PROTECT

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Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

INTRODUCTION TO BENEFIT-RISK ASSESSMENT OF MEDICINAL PRODUCTS

IMI-PROTECT Symposium

Benefit-Risk Integration and Representation Workshop

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Disclaimer

"The processes described and conclusions drawn from the work presented herein relate solely to the testing of methodologies and representations for the evaluation of benefit and risk of medicines.

This report neither replaces nor is intended to replace or comment on any regulatory decisions made by national regulatory agencies, nor the European Medicines Agency."

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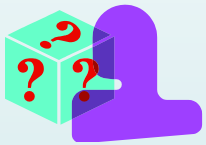
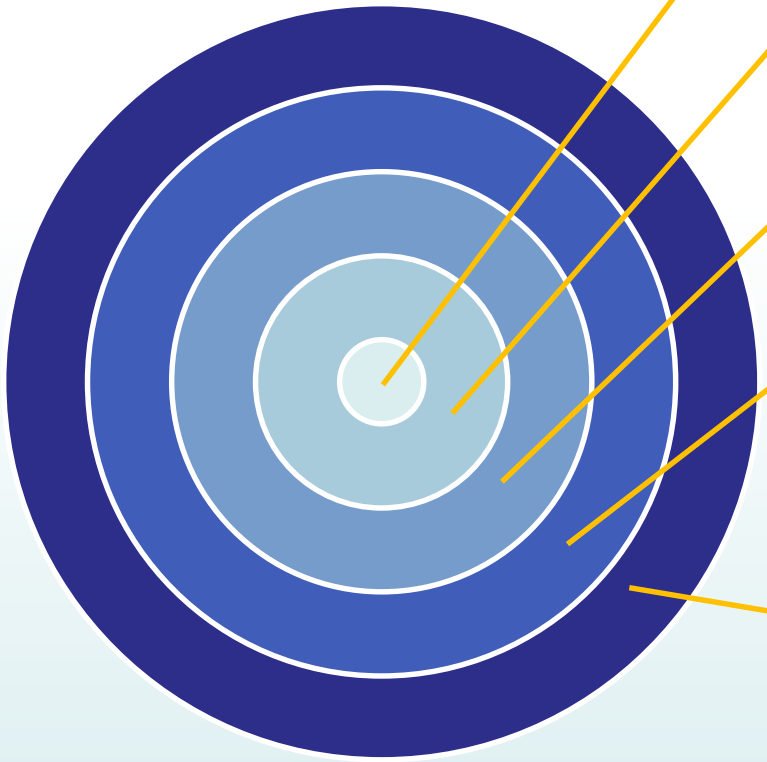
Evidence Based Medicine

"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



Decision makers – hierarchical?



Patients

- Make decisions for themselves

Healthcare providers

- Make decisions based on prescribing lists

Health technology assessors

- Makes decisions on cost-effectiveness

Regulators

- Makes decisions on quality, safety, efficacy and benefit-risk balance to individuals and public health

Pharmaceutical companies

- Makes decisions on what to develop for which licenses to apply

Challenges in medical decision-making

- Should we formalise decision-making at all?
- Which quantitative approach(es) to use?
- Whose value preferences take priority – regulators, pharma, physicians or patients?
- How do we find these preferences – simple elicitation, decision conferencing, discrete choice experiments….?
- Do we need stakeholders' preference a priori, or should we provide tools to allow individual decision-makers to explore their own preferences and the consequent decisions?
- How do we communicate benefits and risks?

A simple example of EBM decision-making

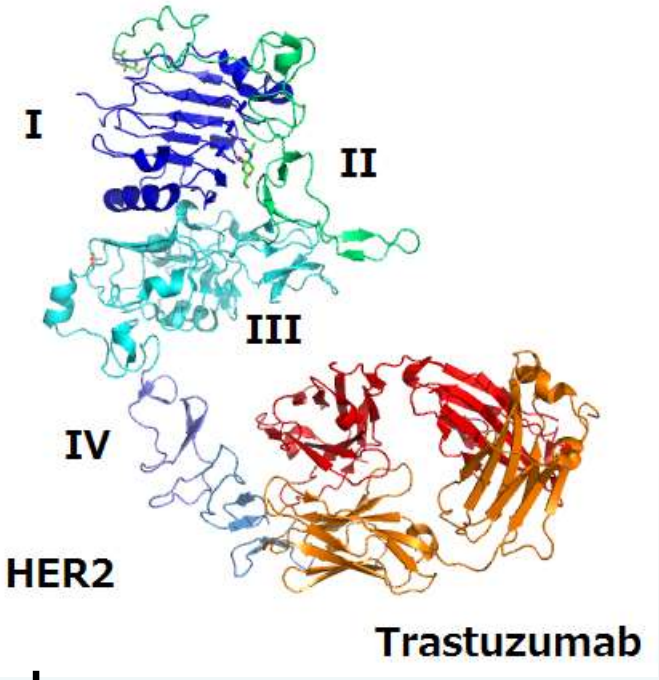
- Decision-maker
- Possible actions
- Uncertain consequences
- Sources of evidence
- Utility assessments

Key reference

Ashby D & Smith AFM, Stats in Medicine, 2000

Trastuzumab
Benefit-Risk captured with a single parameter

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



Trastuzumab
Benefit-Risk captured with a single parameter

- Benefit: Disease-free survival (Placebo vs. Trastuzumab)

	Placebo	Trastuzumab
Proportion with either disease progression or death (due to any cause)	22.0%	13.9%
Proportion of death (due to any cause)	2.4%	1.8%

- Risk: Cardiotoxicity (Placebo vs. Trastuzumab)

	Placebo	Trastuzumab
Significant asymptomatic (NYHA class I) or mildly symptomatic (NYHA class II) cardiac dysfunction	0.53%	3.04%
Symptomatic congestive heart failure of NYHA class III or IV or cardiac death	0.06%	0.6%

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

Simple benefit-risk metrics

Number needed to treat (NNT)	Number needed to harm (NNH)
Number of people to be treated to observe a benefit (or to prevent an adverse event)	Number of people to be treated to observe an adverse event (or to prevent a benefit)
$$\mathrm{NNT} = \frac{1}{\Delta_p} = \frac{1}{\Pr(B\|T) - \Pr(B\|T')}$$ where $\Pr(B\|T)$ = probability of observing a benefit among treated individuals; and $\Pr(B\|T')$ = probability of observing a benefit among untreated individuals	$$\mathrm{NNH} = \frac{1}{\Delta_q} = \frac{1}{\Pr(H\|T) - \Pr(H\|T')}$$ where $\Pr(H\|T)$ = probability of observing an adverse event among treated individuals; and $\Pr(H\|T')$ = probability of observing an adverse event among untreated individuals

NNT and NNH approach for trastuzumab

$$\text{NNT} = \frac{1}{0.861 - 0.780} = 12.3$$

= for every 13 patients treated, one would benefit from progression−free survival

$$\text{NNH} = \frac{1}{0.0304 - 0.0053} = 39.8$$

= for every 40 patients treated, one would experience cardiotoxicity

NNT<NNH is desirable

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.

Recommendation Roadmap

Planning

- critical issues
- think & discuss purpose and context
- documentation
- foundations for future analyses and updates

Evidence gathering and data preparation

- relevant evidence
- data collection
- data aggregation
- missing/incomplete data

Analysis

- Evaluate data
- Quantify benefits and risks
- Weigh or integrate

Exploration

- robustness
- sensitivity
- assumptions and uncertainties
- other consequences
- impact or added value to the RMPs

Conclusion and dissemination

- communicate results/consensus
- any influence on future actions
- transparent audit trail
- ensures "big picture" is not lost

Hughes D, et *al*. Recommendations for the methodology and visualisation techniques to be used in the assessment of benefit and risk of medicines. IMI-PROTECT Website 2014.

Benefits and risks of formalising benefit-risk assessment

Benefits

- Puts benefits and risks on same page
- Gives a framework to include patients' views
- Transparency facilitates discussion
- It's fun!

Risks

- Trade-off between being too simplistic or just incomprehensible
- Can be seen as a 'black box'
- Pharma want to know what regulators want

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