Integrating patient preferences and clinical trial data in a Bayesian model for benefit-risk assessment

H Broekhuizen¹, CGM Groothuis¹, AB Hauber² and MJ IJzerman¹

(1) University of Twente, the Netherlands
(2) RTI Health Solutions, Research Triangle Park, NC
Patient preferences in benefit-risk assessment

- Patient preferences matter
  - They experience the benefits and risks
  - Preferences can differ between regulators and patients
    - Example: Natalizumab case
- Growing interest (FDA, EMA)
- Little known about integrating preferences into assessments
The MCDA model

Risk-benefit plane

Sensitivity graphs

Simulation

Approximation

Patient preferences

Clinical trial data

Clinical trials
Case study: antidepressants

- Preferences: Analytical Hierarchy Process study by Danner et al. (2011)
- Respondents: 12 MDD patients
- Benefit criteria: response and remission
- Risk criterion: adverse events (low and high severity)
- Benefit and risk outcomes assumed to be independent
- Approximated by a bootstrap resampling method
How is preference information approximated?

- Approximated by a bootstrap resampling method
Case study: antidepressants

- Performance: Systematic review by German Institute for Quality and Efficiency in Health Care (IQWIG)
- Drugs: Duloxetine, Venlafaxine and Bupropion
- Odds ratio compared to placebo
How is clinical data approximated?

- Approximated by a normal distribution in the log domain

Remission OR (Bupropion compared to placebo)
Integration of patient preferences and clinical data

- For a particular drug $i$ in simulation run $t$,

$$ Benefits_{i,t} = \begin{bmatrix} W_{response_{t}} \\ W_{remission_{t}} \end{bmatrix} \cdot \begin{bmatrix} OR_{response{i,t}} \\ OR_{remission_{t,i}} \end{bmatrix} $$

$$ Risks_{i,t} = W_{AE_{t}} \cdot OR_{AE_{i,t}} $$

$$ BenefitRiskRatio_{i,t} = \frac{Benefits_{i,t}}{Risks_{i,t}} $$

- Benefits and risks plotted in risk-benefit plane
Risk-benefit plane

- $\mu$ is decision threshold, $\mu=1$ requires drugs to have $>1$ weighted benefit for each weighted risk to be acceptable, i.e:
  - Benefit-risk-ratio $>\mu \rightarrow$ benefits outweigh risks
- Percentage points under line approximates $P(\text{acceptable})$
Risk-benefit plane

- Weighted benefits (odds ratio compared to placebo)
- Weighted risks (odds ratio compared to placebo)

μ=1 line

- Bupropion
- Venlafaxine
- Duloxetine
Sensitivity

- What is the impact of uncertainty surrounding model parameters
- Important distinction (Felli 1998)
  - Value sensitivity (change in expected value)
  - Decision sensitivity (change in decision, i.e. other drug chosen)
  - Ranking sensitivity (change in rank order of drugs)
- Why would we want to know?
  - Robustness
  - Heterogeneity
  - Insight for further research
Value sensitivity

Duloxetine benefit-risk ratio

Adverse events weight

95% CI

μ=3

μ=1

0.15 0.20 0.25 0.30

H Broekhuizen SMDM presentation

18 Oct 2012
Decision sensitivity

- 95% CI
- P(Duloxetine acceptable) at μ=3
- Adverse events weight
Ranking sensitivity

Venlafaxine response performance (OR compared to placebo)
Parameter 1

Parameter 2

Parameter 3

Parameter 4

Parameter 5

Parameter 6
Discussion

- Integration preferences and performance
- Impact uncertainty can be assessed
- Visual representations can help regulators and enrich the discussion during the benefit-risk assessment process.

- Assumptions in antidepressants case
  - Simplified structure
  - Independence
- What probability is convincing?
- Other methods needed to check external validity
- Model cannot make decisions, only assist regulators
Thank you

- Email: h.broekhuizen@utwente.nl
- Web: www.utwente.nl/mb/htsr/Staff/broekhuizen.doc/

“Selective serotonin and noradrenalin reuptake inhibitors (SNRI) with depression patients [Selektive Serotonin- und Wiederaufnahmehemmer (SNRI) bei Patienten mit Depressionen],” Cologne, 2010.