What role should formal risk-benefit decision-making play in the regulation of medicines?

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Outline

- Decision-making: statistical approaches
- Case-studies
- Open questions
- Current regulatory initiatives

Decision Making- Current Applications

- Design of experiments
- Adaptive trials e.g. dose-finding
- Portfolio management of pharmaceutical companies
- National Institute for Health and Clinical Excellence

- Basic approach: Evidence synthesis and Decision Making with Utilities

- Decision-making under uncertainty closely allied with Bayesian statistics for decades, especially in health applications e.g. Raiffa, Schlaiffer, Cornfield, Lindley, Smith AFM, Smith J, Spiegelhalter, Berry, Parmigiani- see Ashby, SiM, 2006 for key references

Evidence Based Medicine

- “EBM is the conscientious explicit, and judicious use of current best evidence in *making decisions* about the care of individual patients” taking into account “individual patients *predicaments, rights and preferences* using *best evidence* from clinically relevant research.” Sackett et al, 1996

EBM as Bayesian Decision-Making

(Ashby D & Smith AFM, Stats in Medicine, 2000)

- Decision-maker
- Possible actions
- Uncertain consequences
- Sources of evidence
- Utility assessments

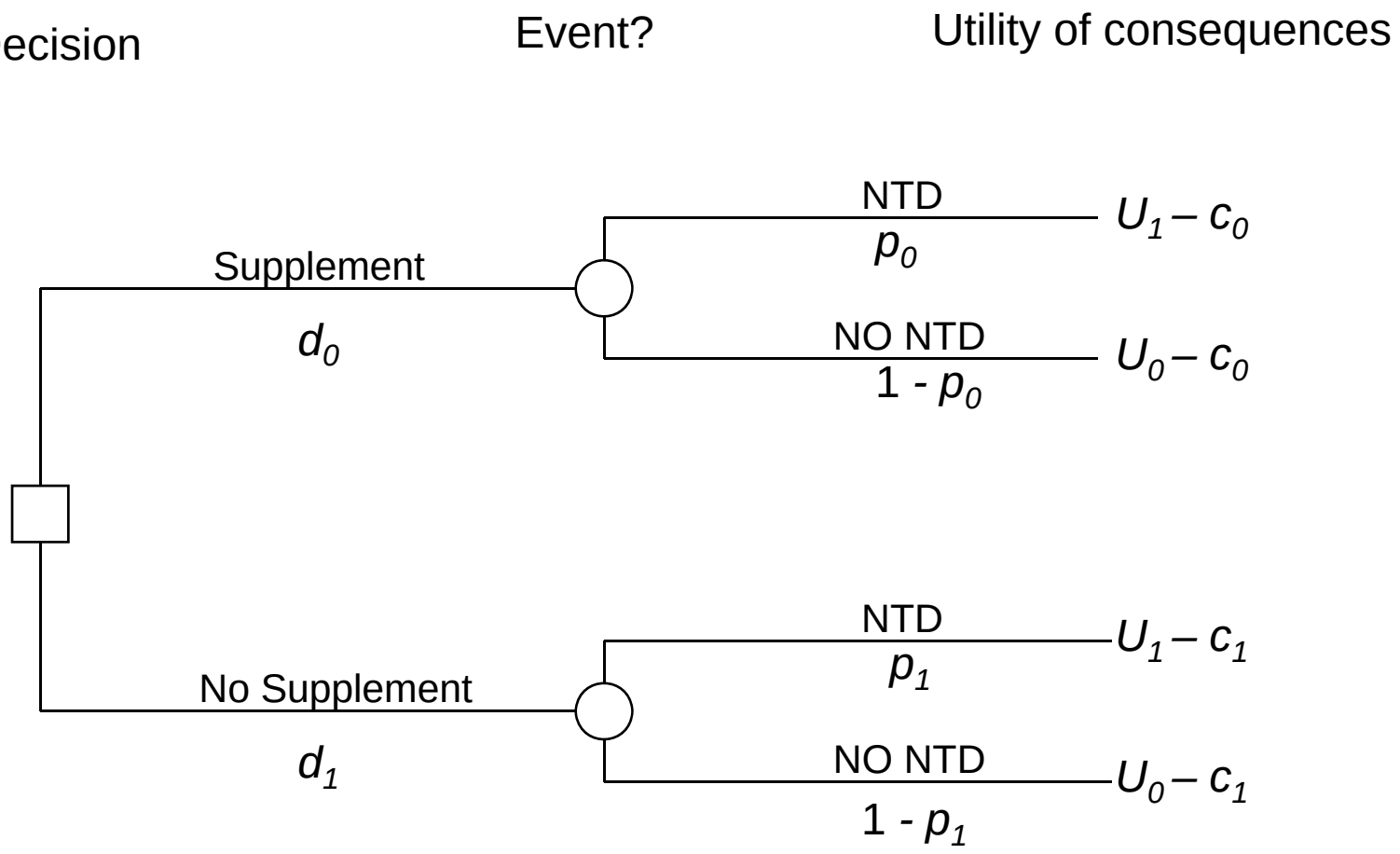
Decision Makers- Who Are they?

- Patients make decisions for themselves, constrained by …
- Prescribing lists of their health care provider who are constrained by …
- NICE who decide on cost-effectiveness, who are constrained by …
- MHRA/ EMEA who decide on quality, safety, efficacy and benefit: risk (to individuals and “the public health”), who are constrained by …
- Pharmaceutical companies who decide what to develop and for which licenses to apply

Couple Wishing to Prevent an NTD

Decision maker	Couple
Possible actions	Take/not take folic acid supplements
Uncertain consequences	Fetus with/without NTD
Sources of evidence	Population statistics
	Randomised trial in high risk women
Utility assessments	Seriousness of NTD
	Financial
	Side-effects

Model


Decision
Event?
Utility of consequences
Supplement
d_0
NTD
p_0
$U_1 - c_0$
NO NTD
$1 - p_0$
$U_0 - c_0$
No Supplement
d_1
NTD
p_1
$U_1 - c_1$
NO NTD
$1 - p_1$
$U_0 - c_1$

Probability Assessment

p_0 Probability of an NTD with folic acid
p_1 Probability of an NTD without folic acid

4mg in high-risk women*:
p_0 = 35 per 1000 births, p_1 = 10 per 1000 births

low-risk women **:
p_1 = 3.3 per 1000 births
p_0 = 1 per 1000 births - assuming 0.4mg folic acid equally effective in low-risk to 4mg folic acid in high-risk

* Data from MRC Vitamin Study, Lancet 1991
** Best estimate from modelling of routine data

Probability Assessment

Choose folic acid if $\frac{U_0-U_1}{c_0-c_1} > \frac{1}{(p_0 - p_1)}$

i.e., if $\frac{U_0-U_1}{c_0-c_1} > \text{NNT}$

Plugging in previous estimates gives

Previous history of NTD $\frac{U_0-U_1}{c_0-c_1} > 40.3$

No previous history of NTD $\frac{U_0-U_1}{c_0-c_1} > 416.7$

Public Health Policy on Folic Acid

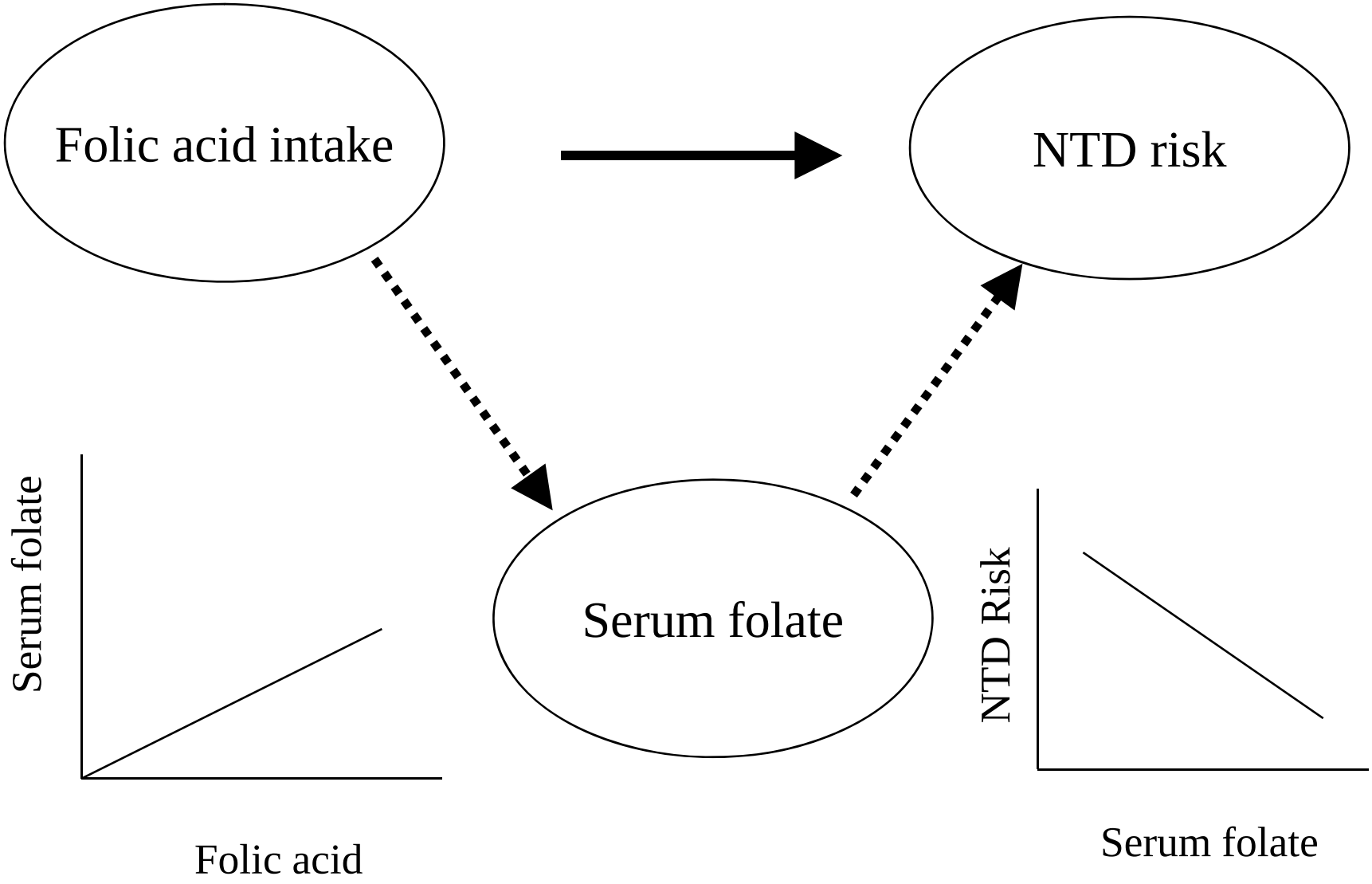
Decision maker	Minister of Health/CMO
Possible actions	Recommend routine supplementation
Uncertain consequences	Incidence of NTD
Sources of evidence statistics	Population
	Randomised trial in high risk women
Utility assessments	Cost of prescriptions
	Costs of termination/ care
	Desirability of reducing disability

Regulatory Decision on Folic Acid

Decision maker	MHRA / CHM or EMEA or FDA
Possible actions	Recommend MA or not
Uncertain consequences	Positive benefit: risk for at least some identifiable patient groups
Sources of evidence	Population statistics Randomised trial in high risk women
Utility assessments	Adequacy of evidence on which to base that judgment

Hypothetical Regulatory Decision

Decision maker	MHRA / CHM or EMEA or FDA
Possible actions	Recommend MA for 5mg for all women
Uncertain consequences	Increased benefit: risk for low-risk women
Sources of evidence doses observational countries	Case- control study, trials at various with surrogate end-points, data from various Randomised trial in high risk women (see Wald NJ et al, Lancet, 2001)
Utility assessments	Adequacy of evidence on which to base that judgment


Folic acid intake
NTD risk
Serum folate
Serum folate
Folic acid
NTD Risk
Serum folate

Technical Points

- Need full power of Bayes for incorporating non-vague prior evidence
- Marginal probabilities for uncertainty about specific parameters in multi-parameter problems
- Handling complex models with non-linear utilities
- Communicating and summarising results prior to decision making

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Herceptin

Benefit: Risk captured with a single parameter

- Pivotal study: randomised, open-label comparing Herceptin and placebo in women with non-metastatic, operable primary invasive breast cancer over-expressing HER2 who had completed … therapy… for primary breast cancer.

- Benefit: Disease-free survival (Placebo vs. Herceptin)
  - proportion with either disease progression or death (due to any cause) 12.9% vs. 7.5%
  - Death (due to any cause) 2.4% vs. 1.8%

- Risk: Cardiotoxicity (Placebo vs. Herceptin)
  - significant asymptomatic (NYHA class I) or mildly symptomatic (NYHA class II) cardiac dysfunction 0.53% vs. 3.04%
  - symptomatic congestive heart failure of NYHA class III or IV or cardiac death 0.06% vs. 0.6%

Herceptin

Benefit: Risk captured with a single parameter

- MHRA Assessment Report: “If disease-free survival and primary cardiac events **were combined into a single endpoint** it would be dominated by the disease-free survival data with the hazard ratio favouring Herceptin.”

- Benefit: Risk captured with a single parameter assuming equal weight for progression, cardiac event and death from any cause.

- Does further quantification add anything in this type of scenario?

- Could estimate weighting that would need to be given to make the benefit: risk unfavourable, or incidence of cardiac events to make benefit: risk unfavourable given equal weight.

Treating menopausal symptoms

Decision maker	Woman
Possible actions	HRT or not? For how long?
Uncertain consequences	Risk of heart attack/stroke
	Risk of breast cancer
	Osteoporosis/fractures
	Vasomotor symptoms
	Skin
	Weight change
Sources of evidence	Epidemiological studies
	Trials
Utility assessment	Woman's trade off between long and short term consequences

Hormone-replacement therapy: safety update (UK Public Assessment Report, MHRA)

i) 5 years' HRT use in women younger than age 60 years

Type of HRT	**Bsline per 1000**	**Absolute risk in 1000 HRT users**	**Attr risk**
Oestrogen-only (no uterus)	42	47 (44–52)	5 (2–10)
Oestrogen-only (w uterus)	44	53 (49–59)	9 (5–15)
Combined HRT	37	51 (48–56)	14 (11–19)

(*similar tables for 60-69s, and for 10 years' HRT use*)

Hormone-replacement therapy: safety update (UK Public Assessment Report, MHRA*)

Baseline rate: Obtained *by adding* the baseline rates for breast cancer, endometrial cancer (in women with a uterus), ovarian cancer, colorectal cancer, venous thromboembolism, CHD, stroke and fracture of femur in non-HRT users.

Absolute risk: Obtained *by subtracting* the number of cases of colorectal cancer and fracture prevented from the total number of cases of breast cancer, endometrial cancer (in women with a uterus), ovarian cancer, venous thromboembolism, CHD, stroke in HRT users.

Attributable risk: Obtained *by subtracting* the baseline risk in non-HRT users from the absolute risk in HRT users.

See http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con2032228.pdf

Hormone-replacement therapy: safety update (UK Public Assessment Report, MHRA)

"A key drawback of this approach is that the benefits of vasomotor symptom relief—the main indication for HRT—are difficult to quantify and have been not taken into consideration. Because the efficacy of oestrogen-only HRT and combined HRT in relief of vasomotor symptoms is similar, however, the safety profile of these two types of HRT can justifiably be compared."

BUT

- not very helpful in deciding whether to use HRT or not for its licensed indications

- Utilities are implicit- that all other endpoints are equally serious

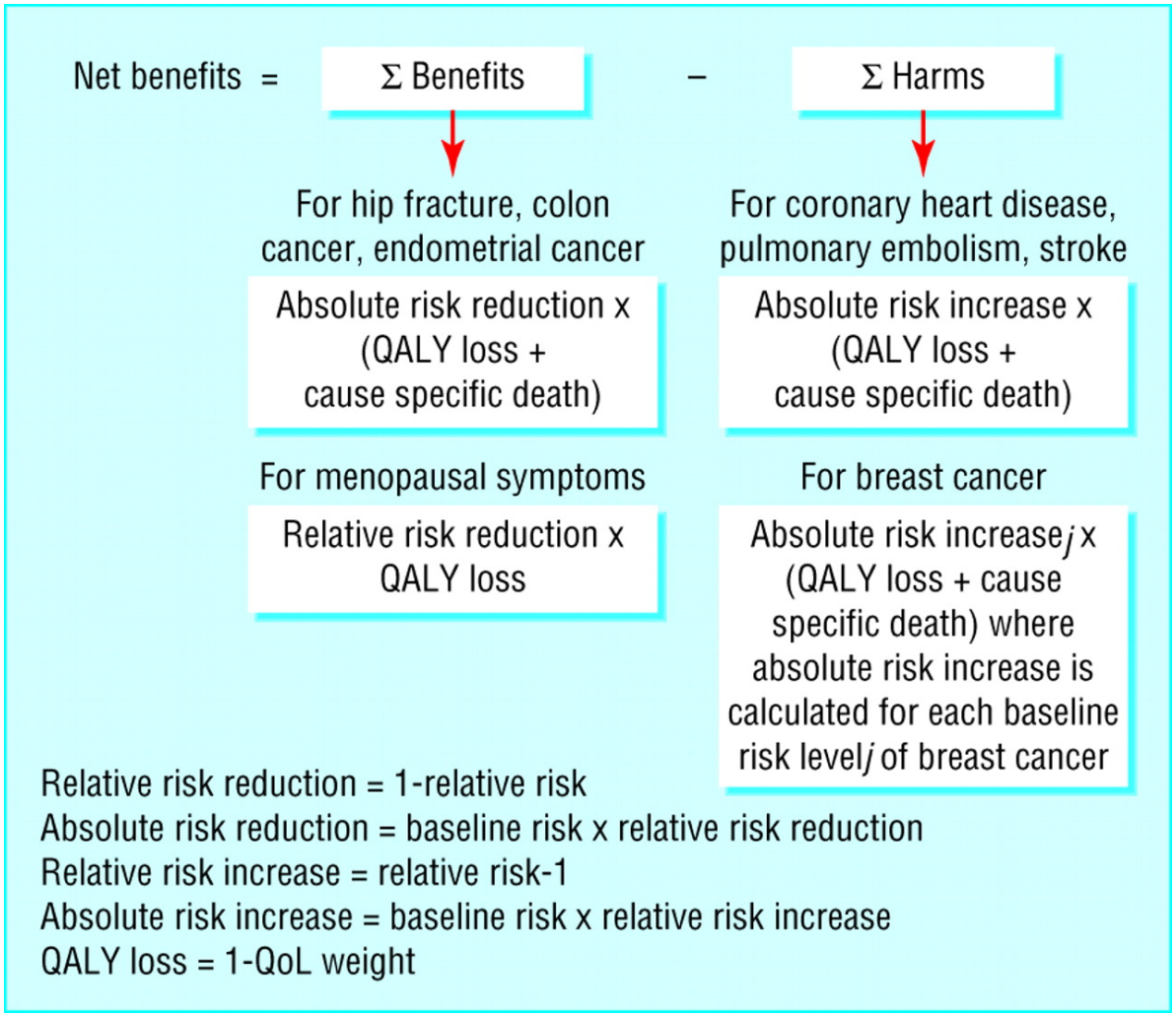
cf data-monitoring for WHI (Freedman et al, CCT, 1996;
Ashby & Tan, Clinical Trials, 2005)

Benefits and Harms of HRT

(Minelli C et al, BMJ, 2004)

- Objective: to evaluate harms and benefits associated with combined HRT for 5 years for varying baseline breast cancer risk
- Setting: Hypothetical population of white UK women aged 50
- Modelling: Bayesian framework with non-informative priors, fitted via MCMC in WinBUGS based on QALYS and deaths, uses average risks, except for breast cancer
- Data: thoroughly referenced, including HERS I & II, EVTET, WHI

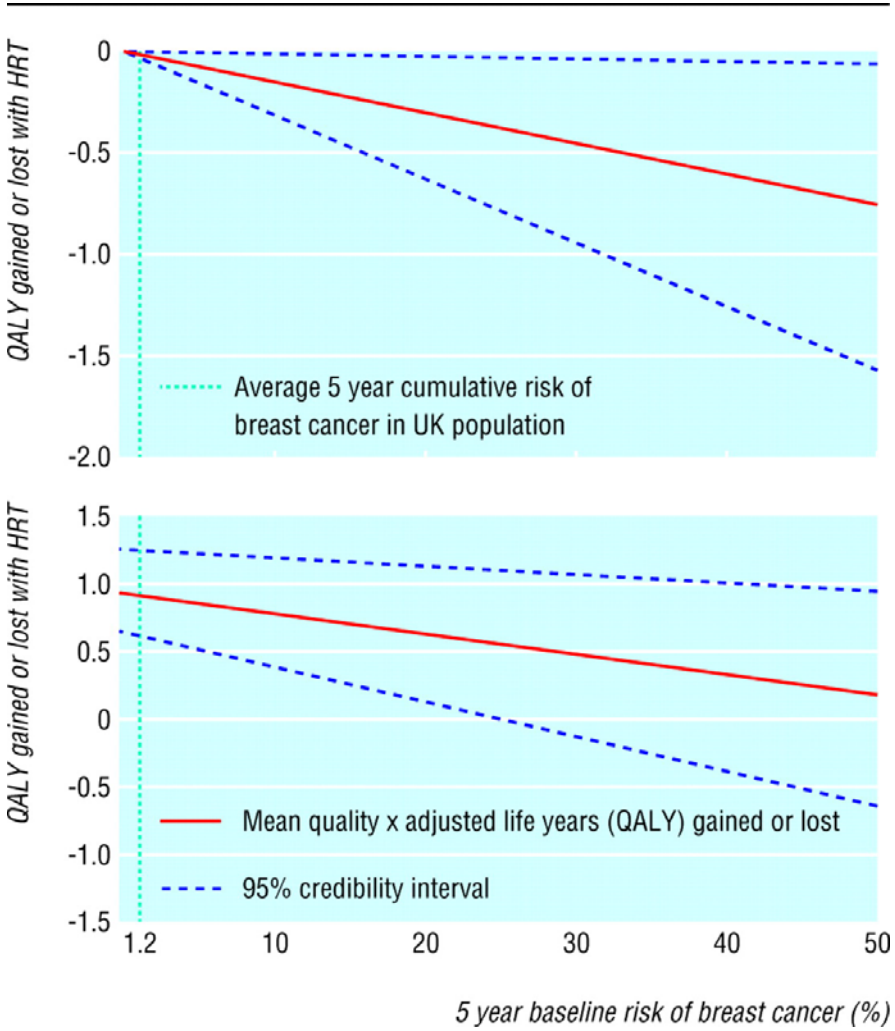
Fig 1 Structure of net benefit decision model



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

BMJ

Fig 2 Graphical presentation of net-benefit model, with 95% credibility intervals, after exclusion of menopausal symptoms (top) or inclusion of symptoms with QoL weight 0.75 (bottom)



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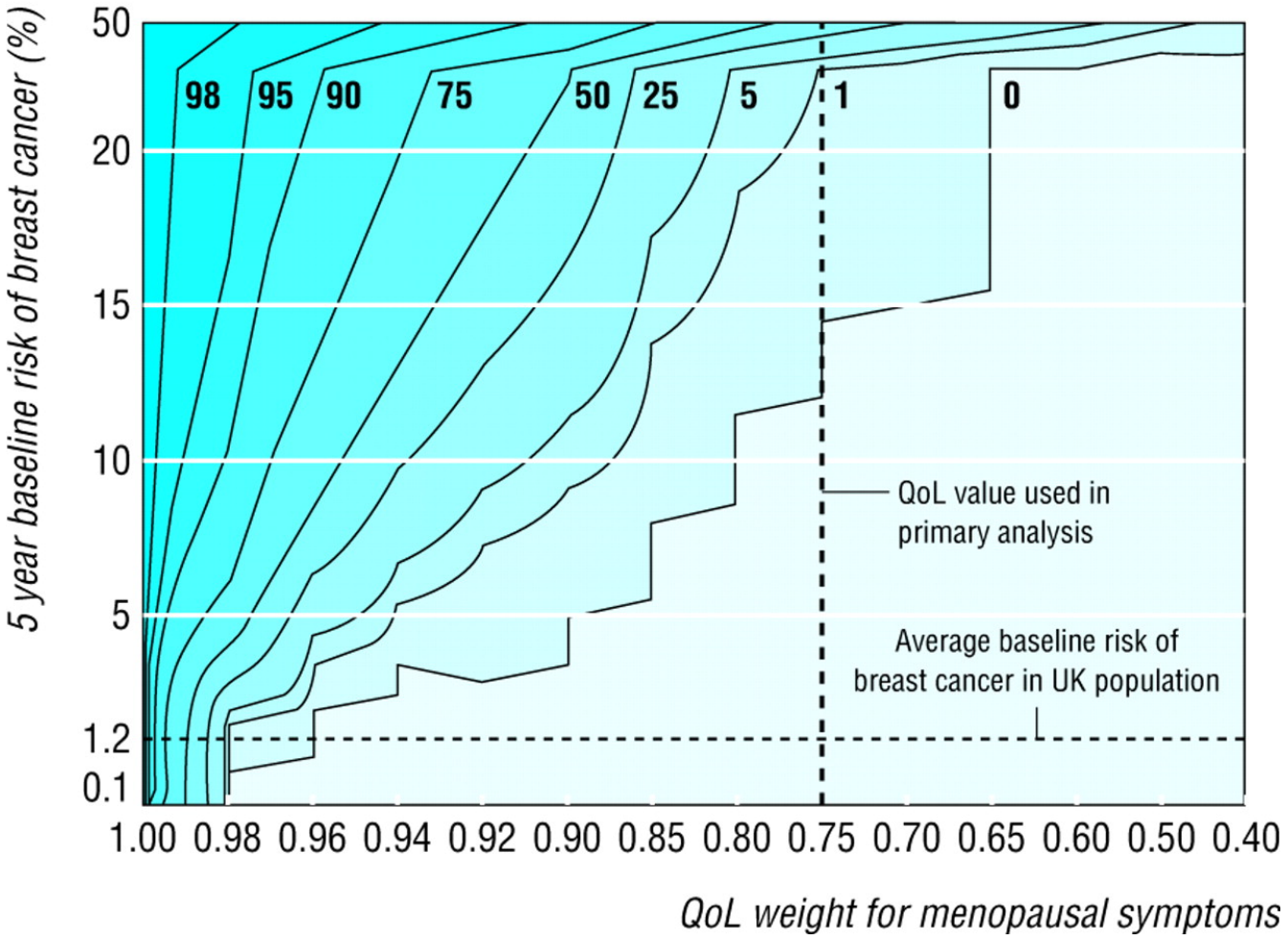
BMJ

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



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BMJ

Benefits and Harms of HRT (Minelli C et al, BMJ, 2004)

- Conclusion: “Women with menopausal symptoms on average benefit from HRT,…which concur[s] with the recommendations of the UK MHRA. The results depend on the QoL attributed to symptoms, which in turn vary greatly,….. Thus a decision analysis tailored to individual women would be more appropriate in clinical practice than a population based approach”

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Open questions

- At what point in the development / licensing process?
  - Importance of pre-specification.
  - Pressure for rapid licensing procedure.
- Regulator or sponsor driven?
- Whose utilities / preferences to use (societal, individual, regulatory)?
- Communication to patients
  - Is it sufficient to describe absolute risks and benefits in product literature and let decision makers determine treatment, or should methods to further elucidate also be presented?

Open questions

- Methodological questions including:
  - Do current trial designs collected a sufficient amount of the correct data to implement the methodology?
  - Frequentist or Bayesian information?
  - How far can models be stressed? How much do we currently stress our own assumptions?
  - Quantification of precision of outputs
  - How to combine observational and RCT data for lifecycle assessment (different designs, different patients etc.)
  - How to quantify the more ‘conceptual’ regulatory considerations:
    - surrogacy, external validity, trial quality, including methodological concerns, biological plausibility, ‘class’ effects etc.

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Risk-Benefit Decision-Making : Current Regulatory Initiatives

- CHMP Working Group on Benefit-risk Assessment Models and Methods (Report and Reflection Paper)
- FDA Workshops and Academic Papers
- MISG Forum on Risk-Benefit Decision-Analysis
- PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium) recently accepted for funding by the Innovative Medicines Initiative Joint Undertaking (IMI JU) including workstream on ‘methods for continuous benefit/risk monitoring’

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