for the difference between mild AD and perfect health
- Evaluate assumptions about whether “permanent severe disability” from stroke is better or worse than death

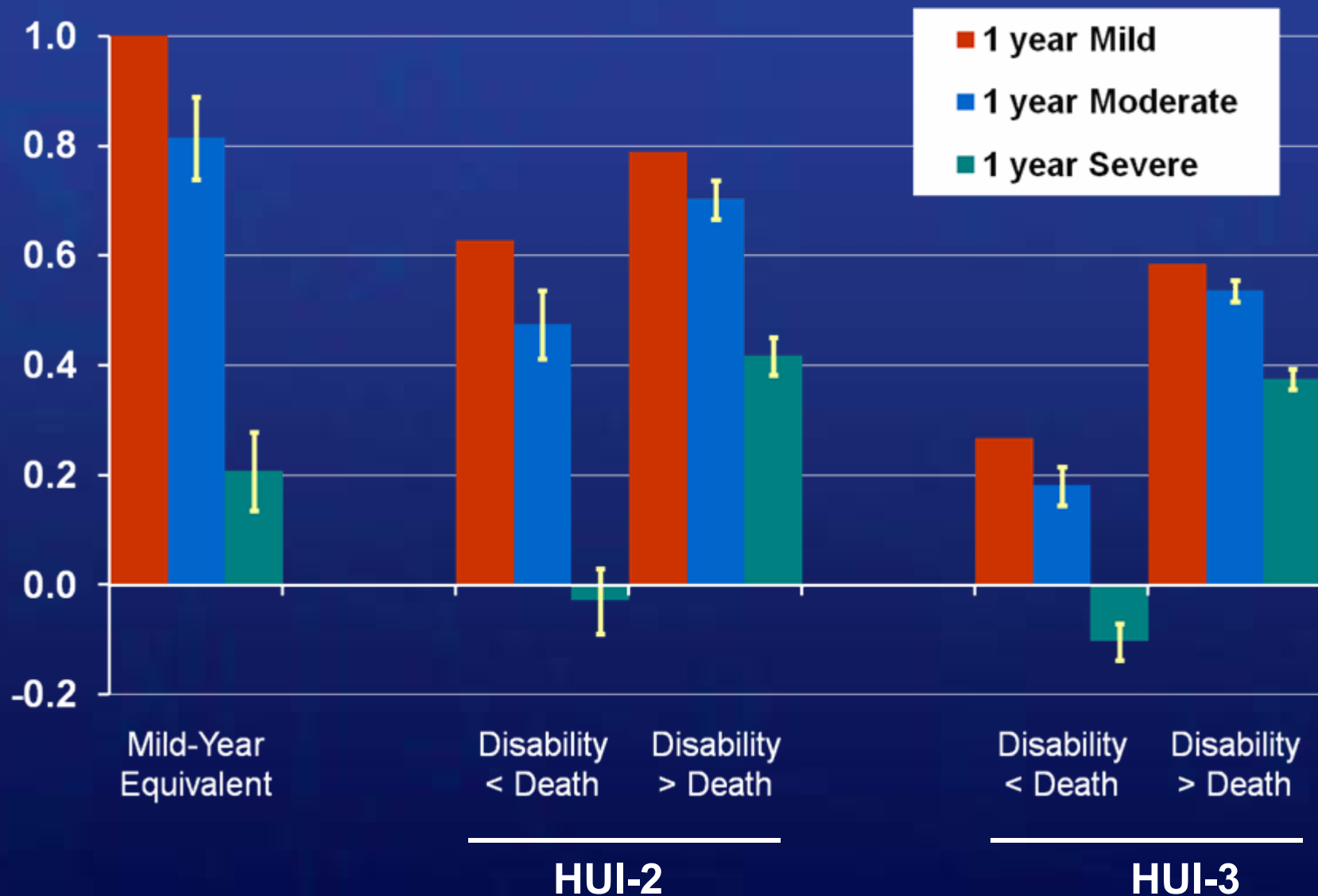
Health-State Utilities Used for Chaining Calculations

Assumption	Utility Value
Mild AD (HUI-2)	0.69
Serious stroke disability worse than death	-0.20
Serious stroke disability better than death	0.32

If severe disability from stroke is
worse than or *better* than death:

$$\begin{aligned} \text{Utility} = & \text{SC mild-year equivalent} \times \text{Mild AD utility} \\ & \times (1 - \text{Stroke disability utility}) \\ & + \text{Stroke disability utility} \end{aligned}$$

MYE and Chained AD Utilities

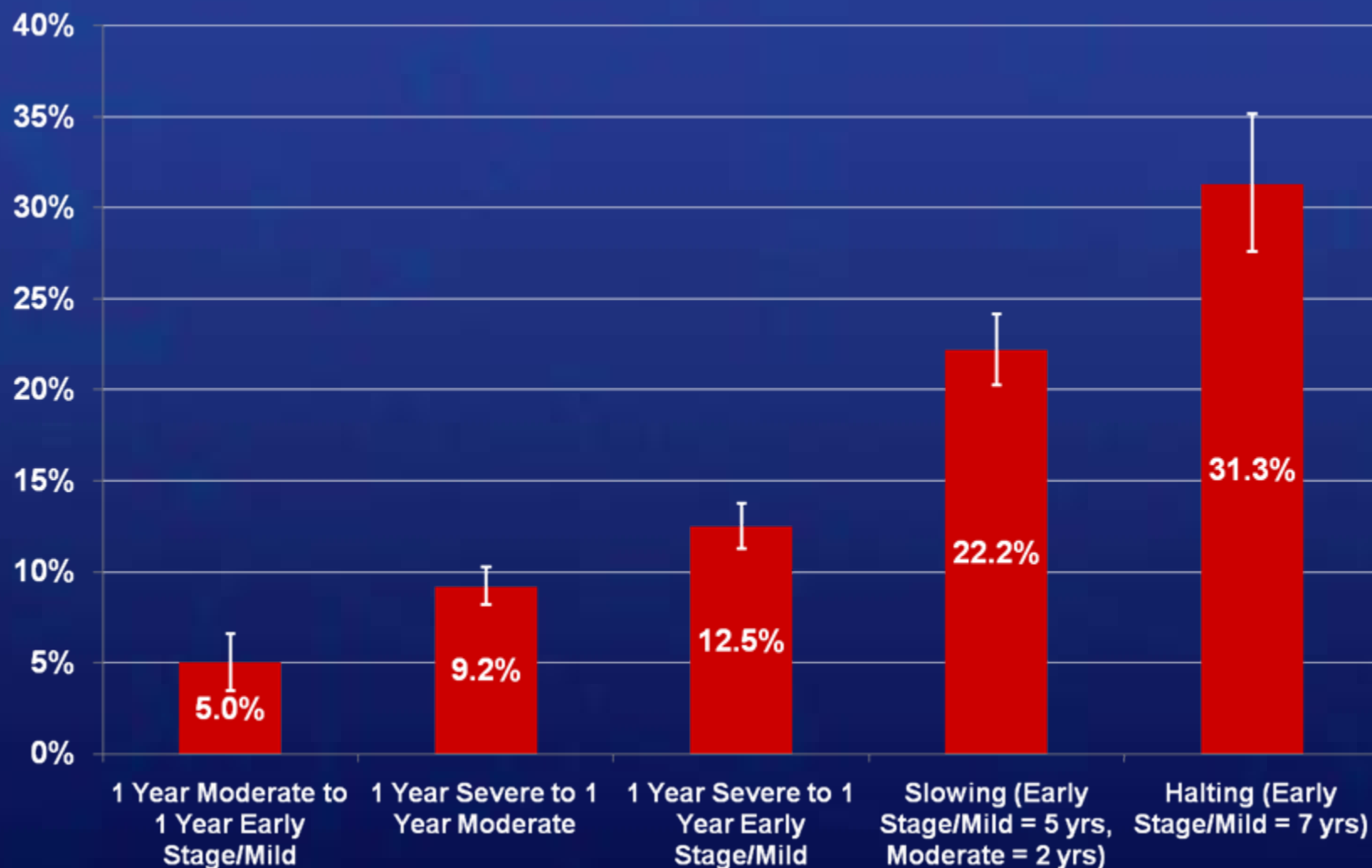


Maximum Acceptable Risk

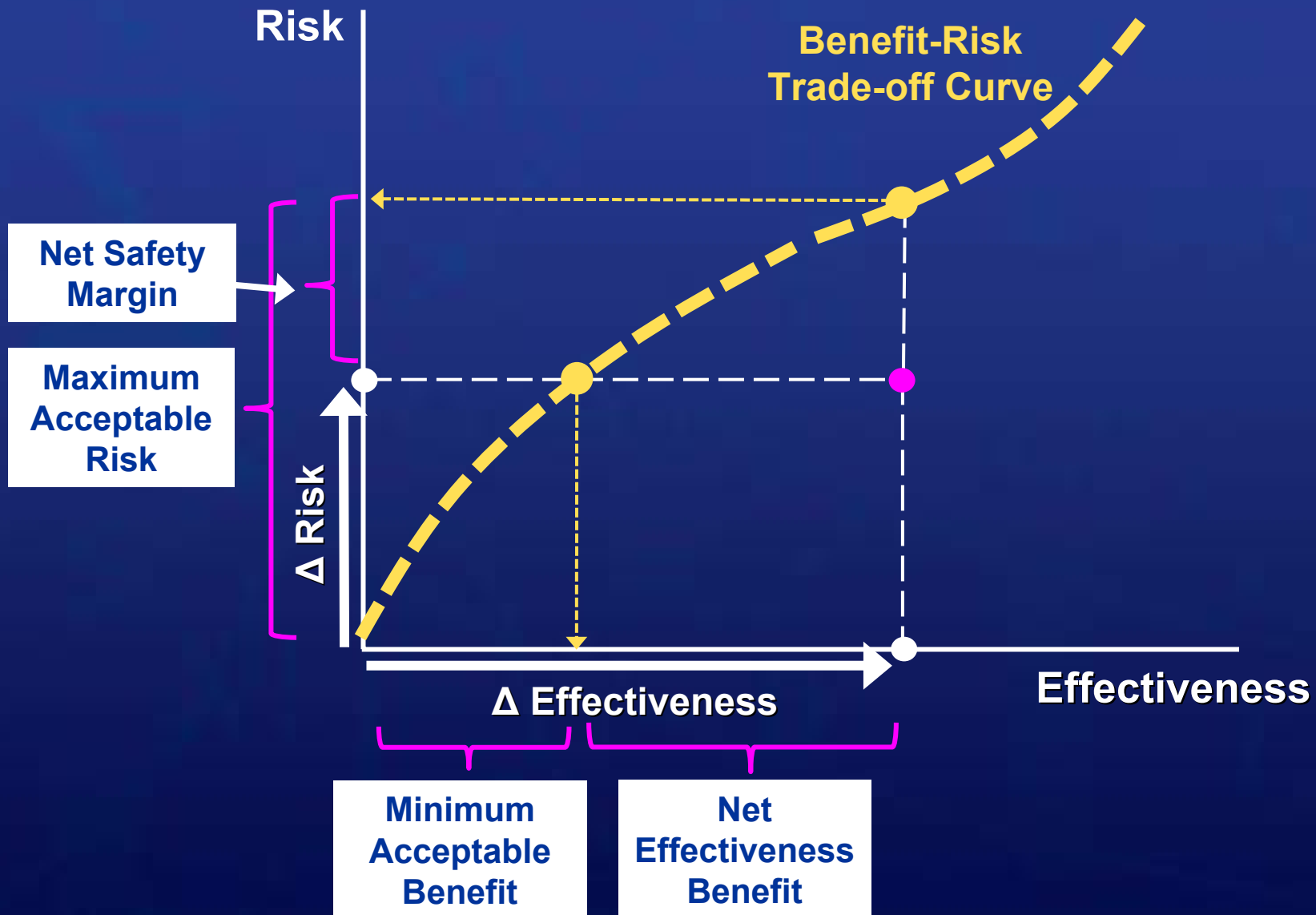
MAR: The increase in treatment risk that exactly offsets treatment benefits.

$$\text{MAR} = \frac{\left(\sum_{i=1}^3 \beta_i \cdot \text{Years}_i^{\text{treat}} \right) - \left(\sum_{i=1}^3 \beta_i \cdot \text{Years}_i^{\text{notreat}} \right)}{-\beta_{\text{risk}}}$$

Risk Tolerance for AD Disease Modification



Four Quantitative Benefit-Risk Measures



Comparison of Preference and Event Measures

- Inverse of maximum acceptable risk is **minimum acceptable number needed to harm**
- Inverse of maximum acceptable benefit is **maximum acceptable number needed to treat**

Alzheimer's Benefit-Risk Trade-off Preferences

	Disease Progression		
	3 Mild 2 Moderate 2 Severe (No Treatment)	4 Mild 1 Moderate 2 Severe	7 Mild
Mild-Year Equivalent (Years)	4.9	5.1	7.0
Incremental Benefit (MYEs)	0	0.2	2.1
Maximum Acceptable Risk (Prob)	0	0.05	0.31
Minimum Acceptable Number Needed to Harm (N)	—	20.0	3.2
Net Safety Benefit (Prob) (Risk = 0.05)	-0.05	0	0.26
Min Acceptable Benefit (Years) (Risk = 0.05)	0.2	0.2	0.2
Net Efficacy Benefit (Years)	-0.2	0	1.9

Conclusions

- **MYEs and MARs indicate the benefits of disease-modifying therapies are substantial**
- **Constructing health utilities from MYEs requires assumptions that significantly affect results**
- **MAR data submitted to 2 FDA advisory committees**
- **FDA supporting studies to evaluate validity of patient benefit-risk preference data**