

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

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The Licensing Challenge

The task of regulators (EMA, FDA etc) is to make good and defensible decisions on which medicines should receive a license for which indications, based on the available evidence of risks and benefits.

It is increasingly important to be able to justify and explain these decisions to patients and other stakeholders.

Can more formal methods of decision making, especially those employing modern methods of graphical display, help us do this better?

Decision Making- Some background

- High school math curricula in the UK
- Math BSc module in many universities
- Not routinely part of MSc medical statistics training in the UK
- 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 patient’s *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 ...
- EMA/ MHRA etc 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

Herceptin in early breast cancer

Decision maker

Woman

Possible actions

Herceptin or not?

Uncertain consequences

Breast cancer recurrence

Death

Cardiotoxicity

Sources of evidence

A pivotal trial

Utility assessment

*Woman's trade off between
increased disease-free survival
and cardiotoxicity*

Herceptin

Benefit: Risk captured with a single parameter

- Pivotal study: randomized, open-label comparing Herceptin and placebo in women with non-metastatic, operable primary invasive breast cancer overexpressing 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 favoring Herceptin.”
- Benefit:risk ratio 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 be given to make the benefit: risk unfavorable, or incidence of cardiac events to make benefit: risk unfavorable given equal weight?

PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium)

“Improving and strengthening the monitoring of the benefit/risk of medicines marketed in the EU”
including graphical representation of risk-benefit led by EMA with 29 public and private partners, 2009-2014 (funding IMI)

PROTECT Risk-Benefit Work Plan

1. Review of methodologies used to model effects of medicines, elucidation of patients' preferences and integrating effects and preferences.

Review of methodologies for graphical representation and visualization techniques.

2. Selection of case studies (waves 1 and 2)
3. Data selection/requirements for case studies
Wave 1: Raptiva, Tysabri, Acomplia, Xigris, Ketek
4. Identification/development of software for B/R.
5. Application of methodology, recommendations, finalization of tools, protocols for validation studies.

B-R Review: Comparison of Techniques

| | J | U | S | w | I | T | ζ | G | Resultant metric | Level of Complexity |
|-----------------------|---|---|---|---|---|---|---|---|------------------------|---------------------|
| Conventional approach | X | | | | | | | | Rates/Odds (ratios) | Easy |
| NNT/NNH | X | | | | | | | | Rates threshold | Easy |
| AE-NNT | X | | | | X | | | | Rates threshold | Easy |
| RV-NNT/NNH | X | X | X | | | | | | Rates threshold | Medium |
| MCE | X | X | X | | X | | | | Rates threshold | Medium |
| CUI | X | | X | X | X | | X | X | Expected utility | Medium |
| DI | X | X | X | X | X | | X | X | Expected utility | Complex |
| BLRA | X | X | X | X | X | | X | | Weighted utility | Complex |
| QALY/DALY | | X | X | X | | X | | | Expected utility | Medium |
| RVALY | | X | X | X | | X | | | Expected utility | Medium |
| INB | | X | X | X | X | X | X | | Expected utility | Medium |
| TURBO | X | | X | | X | | | X | Utility | Easy |
| Decision tree | X | X | X | | X | | | X | Expected utility | Easy - complex |
| MCDA | X | X | X | X | X | O | X | X | Weighted utility | Complex |

J = probability; S = Scoring; U = Utility, w = weights; I = Integrated risk and benefit; T = integrate time trade-off;
 ζ = explicit sensitivity analysis; G = Graphical methods readily available
 X indicates required parameters; O indicates optional parameters

Other Benefit –Risk Initiatives

Regulatory:

EMA has a reflection paper, is developing a template and has commissioned Larry Phillips to review regulatory decision-making practice

FDA is very active, including meeting on ‘Risk-Benefit Considerations in Drug Regulatory Decision-Making’ in April 2010

Pharma:

Pharmaceutical Research and Manufacturers of America’s Benefit-Risk Action Teams (PhRMA BRAT) are developing a comprehensive framework

Academia:

Many papers, reviews and books are emerging

Treating menopausal symptoms

Decision maker

Woman

Possible actions

HRT or not? For how long?

Uncertain consequences

Heart attack/stroke

Breast cancer

Osteoporosis/fractures

Vasomotor symptoms

Skin

Weight change

Sources of evidence

Epidemiological studies

Trials

Utility assessment

*Woman's trade-off between long-term
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

| <i>Type of HRT</i> | <i>Baseline, Absolute risk, Attr risk</i> | | |
|----------------------------------|---|------------|------------|
| <i>Estrogen-only (no uterus)</i> | 42 | 47 (44–52) | 5 (2–10) |
| <i>Estrogen-only (w uterus)</i> | 44 | 53 (49–59) | 9 (5–15) |
| <i>Combined HRT</i> | 37 | 51 (48–56) | 14 (11–19) |

(similar tables for ages 60-69, and for 10 years of 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 estrogen-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

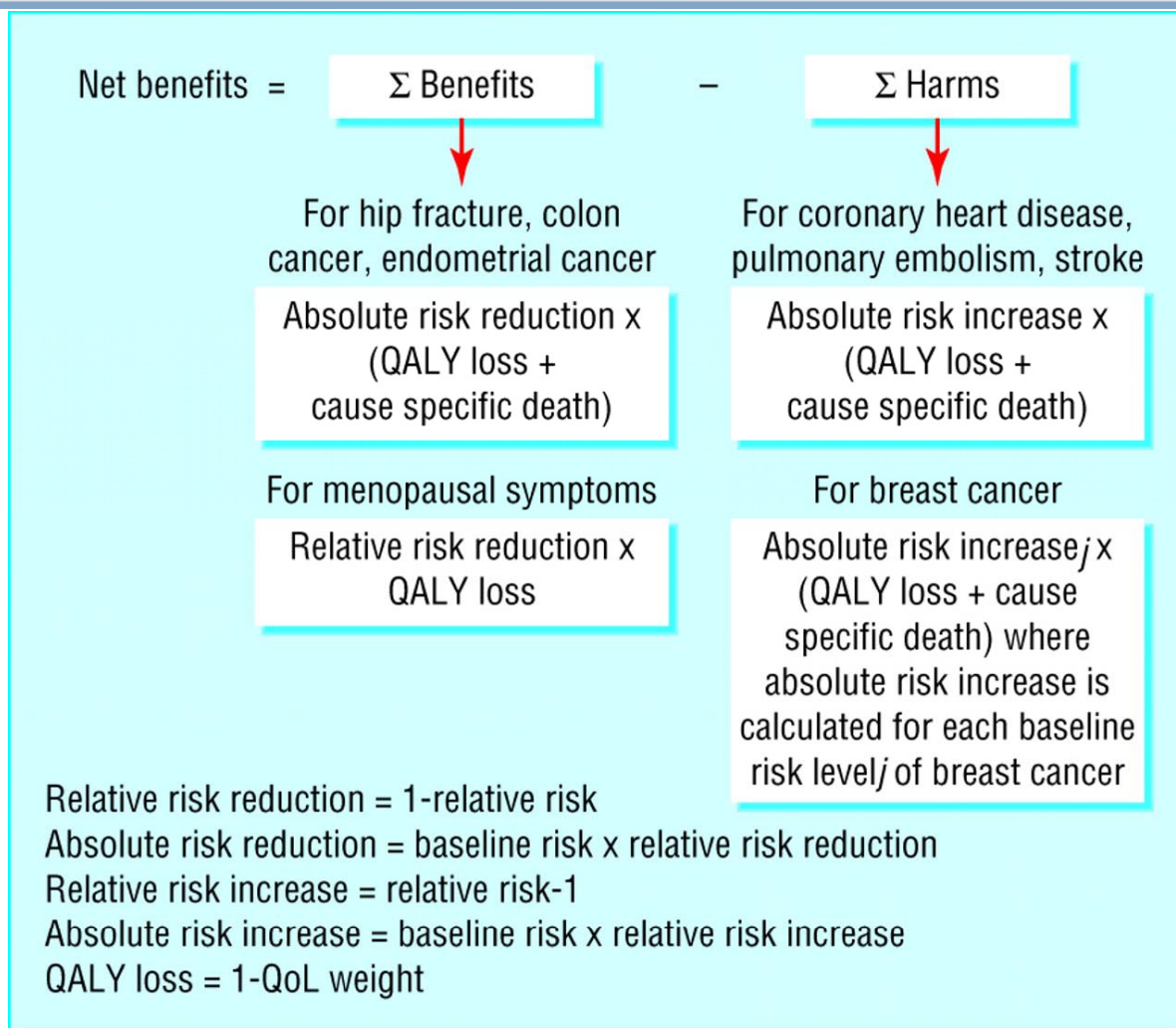
- *not very helpful in deciding whether to use HRT or not for its licensed indications*
- *Utilities are implicit- that all other endpoints are equally serious
cf data-monitoring for WHI (Freedman et al, CCT, 1996;
Ashby & Tan, Clinical Trials, 2005)*

Benefits and Harms of HRT

(Minelli C et al, BMJ, 2004)

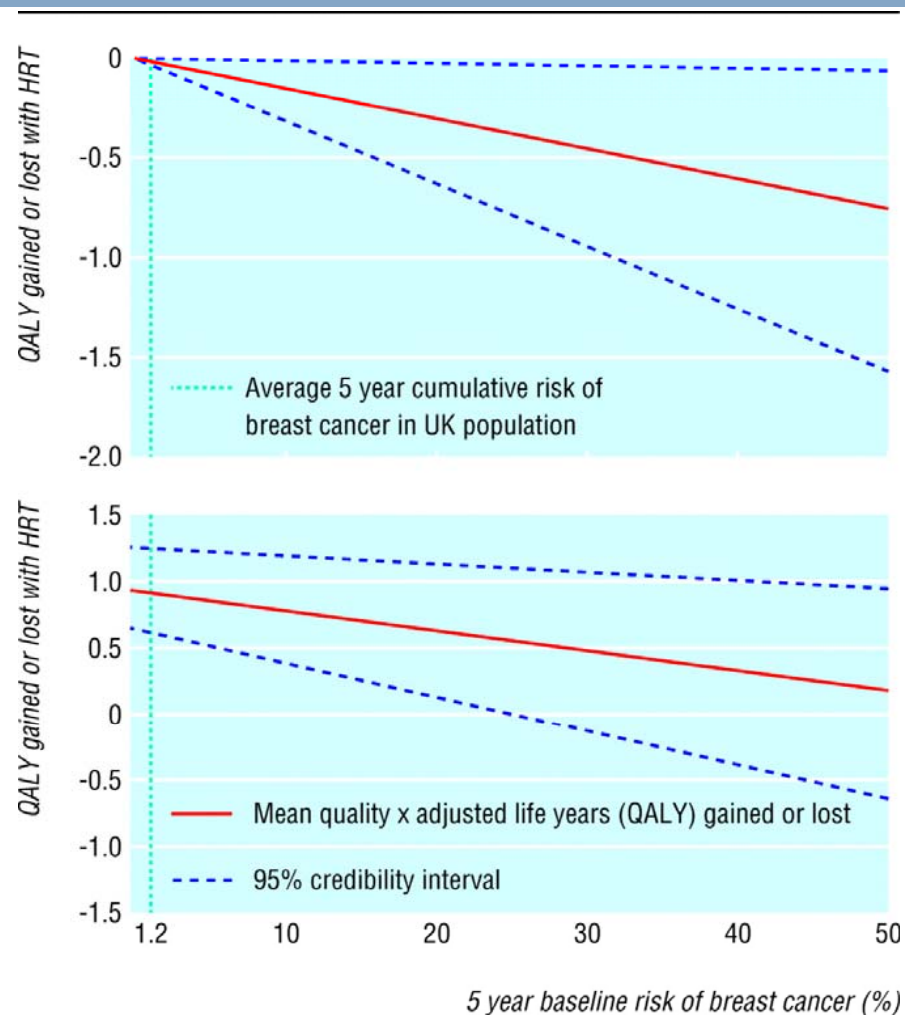
- Objective: to evaluate harms and benefits associated with combined HRT for 5 years for varying baseline breast cancer risks
- Setting: Hypothetical population of white UK women aged 50
- Modeling: Bayesian framework with non-informative priors, fitted via MCMC in WinBUGS based on QALYS and deaths,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

Fig 1 Structure of net benefit decision model



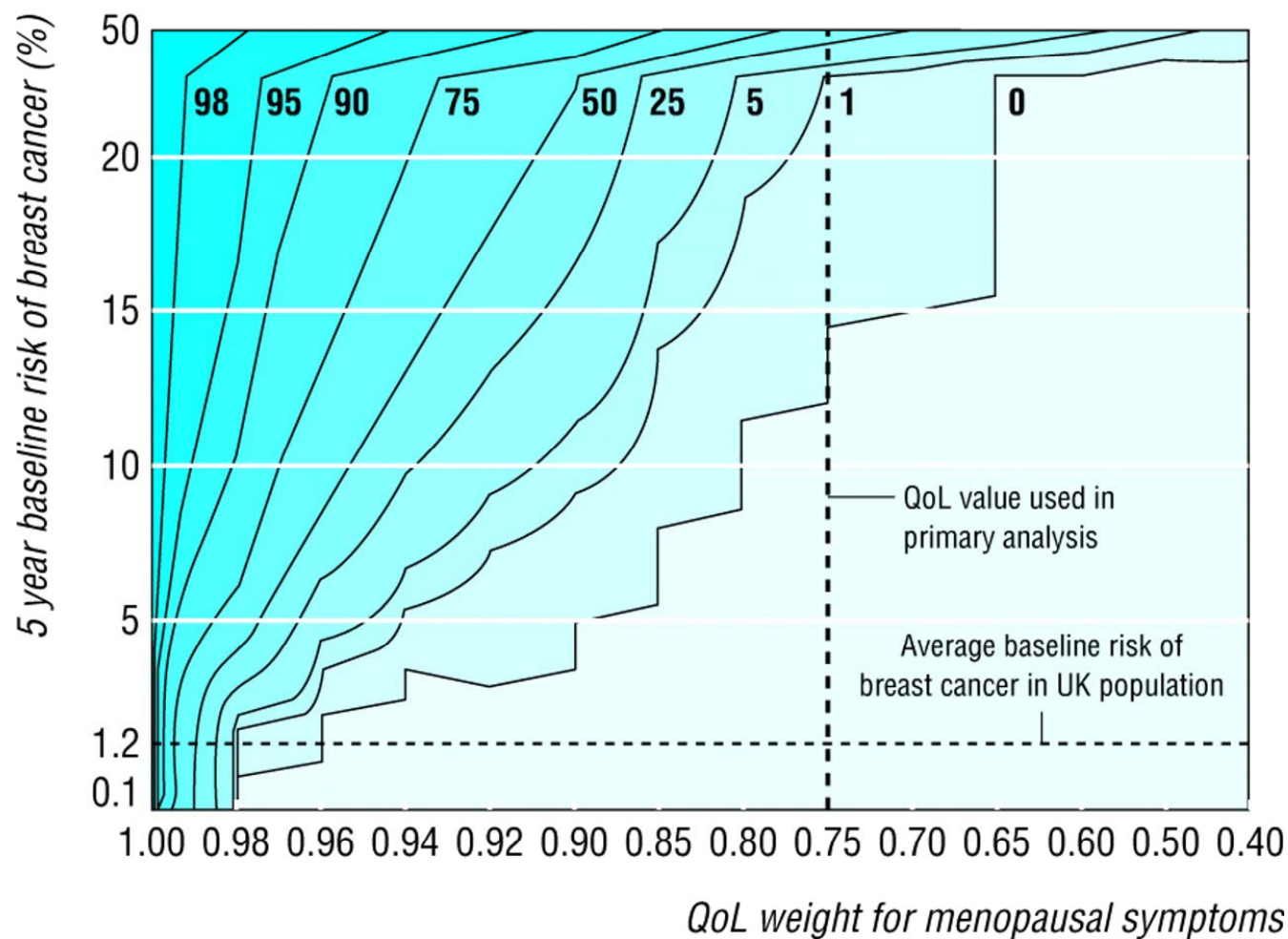
Minelli, C. et al. *BMJ* 2004;328:371

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)



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

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

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.”

Conclusions

- Risk-benefit decision making for stakeholders, including patients and regulators, is an important emerging area
- Statisticians need to engage to ensure the best methods are used to inform decisions about medicines
- What seem to be well-established techniques to us are still very novel to regulators who are used to more traditional statistical approaches
- Risk-benefit assessment is a natural arena for Bayesian approaches, so there is plenty of opportunity!

References

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