RTI Health Solutions

COMPARING APPLES AND ORANGES: USING CONJOINT-ANALYSIS DATA TO OBTAIN SEVEN QUANTITATIVE BENEFIT-RISK MEASURES (PLUS ONE)

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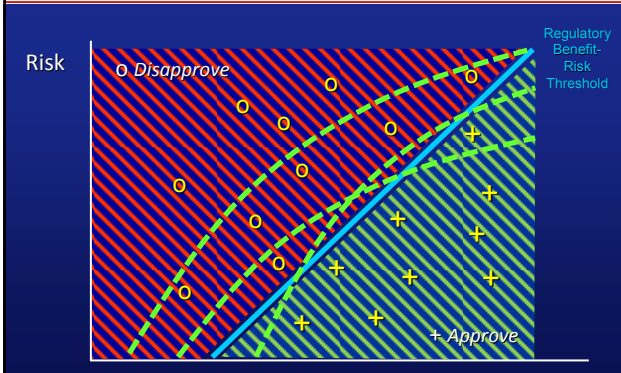
The regulator's problem

- **Internationally, regulators are struggling to find methods to inform and support decisions**
- **When reviewing a new drug, regulators need to approve if it is "safe and effective when used as directed."**
- **Most drugs have both benefits and risks, requiring the regulators to judge if the benefits outweigh the risks.**
- **This requires the direct comparison of "oranges and apples"**

The regulator's decision space



The regulators call for help

1997	CIOMS IV
2007	Institute of Medicine
August 2007	Presentations to FDA/CDER
September 2007	FDA Amendments Act
October 2007	Office of Health Economics Conference, London
November 2007	First joint FDA, EMEA, PhRMA, BIO, academic conference, Washington DC
September 2008	FDA support contract initiatives
November 2009	Second joint FDA, EMEA, PhRMA, BIO, academic conference, Washington DC
Ongoing	Next Steps Working Group PhRMA Case Studies

The regulator's possible options

Proposed Approaches
1. PhRMA Benefit-Risk Assessment Team Framework
2. Patient-preference measures of maximum acceptable risk and other metrics
3. Incremental net health benefits
4. Regulatory decision-analytic modeling
5. Multi-criteria decision analysis
6. Number needed to treat/Number needed to harm

The regulator's possible options

Proposed Approaches	Role for conjoint Data
1. PhRMA Benefit-Risk Assessment Team Framework	**Yes**
2. Patient-preference measures of maximum acceptable risk and other metrics	**Yes**
3. Incremental net health benefits	**Yes**
4. Regulatory decision-analytic modeling	**Maybe**
5. Multi-criteria decision analysis	**Maybe**
6. Number needed to treat/Number needed to harm	**Yes**

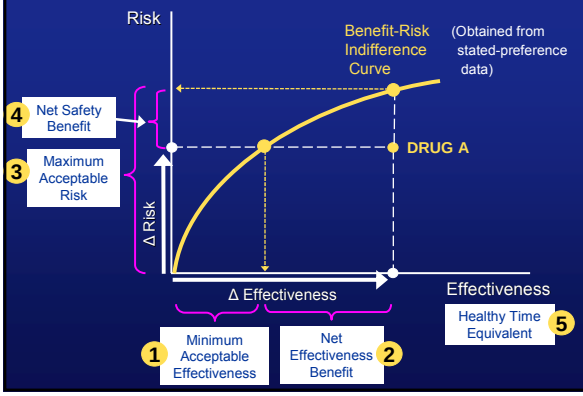
Pain Survey Conjoint Choice Question

Treatment Features		Treatment A		Treatment B	
Pain control each month	Pain Level	6 (Very Distressing)	0 (No pain)	3 (Uncomfortable)	0 (No pain)
	How many days per month	5 days	25 days	20 days	10 days
Increased risk of heart attack		3 in 1000		None	
Medication cost per month		None		$250	

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

☐ Prefer A ☐ Prefer B

Four Preference-Based Benefit-Risk Measures



Comparison of Preference and Event Measures

- Minimum Acceptable Benefit (MAB)
  - Minimum therapeutic benefit required to accept a given level of risk

$$MAB = \frac{\min \Delta N_B}{N}$$

6 - Inverse of MAB is maximum acceptable number needed to treat

$$\max NNT = \frac{N}{\min \Delta N_B}$$

- Maximum Acceptable Risk (MAR)
  - Maximum risk people would accept for a given level of benefit

$$MAR = \frac{\max \Delta N_{AE}}{N}$$

7 - Inverse of MAR is minimum acceptable number needed to harm

$$\min NNH = \frac{N}{\max \Delta N_{AE}}$$

QUANTIFYING THESE MEASURES

The Problem and the Solution

- **Goal: devise metrics based on utility-theoretic principles analogous to metrics used in the physical sciences**
- **But: people cannot provide reliable numeric evaluations of their preferences**
- **Solution:**
  - People can provide reliable ordinal rankings for outcome profiles
  - Conjoint data reveal implicit relative importance weights

Pain Example

Pain Survey Conjoint Choice Question

Treatment Features		Treatment A	Treatment B
Pain control each month	Pain Level	6 (Very Distressing) / 0 (No pain)	3 (Uncomfortable) / 0 (No pain)
	How many days per month	5 days / 25 days	20 days / 10 days
Increased risk of heart attack		3 in 1000	None
Medication cost per month		None	$250
Which treatment would you choose if these were the only options available?		☐ Prefer A	☐ Prefer B

As little actual theory as possible

Benefit-Risk Tradeoff Preferences

Patient Rankings for Pain-Control Medications

Risk per 10,000 patients	VAS = 60 mm	VAS = 70 mm	VAS = 90 mm
10			
25			
40			

Benefit-Risk Tradeoff Preferences

Patient Rankings for Pain-Control Medications

Risk per 10,000 patients	VAS = 60 mm	VAS = 70 mm	VAS = 90 mm
10		B	A
25			B
40			

Benefit-Risk Tradeoff Preferences

Patient Rankings for Pain-Control Medications

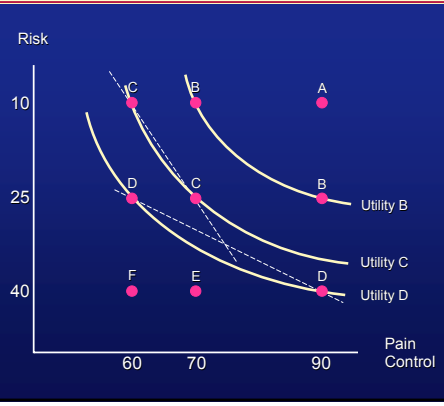
Risk per 10,000 patients	VAS = 60 mm	VAS = 70 mm	VAS = 90 mm
10	C	B	A
25	D	C	B
40			D

Benefit-Risk Tradeoff Preferences

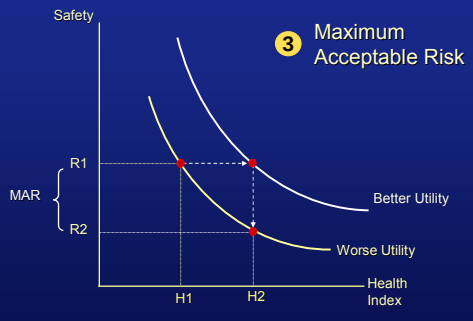
Patient Rankings for Pain-Control Medications

Risk per 10,000 patients	VAS = 60 mm	VAS = 70 mm	VAS = 90 mm
10	C	B	A
25	D	C	B
40	F	E	D

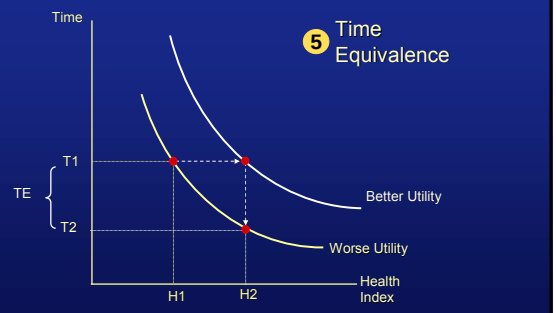
Indifference Curves Indicate Similar Utility Levels



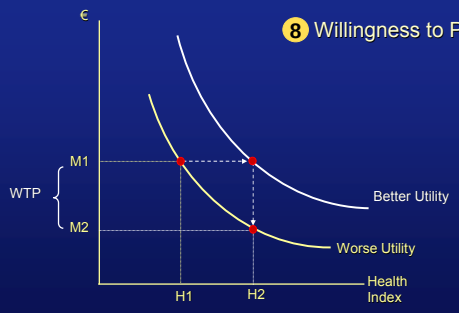
Risk Equivalent of a Health Improvement



Time Equivalence of a Health Improvement

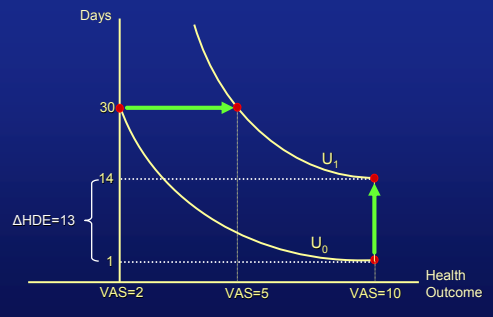


Risk Equivalent of a Health Improvement



A Numerical Example

Healthy-Days Equivalent



Time, Risk, and Money Equivalents

PROFILE	SYMPTOM SEVERITY				HDE (5)	MAR (3)	WTP (8)
	VAS=4	VAS=6	VAS=8	VAS=10			
1			14	16	25.4	14.1	€1054
2		7		23	23.9	13.4	1003
3	4			26	23.2	13.1	979
4	4	7	14	5	20.8	12.0	897

7 Quantitative Benefit-Risk Measures

Risk	Maximum Acceptable Risk (3)	Minimum Acceptable NNH [1/MAR] (7)	Net Safety Benefit MAR-Risk (4)
0.5%	1.2%	83.3	0.70%
1.0%			0.20%
1.5%			-0.30%

7 Quantitative Benefit-Risk Measures

Risk	Maximum Acceptable Risk (3)	Minimum Acceptable NNH [1/MAR] (7)	Net Safety Benefit MAR-Risk (4)	Healthy-Day Equivalent (5)	Minimum Acceptable Benefit (1)	Net Effectiveness Benefit [HDE-MAB] (2)
0.5%	1.2%	83.3	0.70%	20.8	7.0	13.8
1.0%			0.20%		16.6	4.2
1.5%			-0.30%		27.6	-6.8

7 Quantitative Benefit-Risk Measures

Risk	Maximum Acceptable Risk (3)	Minimum Acceptable NNH [1/MAR] (7)	Net Safety Benefit MAR-Risk (4)	Healthy-Day Equivalent (5)	Minimum Acceptable Benefit (1)	Net Effectiveness Benefit [HDE-MAB] (2)	Maximum Acceptable NNT [1/MAB] (6)
0.5%	1.2%	83.3	0.70%	20.8	7.0	13.8	Can't be calculated unless efficacy measured as probability or rate.
1.0%			0.20%		16.6	4.2	
1.5%			-0.30%		27.6	-6.8	

Back to the regulator's problem

- **Conjoint analysis methods can provide regulators with a systematic and scientific method to compare benefits and risks.**
- **Conjoint methods can provide relevant statistics that can be denominated in:**
  - Benefits
  - Risks
  - Money

Back to the regulator's problem

- **Conjoint analysis methods can provide regulators with a systematic and scientific method to compare benefits and risks.**
- **Conjoint methods can provide relevant statistics that can be denominated in:**
  - Benefits (The good)
  - Risks (The bad)
  - Money (The ugly)

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