

**First steps in developing a risk-benefit  
analysis framework: a systematic review and  
critical evaluation of risk-benefit analysis  
methods**

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# Background to Risk-Benefit Evaluation

- **Historically in risk-benefit analysis, only benefit was deemed important**
- **Current paradigm – Frequentist**
  - **Independent evaluation of risks and benefits**
  - **Arbitrary threshold of  $p=0.05$**

# Limitations of current paradigm

- R-B ratio most often discussed in absolute terms, if at all
- Often based on RCT data – limited precision in estimating differences in risk
- Does not consider the valuation of the risks and benefits
- Fails to consider:
  1. The nature of the risks or benefits
  2. The precision or uncertainty of the incremental risks and benefits
  3. Risk preferences
  4. Risks and benefits concurrently

# The way of the future

- Regulatory bodies increasingly requiring explicit R-B evaluation
- Quantitative methods for concurrently evaluating risks and benefits → EVIDENCE BASED DECISIONS
- Evaluating multiple risks and multiple benefits
- Incorporate:
  - Relevant preferences
  - Uncertainty
  - Different patient characteristics (risk)
- PROCESS NEEDS TO BECOME SYSTEMATIC & EXPLICIT

## Change in Nomenclature

- Traditionally referred to 'risk-benefit' analysis
- 'Risk' refers to both "BENEFITS", and "ADVERSE EVENTS"
- Rather, we are comparing 'harms' and 'benefits'
- Therefore, appropriate nomenclature:

## HARM-BENEFIT ANALYSIS

## **Objectives:**

- **Identify and establish criteria necessary for a practical, applied HBA methodology**
- **Perform a systematic review to identify all currently proposed HBA methods**
- **Propose a methodologic framework that best meets the proposed criteria**

# Criteria

## 1. Universal

- All interventions and health states

## 2. Inclusive

- Multiple benefits and multiple harms

## 3. Comprehensive

- Objective and subjective harms and benefits

## 4. Patient-sensitive

- Stratified risk analysis

## 5. Easily interpreted

- By all potential stakeholders/perspective

# Criteria

## 6. Explicit preferences

- For both harms and benefits

## 7. Threshold

- Inherently defined H-B threshold

## 8. Incorporates uncertainty

- Quality and source of data, and in the final metric

## 9. Flexible/Adaptable

- Rapid, efficient, incorporate new knowledge

## 10. Integrate with Economic Evaluations



# Results

- **10 metrics / methods identified**
- **Not all are HB methods**
  - **Some only evaluate benefits**
  - **Chronological progression**
    - **Complexity**
    - **Increasingly satisfy more criteria**

# Methods in Chronology

- **NNT , NNE / NNH**
- **Integration of Benefit and Harm**
  - **Unqualified Success/Unmitigated Failures**
  - **$R_1$  &  $R_2$  (Chuang Stein)**
- **Preference / Threshold based**
  - **$NNT_T$ ,  $NNT_{U\&T}$ ,  $NNT_{MCE}$**
  - **Risk and preference adjusted surplus efficacy**

# Methods in Chronology

- Risk Benefit Contour
- Q-TWiST
- 'Net benefit' – decision analytic methods

	METHODS													
CRITERIA	Chuang-Stein $r_1$ & $r_2$	RV-NNT	NNT	NNE	NNT <sub>US</sub> & NNT <sub>UF</sub>	RB Contour	Surplus Efficacy	RV-MCE	NNT <sub>U&amp;T</sub>	Benefit-less-risk	NNT <sub>T</sub> & MERT	Benefit-Risk Ratio	Q-TWIST	INB
<b>Patient-sensitive</b> - Accounts for differing baseline risks among patients	+	+	+	+	+	+	+	+	+	+	+	+	+	+
<b>Universal</b> - Can be applied across interventions and diseases; Can be used to assess the population at risk or the patient at risk	+	+	+	+	+	+	-	+	+	+	+	+	+	+
<b>Flexible</b> - Can be conducted rapidly and with few resources; Can easily incorporate new knowledge acquired over time	-	+	+	+	+	+	+	+	+	+	+	+	+	+
<b>Explicit Preferences</b> - Weighs individual harms and benefits according to an explicit set of preferences from a relevant group	+	+	-	-	-	+	+	+	+	+	+	-	+	+
<b>Easily-interpreted</b> - Produces a graphical harm-benefit profile to facilitate comparison against no therapy or an appropriate comparator	-	-	-	-	-	+	+	+	-	-	+	+	+	+
<b>Threshold</b> - Has an intrinsic harm-benefit acceptability threshold	+	-	-	-	-	-	+	+	-	+	+	+	+	+
<b>Integrates with Economic Evaluation Measures</b>	-	-	+	+	+	-	-	-	+	+	-	+	+	+
<b>Incorporates Uncertainty</b> - Accounts for the quality and source of the benefit / harm information entered into the model; Provides a measure of precision (uncertainty) around the harm-benefit metric	-	-	+	+	+	-	-	-	-	-	-	+	-	+
<b>Inclusive</b> - Can incorporate multiple harms AND multiple benefits	-	-	-	-	-	-	-	-	+	-	+	-	-	+
<b>Comprehensive</b> - Can quantify both objective harms (e.g. mortality) and subjective benefits (e.g. QoL); Can quantify the duration, intensity, and reversibility of harms and benefits	-	-	-	-	-	-	-	-	-	-	-	-	+	+

## **Example of 'net benefit'/decision analysis: HB analysis of HRT post-menopause**

- **Probabilistic clinical decision model**
- **Benefits:**
  - Improved sx, ↓ rate of hip fracture, ↓ risk of colorectal and endometrial CA
- **Harm:**
  - Breast CA, coronary heart disease, stroke, PE

Net benefits =

$\Sigma$  Benefits

-

$\Sigma$  Harms



For hip fracture, colon cancer, endometrial cancer

Absolute risk reduction x (QALY loss + cause specific death)

For menopausal symptoms

Relative risk reduction x QALY loss



For coronary heart disease, pulmonary embolism, stroke

Absolute risk increase x (QALY loss + cause specific death)

For breast cancer

Absolute risk increase<sub>j</sub> x (QALY loss + cause specific death) where absolute risk increase is calculated for each baseline risk level<sub>j</sub> of breast cancer

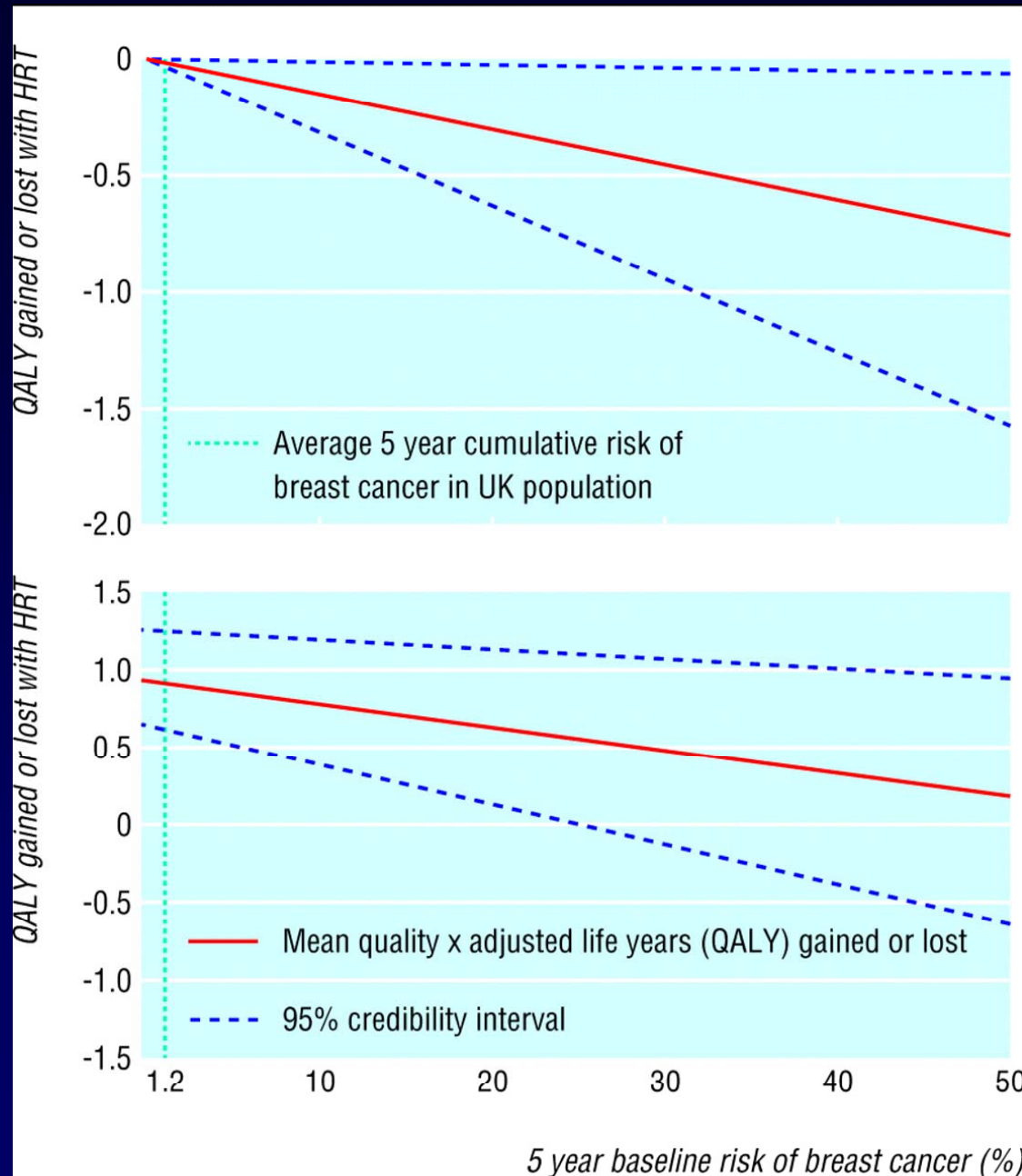
Relative risk reduction = 1 - relative risk

Absolute risk reduction = baseline risk x relative risk reduction

Relative risk increase = relative risk - 1

Absolute risk increase = baseline risk x relative risk increase

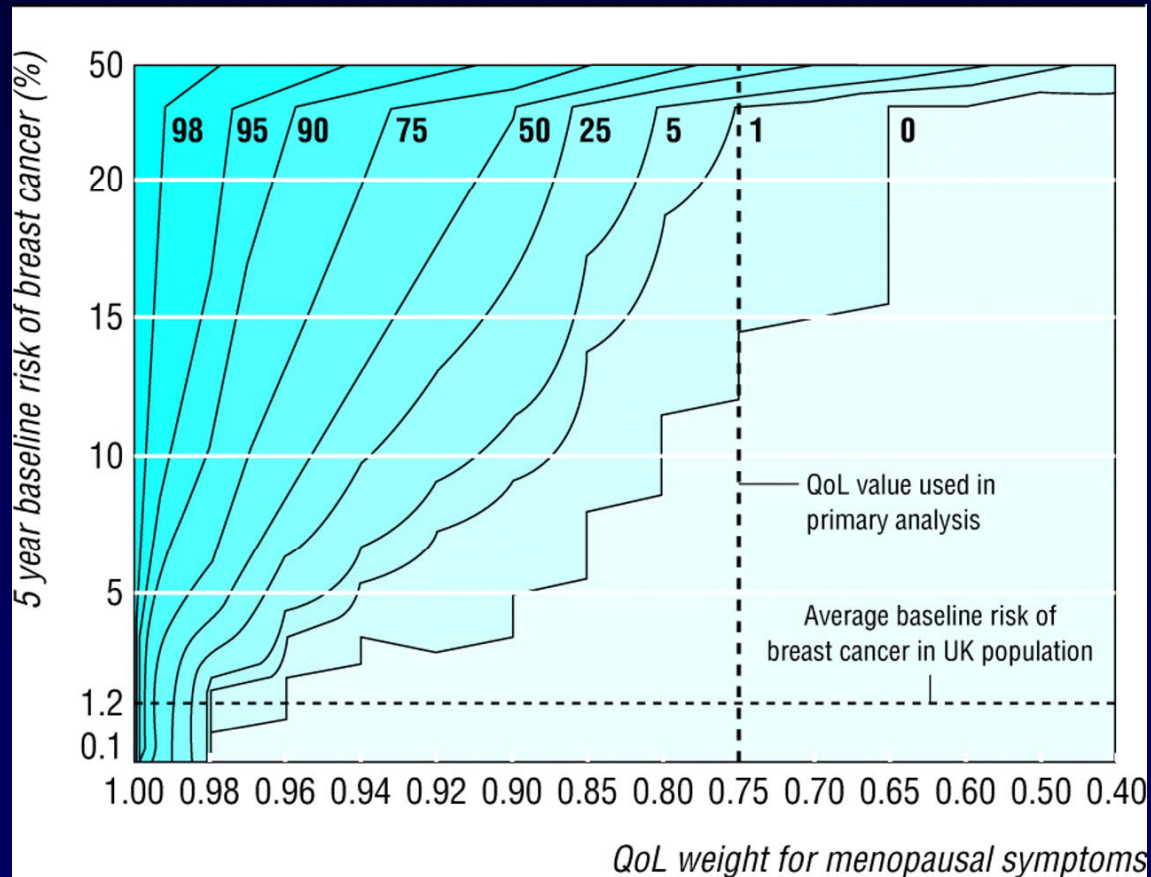
QALY loss = 1 - QoL weight



Asymptomatic  
Women

Symptomatic  
Women

**Fig 3: Probability of net harm (%) associated with HRT use for five years according to utility attributed to menopausal symptoms by individual women and their baseline risks of breast cancer. Isolines define combinations of utility and baseline risk with same probability of net harm**



Minelli, C. et al. BMJ 2004;328:371



# Recommendations and Conclusions

- *Net benefit* (decision analysis) meets all *a priori* established criteria
  - Universal
    - All interventions, health states & scales
  - Inclusive
    - Multiple benefits and multiple harms
  - Comprehensive
    - Objective and subjective harms and benefits
  - Patient-sensitive
    - Stratified risk analysis
  - Easily interpreted (we think)
    - By all potential stakeholders/perspective

# Recommendations and Conclusions

- **Explicit preferences**
  - **For both harms and benefits**
- **Threshold**
  - **Naturally zero (net health benefit)**
- **Incorporates uncertainty**
  - **Quality and source of data, final metric, decision**
- **Flexible/Adaptable**
  - **Rapid, efficient, incorporate new knowledge**
  - **Facilitates modeling, when necessary**
- **Integrates with Economic Evaluations**

# Implementation issues

- **Data synthesis**
- **Availability of preferences**
  - **Utilities**
  - **Contingent valuation**
  - **Conjoint analysis or Discrete Choice Experimentation**
- **Perspective**
- **Acceptance of methods/results by decision-makers**