Beware of risk aversion! The role of Probabilistic Sensitivity Analysis in health economic evaluation

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NICE and the cost-effectiveness threshold: Can good intentions compensate for bad practice?

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Outline of presentation

1. **Health economic evaluation & PSA**
   - General structure
   - Monetary net benefit
   - The nature of PSA
2. **Risk aversion**
   - Why?
   - How?
   - So what?
3. **Conclusions(?)**
   - Potential & limitations
   - Open questions

Uncertainty analysis

- Assesses the impact of uncertainty (eg in parameters or model structure) on the economic results
- Fundamentally Bayesian!

Statistical model

- Estimates relevant **population** parameters
- Varies with the type of available data (& statistical approach!)

Economic model

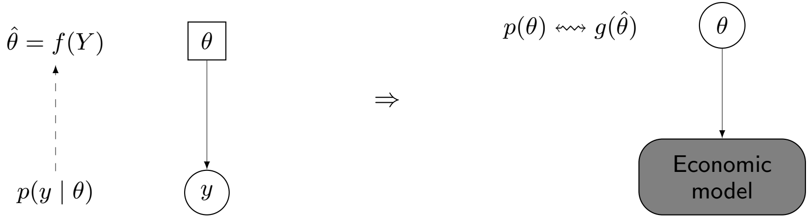
- Combines the parameters to obtain a population average measure for costs and clinical benefits
- Varies with the type of available data & statistical model used

Decision analysis

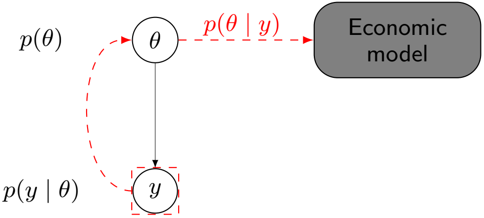
- Summarises the economic model by computing suitable measures of "cost-effectiveness"
- Dictates the best course of actions, given current evidence
- Standardised process

1. Estimation (base-case)

2. PSA



Estimation & PSA (one stage)



Choosing a utility function

- Typically, we do health economic evaluation based on the monetary net benefit

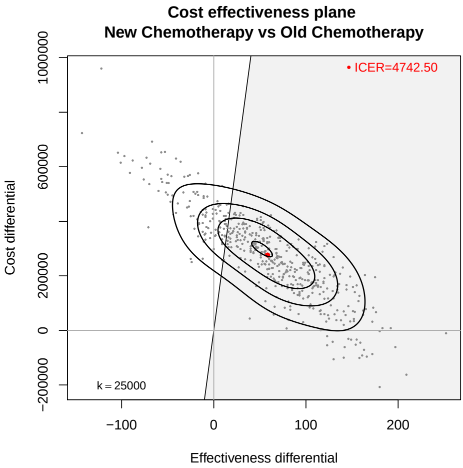
$$u(e, c; t) := ke - c$$

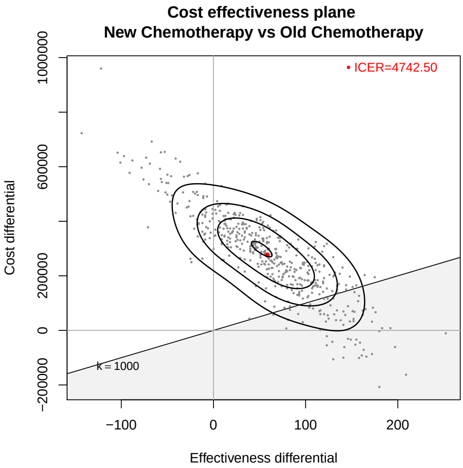
  - k is the "willingness to pay", i.e. the *cost per extra unit of effectiveness gained* — today's star!

- The main advantages of using the MNB are that
  - It has a fixed form, once e, c are observed
  - It is a linear function in e, c, which simplifies computations

- However, MNB presupposes that the DM is *risk neutral*
  - Of course, that's not necessarily true
  - However, it **implies** that, given current uncertainty, the DM only requires 50% chance that a treatment is cost effective to deem it so!

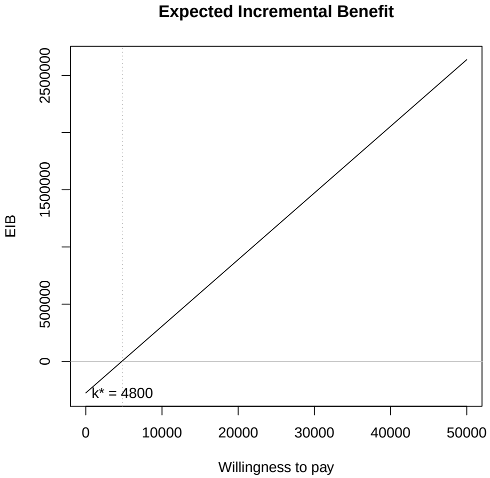
Cost-effectiveness plane vs ICER





$$\text{ICER} = \frac{\text{E}[\Delta_c]}{\text{E}[\Delta_e]}$$

EIB vs ICER

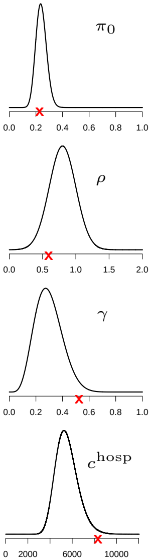


Assuming the MNB as utility:

- $\text{EIB} = \mathcal{U}^1 - \mathcal{U}^0 = \text{E}[k\Delta_e - \Delta_c] = k\text{E}[\Delta_e] - \text{E}[\Delta_c]$
- Thus $\text{EIB} > 0 \Rightarrow k > \frac{\text{E}[\Delta_c]}{\text{E}[\Delta_e]} = \text{ICER} = \text{Break even point}$

PSA to **parameter** uncertainty

Parameters



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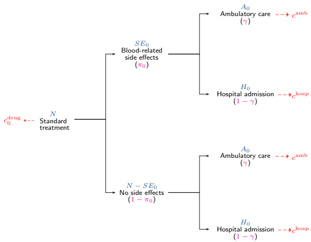
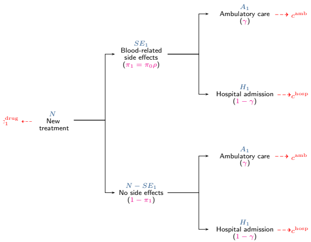
Model structure

Old chemotherapy



New chemotherapy



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Decision analysis

Old chemotherapy	
Benefits	**Costs**
741	670 382.1
699	871 273.3
...	...
726	425 822.2
716.2	**790 381.2**

New chemotherapy	
Benefits	**Costs**
732	1 131 978
664	1 325 654
...	...
811	766 411.4
774.5	**1 066 849.8**

$$\text{ICER} = \frac{276\,468.6}{58.3} = 4\,742.5$$

Iter/n	Parameters simulations $t=0$ Benefits	Costs	$t=1$ Benefits	Costs	Expected utility $U(\boldsymbol{\theta}^0)$	$U(\boldsymbol{\theta}^1)$	Incremental benefit IB($\boldsymbol{\theta}$)
1	741	670 382.1	732	1 131 978.0	19 214 751	19 647 706	432 955.8
2	699	871 273.3	664	1 325 654.0	17 165 526	17 163 407	-2 119.3
3	774	639 071.7	706	1 191 567.2	18 710 928	16 458 433	-2 252 495.5
4	721	1 033 679.2	792	1 302 352.2	16 991 321	18 497 648	1 506 327.0
5	808	427 101.8	784	937 671.1	19 772 898	18 662 329	-1 110 569.3
6	731	1 168 864.4	811	717 939.2	17 106 136	18 983 331	1 877 195.1
...		...			...		...
1000	726	425 822.2	811	766 411.4	18 043 921	16 470 805	-1 573 116.0
					$\mathcal{U}^0$=18 659 238	$\mathcal{U}^1$=19 515 004	EIB= 855 766

Effectively, PSA is based on the comparison between

- The *ideal* decision process — with uncertainty "resolved":

$$U(\boldsymbol{\theta}^t) = k\text{Benefits} - \text{Cost} \qquad \text{(under treatment } t\text{)}$$

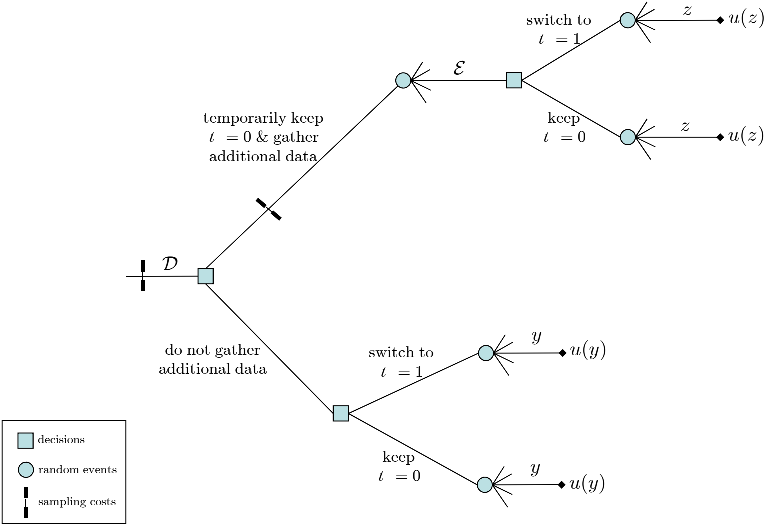
$$= \int u(e,c;t)p(e,c \mid \boldsymbol{\theta}^t)dedc \qquad \text{(expected utility \textbf{given parameters})}$$

- The *actual* decision process — marginalising out all uncertainties:

$$\mathcal{U}^t = k\text{E[Benefits]} - \text{E[Costs]} \qquad \text{(under treatment } t\text{)}$$

$$= \int U(\boldsymbol{\theta}^t)p(\boldsymbol{\theta}^t \mid e,c)d\boldsymbol{\theta}^t \qquad \text{(\textbf{overall} expected utility)}$$

A two-stage decision process



The big soup?

- Some times the two steps are actually **conflated**
  - Particularly, given large uncertainty (eg small CEAC), the process is just stopped and marketing authorisation/reimbursement is denied
- Intuitively, this is related to the perceived level of riskiness of a given decision
  - For example, it may be implicitly felt that allowing a treatment with only 65% of cost-effectiveness on the market may be a bad decision

- But:
  1. The CEAC is only telling one side of the story — how likely is it that the future will turn out very different than the ICER?
  2. If PSA makes sense in the two-stage decision process (and **I** think it does!), then the EVP(P)I is a better tool — also tells about the pay-offs of uncertainty
  3. In any case, if riskiness is such a big deal, then the MNB is probably not the best choice for a cost-effectiveness analysis

Risk aversion in the utility function

- Can modify the utility function to formally account for risk-aversion
- This is not a new concept, not even in health economics
  - O'Brien & Schulpher (2000). *Medical Care*, 38:460-468
  - Graff Zivin (2001). *Health Economics*, 10(6):499-508
  - Elbasha (2005). *Health Economics*, 14(5):457-70
  - Baio & Dawid (2011). *Stat Meth Med Res*, doi: 10.1177/0962280211419832
- Can use different forms, **eg**
  - $u_{\mathsf{GZ}}(b,r,t) = b - \frac{r}{2}\left(b - \mathsf{E}[B]\right)^2 \qquad b = ke - c, \quad r < 0$ (Graff Zivin)
  - $u_{\mathsf{R}}(b,r,t) = \frac{1}{r}\left[1 - \exp(-rb)\right] \qquad b = ke - c, \quad r > 0$ (Raiffa)
- In both cases, b is the MNB, while r is a parameter of risk-aversion
  - In the first case: $\downarrow r \Rightarrow$ DM is more risk-averse
  - In the second one: $\uparrow r \Rightarrow$ DM is more risk-averse

Risk aversion in the utility function

- The quantities we need to investigate for PSA are

$$\begin{aligned} U_{\text{GZ}}(\theta^t) &= \mathsf{E}[u_{\text{GZ}}(b;t,r) \mid \theta^t] = \int \left[b - \frac{r}{2}(b - \mathsf{E}[b])^2\right] p(b \mid \theta^t)\, db \\ &= U(\theta^t) - \frac{r}{2}\mathsf{Var}[B \mid \theta^t] \end{aligned}$$

and

$$\begin{aligned} U_{\text{R}}(\theta^t) &= \mathsf{E}[u_{\text{R}}(b;t,r) \mid \theta^t] = \int \frac{1}{r}\left[1 - \exp(-rb)\right] p(b \mid \theta^t)\, db \\ &= \frac{1}{r}\left[1 - M_{B|\theta^t}(-r)\right] \end{aligned}$$

- Complex mathematical form — no longer linear!
- However, can get them as a by-product of MCMC estimation (in a fully Bayesian setting)

Risk aversion in the utility function — comments

$U_{\mathsf{GZ}}(\theta^t) = U(\theta^t) - \frac{r}{2}\mathsf{Var}[B \mid \theta^t]$

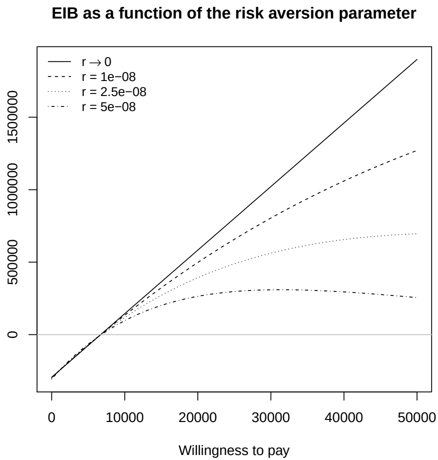
- Obviously, when $r = 0$, then $U_{\mathsf{GZ}}(\theta^t) = U(\theta^t)$
- The additional term (involving r) can be considered as some sort of *penalty* — the larger the variability in the MNB, the lower the overall utility
- **Drawback**: need to obtain both the population average and variance of costs and benefits from the statistical model, in order to use GZ

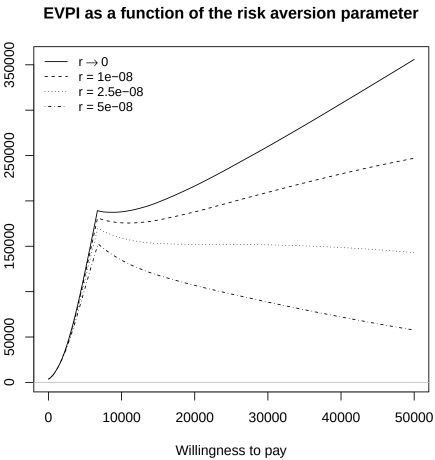
$U_{\mathsf{R}}(\theta^t) = \frac{1}{r}\left[1 - M_{B|\theta^t}(-r)\right]$

- Not intuitive — but can prove that for $r \to 0$ then retrieves the MNB
- **Advantage**: only need to obtain the population average costs and benefits from the statistical model (that's what we normally have!)
- In addition, the EVPI is appropriately sensitive to the choice of r, but the CEAC is not, using this utility

- **Main complication**: In any case, it is difficult to determine the scale of r

Example (Raiffa's utility function)





Conclusions

- The choice of the utility function is instrumental to the economic evaluation
  - Assuming the MNB implies risk neutrality — but we do not always mean that!

- If riskiness is a big deal (eg MenB vaccine?), then it would be appropriate to include a form of risk aversion in the model
  - This would be in contrast to modifying the cost-effectiveness thresholds *post-hoc*
  - Utility functions including risk aversion will typically modify the break-even point and thus the decision under current evidence
  - Most likely, the results of PSA are affected too

- It is objectively difficult to elicit the level of risk aversion
  - In general we understand the limiting value and the sign of r
  - But the actual scale (determining how risk averse the decision-maker is) is difficult to determine
  - So what do we do?

Thank you!