Drug Information Association (DIA) 23rd Annual EuroMeeting

29 March 2011 Geneva, Switzerland

Presented by: Deborah Ashby
Imperial Clinical Trials Unit
School of Public Health
Imperial College London

'Current methodological approaches to risk-benefit decision-making'

PROTECT

The Licensing Challenge

- The task of regulators (EMA, FDA etc) is to make a 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 and especially more modern methods of graphical display help us do these better?

Decision Making – Some background

- In high school maths curricula in UK
- Maths BSc module in many universities
- Not routinely part of MSc Medical Statistics training in 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 patients predicaments, rights and preferences using best evidence from clinically relevant research*." Sackett et al, 1996

PROTECT

EBM as Bayesian Decision-Making*

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

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

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

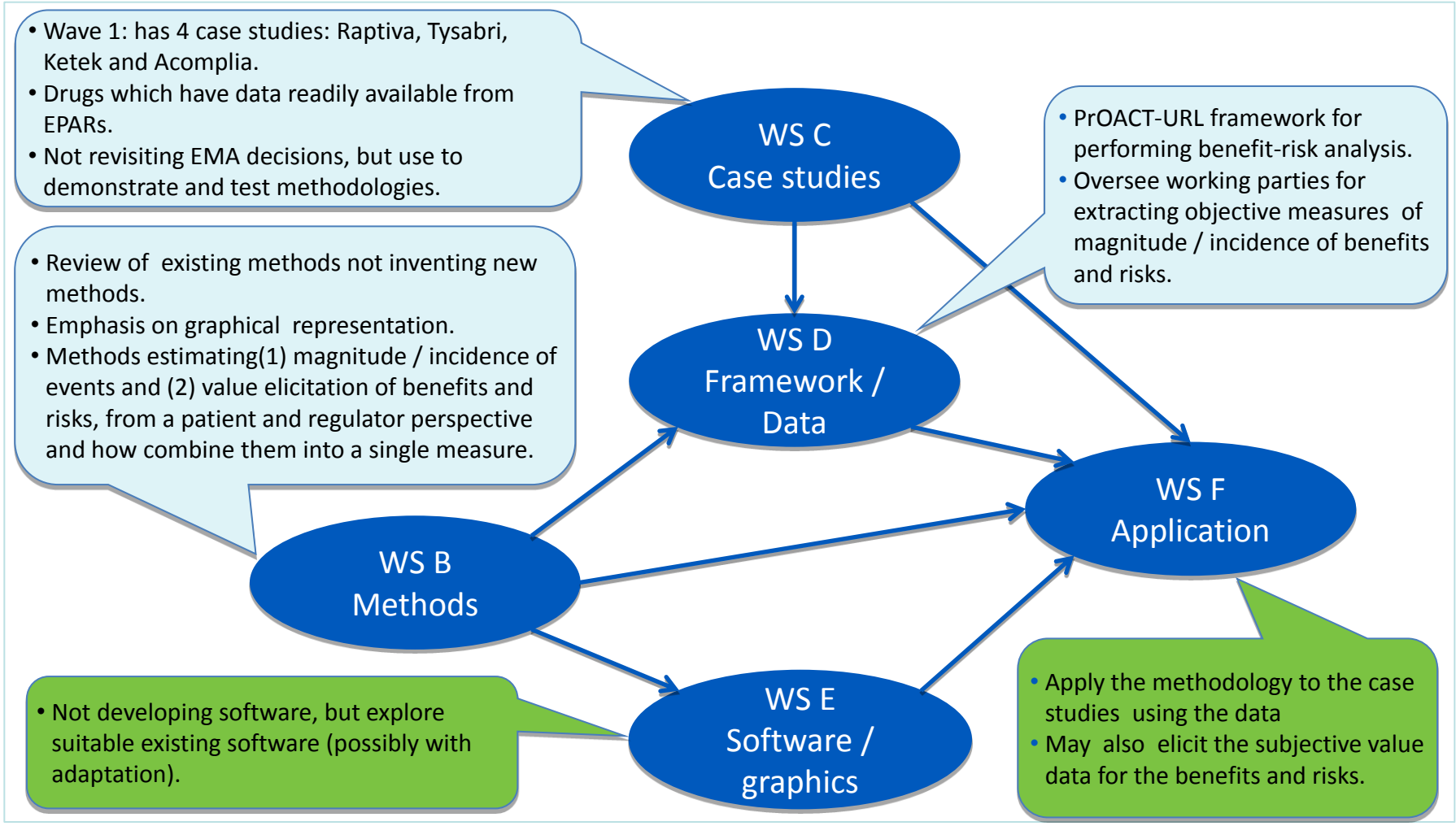
About us: IMI-PROTECT

- PROTECT[1] (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 31 public and private partners, 2009-2014 (www.imi-protect.eu)

[1] PROTECT is receiving funding from the European Community's Seventh Framework Programme (F7/2007-2013) for the Innovative Medicine Initiative (www.imi.europa.eu)

Work Package 5: Overview



Example: Trastuzumab for early breast cancer*

Decision-maker	The woman
Possible decisions	• Take trastuzumab • Not take trastuzumab
Uncertain consequences	• Breast cancer recurrence • Death • Cardiotoxicity
Sources of evidence	A pivotal trial
Utility assessment	Increased disease-free survival and cardiotoxicity

(*European Medicines Agency (2006). Scientific discussion on Herceptin. Report reference EMEA/H/C/278/II/0026)

PROTECT

Trastuzumab:
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 trastuzumab."
- 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.

Number needed to treat approach for trastuzumab

- NNT=$1/\Delta_p$ patients to be treated to observe one benefit (or to prevent an adverse event)
- NNH=$1/\Delta_q$ patients to be treated to observe an adverse event (or to prevent a benefit)
- $\mathrm{NNT} = \frac{1}{0.861-0.780} = 12.3$
  = for every 13 patients treated, one will benefit from progression-free survival
- $\mathrm{NNH} = \frac{1}{0.0304-0.0053} = 39.8$
  = for every 40 patients treated, one will experience cardiotoxicity

NNT<NNH is desirable

Treating menopausal symptoms*

Decision-maker	The woman
Possible decisions	• 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 and short term consequences

(*Medicines and Healthcare Regulatory Agency (2007). Hormone-replacement therapy: safety update. UK Public Assessment Report MHRA/2032228)

Hormone-replacement therapy: safety update*

- 5 years' HRT use in women younger than age 60 years

Type of HRT	Baseline	Absolute risk	Attributable risk
Oestrogen-only (no uterus)	*42*	*47 (44-52)*	*5 (2-10)*
Oestrogen-only (with 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)

(*UK Public Assessment Report, MHRA
See http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con2032228.pdf)

Hormone-replacement therapy: safety update

- 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.

Hormone-replacement therapy: safety update

"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;

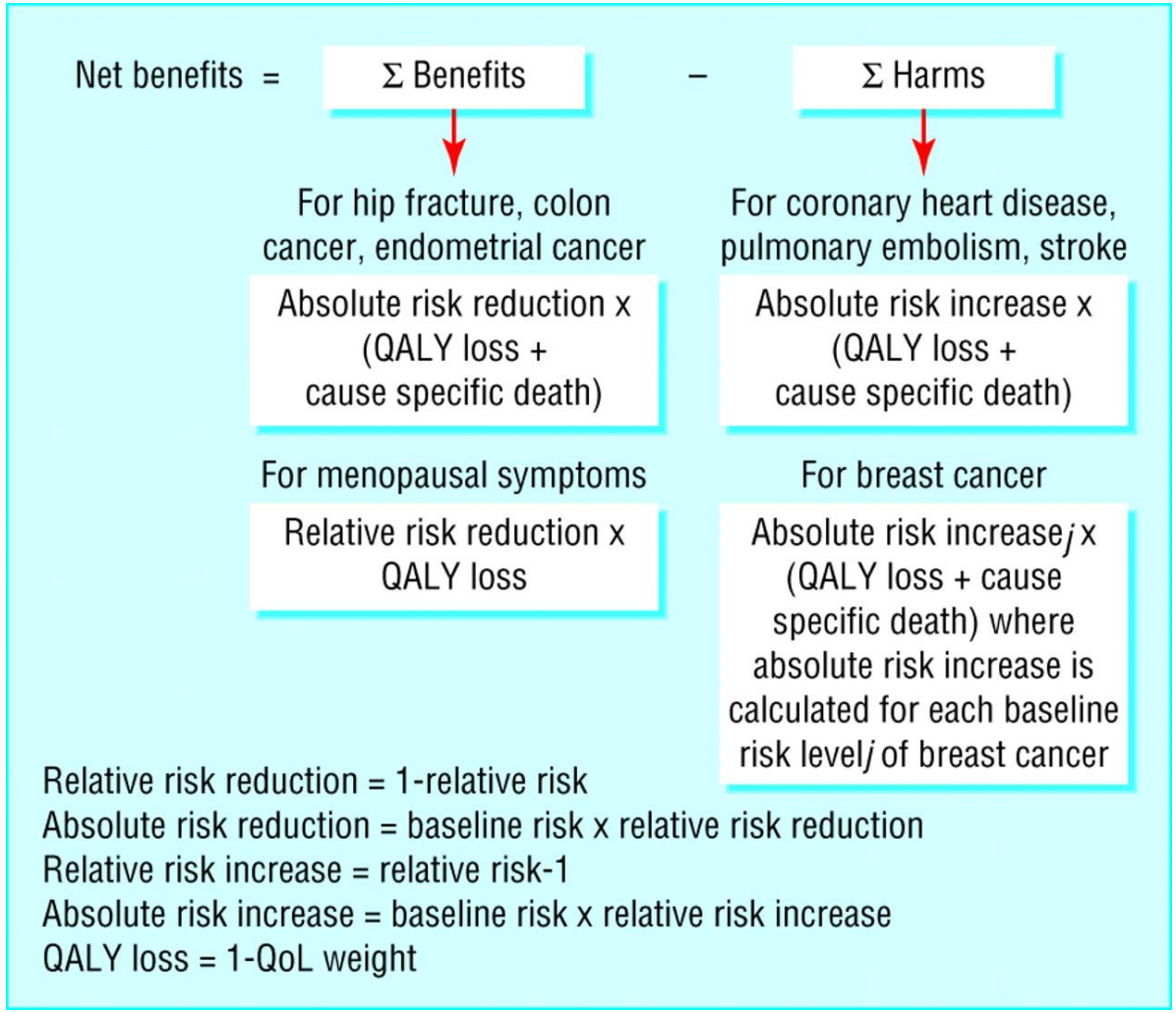
Ashby & Tan, Clinical Trials, 2005)

Benefits and Harms of HRT*

- 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

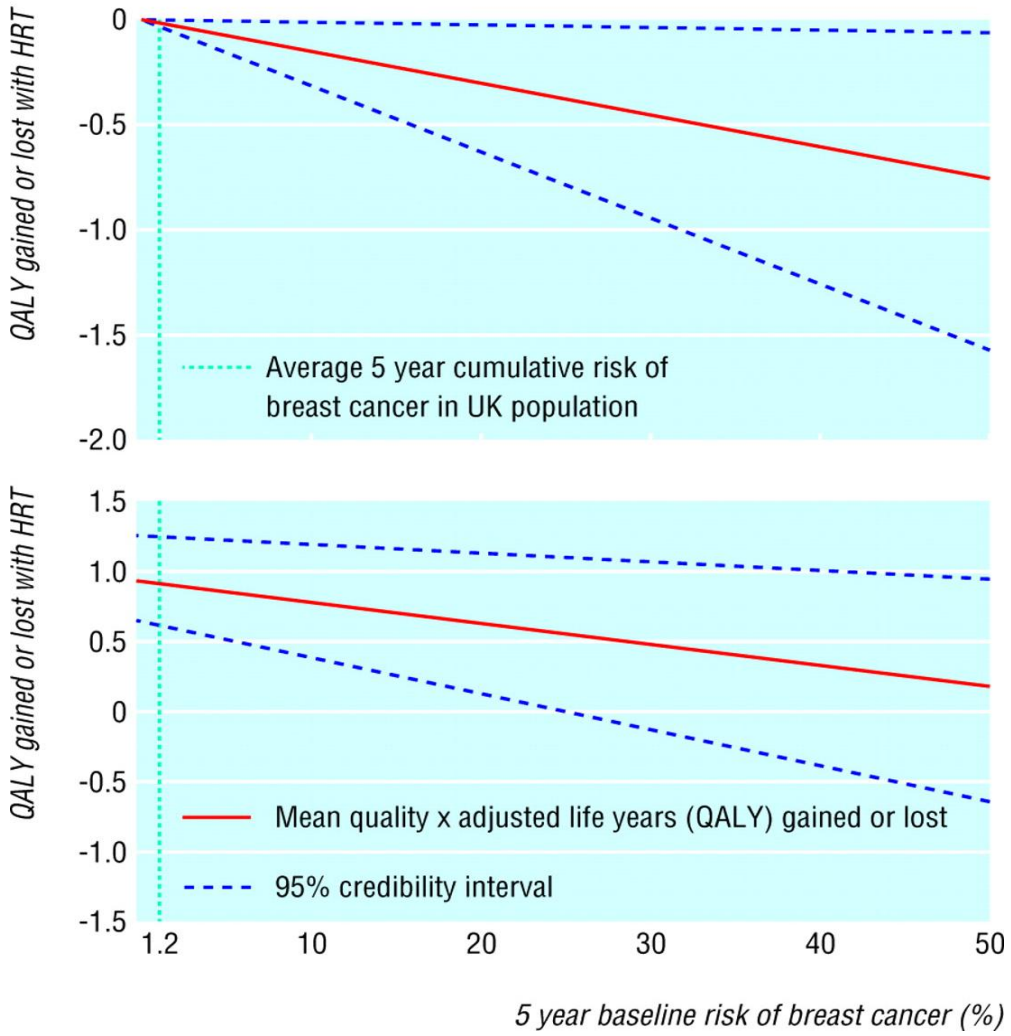
(*Minelli C et al, BMJ, 2004)

Fig 1 Structure of net benefit decision model



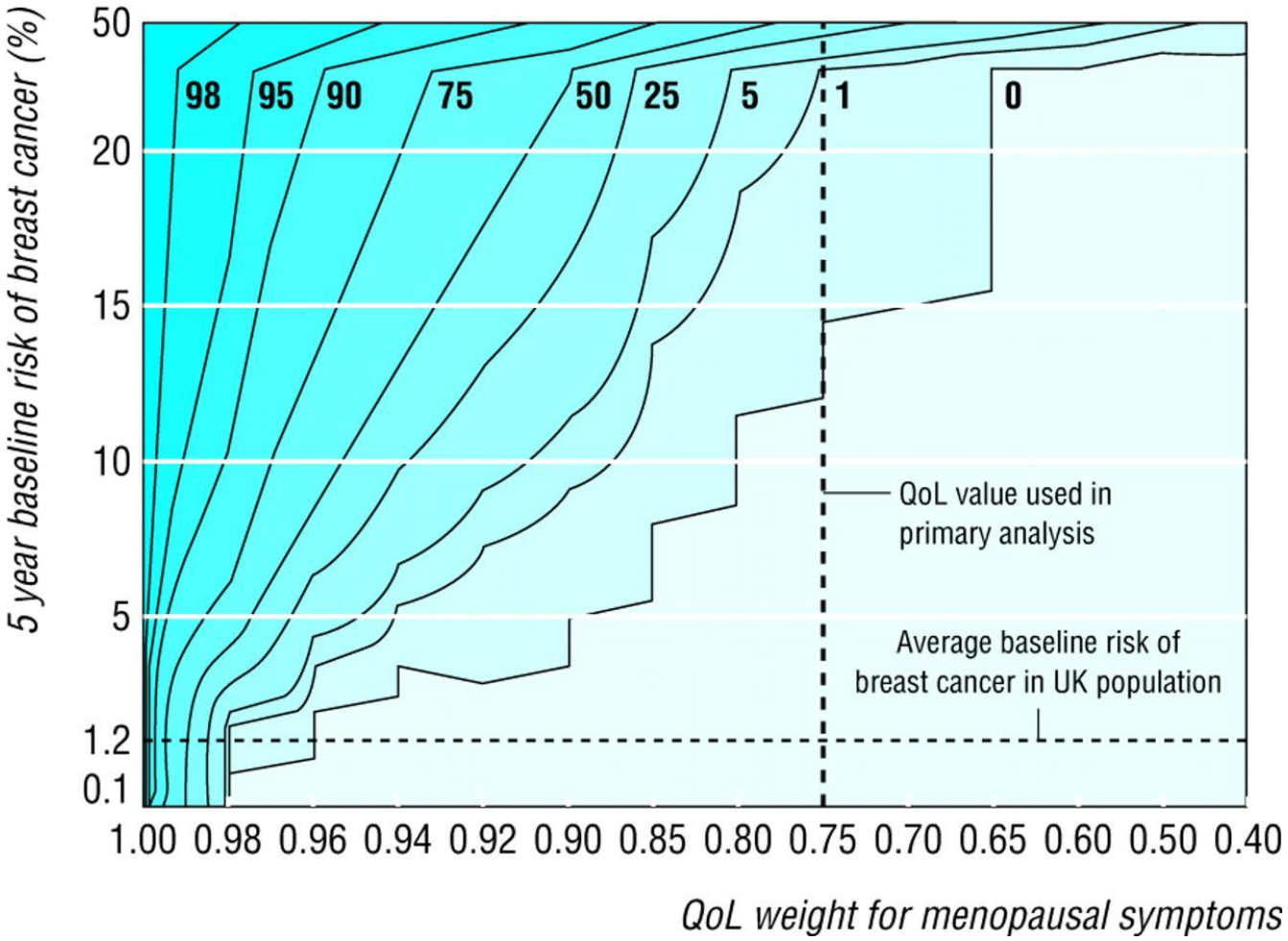
Minelli, C. et al.
BMJ 2004;328:371

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

BMJ

Benefits and Harms of HRT*

- 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*"

(*Minelli C et al, BMJ, 2004)

Example: Rizatriptan for acute migraine attacks*

Decision-maker	Physicians
Possible decisions	• Administer rizaptriptan • Administer sumatriptan • Do nothing
Uncertain consequences	• Benefits – pain relief at 2hr, efficacy in subgroups (men vs. women), anticipated compliance in trials • Risks – dizziness, somnolence, asthenia/fatigue, chest pain, potential off-label use leading to safety hazards
Sources of evidence	Three pivotal trials from MA application
Utility assessment	Physicians' value judgments and weightings for each uncertain consequence

(*See Mussen F. et al. (2009). Development and Application of a Benefit-Risk Assessment Model Based on Multi-Criteria Decision Analysis. In Benefit-Risk Appraisal of Medicines. pp. 111-149, John Wiley & Sons, Ltd.)

Multi-Criteria Decision Analysis (MCDA)

Steps in MCDA	Application to rizatriptan example
1. Establish decision context	Rizatriptan treatment in acute migraine attacks in over 18 using pivotal MA application data from physicians' view
2. Identify options to appraise	Rizatriptan vs. sumatriptan vs. placebo
3. Identify objectives and criteria	High-level criteria are benefits and risks
4. Score options	Least preferred benefits and most preferred risks = placebo rates.
5. Weight criteria	Swing-weighting and using authors' view
6. Combine weights and scores	Weights are normalised and given as cumulative weights and weighted utilities
7. Examine results	Rizatriptan: 27.8 benefits, 39.0 risks. Total=67 Sumatriptan: 26.2 benefits, 35.0 risks. Total=61 Placebo: 0 benefits, 50 risks. Total=50
8. Conduct sensitivity analysis	Placebo is favoured if weights on benefit <30 or weights on risks > 70

Comparison of technologies (legend)

- π = 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.

Comparison of technologies (table)

	NNT / NNH	INB	MCDA
π	X		X
U		X	X
S		X	X
w		X	X
I		X	X
T		X	O
ζ		X	X
G			X
Resultant metric	Rates threshold	Expected utility	Weighted utility
Complexity	Easy	Medium	Complex
Perspective for stakeholders	Individual level decisions and for decisions not strictly regulated e.g. patients, physicians	Population or individual level decisions in strictly regulated conditions e.g. pharmaceutical companies, healthcare providers, regulatory agencies	Population or individual level decisions in strictly regulated conditions e.g. pharmaceutical companies, healthcare providers, regulatory agencies

Other Benefit –Risk Initiatives

- **Regulatory:**
  - EMA have a reflection paper, are developing a template and have commissioned Larry Phillips to review regulatory decision-making practice
  - FDA very active, including meeting on 'Risk-Benefit Considerations in Drug Regulatory Decision-Making' April 2010
- **Pharma:**
  - Pharmaceutical Research and Manufacturers of America's Benefit-Risk Action Team's (PhRMA BRAT) developing a comprehensive framework
- **'Academic':**
  - Many papers, reviews and books are emerging

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 well-established techniques to us are still very novel to regulators used to more traditional statistical approaches
- Risk-benefit assessment a natural arena for Bayesian approaches, so plenty of opportunity!

References

- Ashby D Bayesian Statistics in Medicine: a 25 year review (2006). Statistics in Medicine, 25, 3580-3631.
- Ashby D and Smith AFM (2000). Evidence based medicine as Bayesian decision-making. Statistics in Medicine. 19, 23, 3291-3305.
- Ashby D and Tan SB (2005). Where's the utility in Bayesian data monitoring in clinical trials. Clinical Trials 2, 197-208.
- European Medicines Agency (2006). Scientific discussion on Herceptin. Report reference EMEA/H/C/278/II/0026.
- Freedman L, Anderson G, Kipnis V, Prentice R, Wang CY, Rossouw J, Wittes J and DeMets D (1996). Approaches to monitoring the results of long-term disease prevention trials: examples from the Women's Health Initiative. Controlled Clin. Trials, 17, 509–525
- Minelli C, Abrams KR, Sutton AJ, Cooper NJ (2004). Appropriate use of hormone replacement therapy (HRT): A clinical decision analysis. British Medical Journal 328: 371-5.
- Mussen F, Salek S and Walker S (2009). Development and Application of a Benefit-Risk Assessment Model Based on Multi-Criteria Decision Analysis. In Benefit-Risk Appraisal of Medicines. pp. 111-149, John Wiley & Sons, Ltd.