CER in the US and HTA in Europe: Similar Methods Challenges in Different Policy Landscapes?

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Common research methods challenges for policy making

Health technology assessment →

- Does this therapy generate incremental clinical effectiveness compared to other treatments?
- Will these effects exist in routine practice?
- Is there a net overall benefit as perceived by patients?

Comparative effectiveness research →

- Will some patients benefit more than others?
- ~~Does the net incremental benefit justify the additional cost?~~

Methods challenge 1

Does this therapy generate incremental clinical effectiveness compared to other treatments?

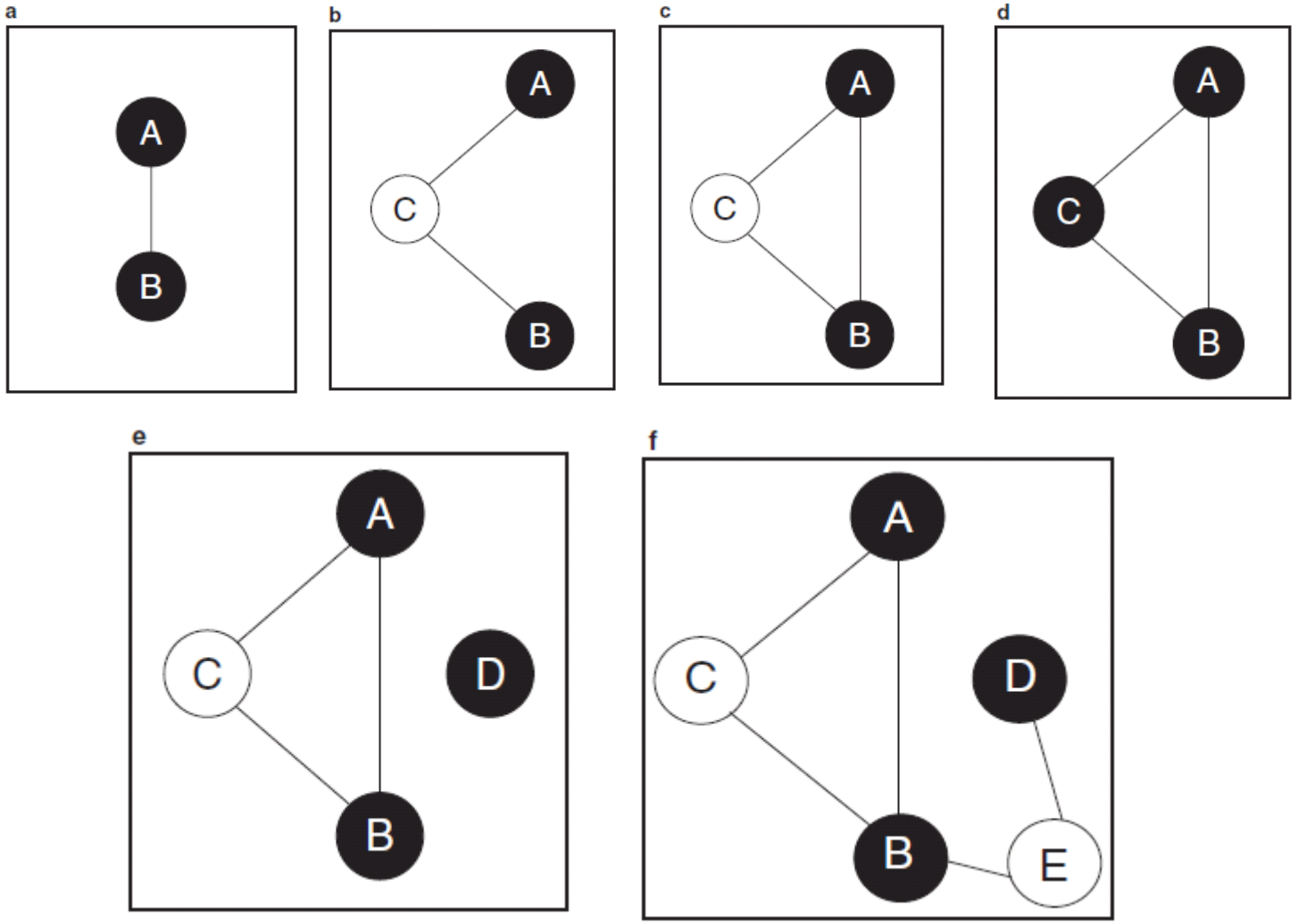
Incremental effectiveness

Context

- Randomised trial evidence for treatment effects
  - Formally addresses selection bias
  - High internal validity
- Typically expensive and slow
- Range of existing therapies often significant
- Typically full range of alternatives not compared head – to-head

Incremental effectiveness

Indirect and mixed treatment comparisons



Sutton *et al. Pharmacoeconomics* 2008; 26 (9): 753-767

Incremental effectiveness

Example of thrombolytics

No. of RCTs	SK	t-PA	Acc t-PA	Sk+t-PA	r-PA	TNK
8	✓	✓				
1	✓		✓	✓		
1	✓			✓		
1	✓				✓	
2			✓		✓	
1			✓			✓

Acc t-PA = acclerated alteplase; **r-PA** = reteplase; **SK** = streptokinase; **Sk+t-PA** = streptokinase + alteplase; **TNK** = tenecteplase; **t-PA** = alteplase.

Caldwell *et al. BMJ* 2005; 331: 897-900

Incremental effectiveness

Example of thrombolytics

Treatment	Fixed effect (%)	
	35-day mortality	probability treatment the best
SK	6.5	0
t-PA	6.4	0
Acc t-PA	5.6	40
SK+t-PA	6.2	1
r-PA	5.8	15
TNK	5.6	43

Caldwell *et al. BMJ* 2005; 331: 897-900

Incremental effectiveness

Issues

- Key assumptions
  - Similarity of trials
  - Consistency
- Defining relevant comparators
- Defining the network
- Complexity of analysis and presentation

ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices, *Value in Health* 2011; 429-437

Methods challenge 2

Will these effects exist in routine practice?

The ‘real world’ study

- Pre-launch
  - Limited scope for more ‘pragmatic’ studies
  - Study design determined by regulatory authorities
- Post-launch
  - ‘Pragmatic’ randomised head-to-head studies
  - Who pays?
  - Limited number of comparators
- Use of linked administrative databases
  - Range of non-treatment effect evidence
  - Challenge of characterising and adjusting for selection bias
- Likely link with coverage with evidence development

Methods challenge 3

Is there a net overall benefit as perceived by patients?

Benefit assessment for decision making: the role of PROs

- Designed around basic science
- Focus on anticipated clinical effects

- 'Objective measures' e.g. cancer progression
- Clinical interpretation e.g. Psoriasis Area and Severity Index (PASI)

- Subjective well-being
- Varies by underlying concept e.g. function
- Potentially broader than clinical

Using patients' preference to make trade-offs

Example from prostate cancer

Patients' preferences for the management of non-metastatic prostate cancer: discrete choice experiment

Mark Sculpher, Stirling Bryan, Pat Fry, Patricia de Winter, Heather Payne, Mark Emberton

Abstract

Objective To establish which attributes of conservative treatments for prostate cancer are most important to men.
Design Discrete choice experiment.
Setting Two London hospitals.
Participants 129 men with non-metastatic prostate cancer, mean age 70 years; 69 of 118 (58%) with T stage 1 or 2 cancer at diagnosis.
Main outcome measures Men's preferences for, and trade-offs between, the attributes of diarrhoea, hot flushes, ability to maintain an erection, breast swelling or tenderness, physical energy, sex drive, life expectancy, and out of pocket expenses.
Results The men's responses to changes in attributes were all statistically significant. When asked to assume a starting life expectancy of five years, the men were willing to make trade-offs between life expectancy and side effects. On average, they were most willing to give up life expectancy to avoid limitations in physical energy (mean three months) and least willing to trade life expectancy to avoid hot flushes (mean 0.6 months to move from a moderate to mild level or from mild to none).
Conclusions Men with prostate cancer are willing to participate in a relatively complex exercise that weighs up the advantages and disadvantages of various conservative treatments for their condition. They were willing to trade off some life expectancy to be relieved of the burden of troublesome side effects such as limitations in physical energy.

Individuals' preferences for alternative treatments need to be considered in the light of the attributes of the treatments. Discrete choice experimentation, an approach for elicitation of preferences, is now being used widely in health care.[4 5] This approach identifies the key characteristics of alternative treatments, such as hot flushes, and selects a series of levels for each (for example, absent, mild, moderate). Respondents choose from several options, each of which details a series of attributes at different levels. The relative importance of attributes to individuals and the trade-offs made between them, can be assessed by changing the levels of the attributes and asking participants to make their choice again. Findings on the reliability and validity of discrete choice experimentation in healthcare settings are encouraging.

Sculpher *et al. British Medical Journal* 2004, vol 328, pp382

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The importance of trade-offs

	Treatment A	Treatment B
Diarrhoea	Moderate	Absent
Hot flushes	Present, mild	Present, mild
Breast swelling	Absent	Present
Physical energy	Lacking energy	No problems
Life expectancy	Option A better by 2 months	

Sculpher *et al. British Medical Journal* 2004, vol 328, pp382

Net benefit analysis

Example in irritable bowel syndrome

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VALUE IN HEALTH

Using the Incremental Net Benefit Framework for Quantitative Benefit–Risk Analysis in Regulatory Decision-Making—A Case Study of Alosetron in Irritable Bowel Syndrome

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ABSTRACT

Objective: There is consensus that a more transparent, explicit, and rigorous approach to benefit–risk evaluation is required. The objective of this study is to evaluate the incremental net benefit (INB) framework for undertaking quantitative benefit–risk assessment by performing a quantitative benefit–risk analysis of alosetron for the treatment of irritable bowel syndrome from the patients' perspective.

Methods: A discrete event simulation model was developed to determine the INB of alosetron relative to placebo, calculated as "relative value-adjusted life-years (RVALYs)."

Results: In the base case analysis, alosetron resulted in a mean INB of 34.1 RVALYs per 1000 patients treated relative to placebo over 52 weeks of treatment. Incorporating parameter uncertainty into the model, probabilistic sensitivity analysis revealed a mean INB of 30.4 (95% confidence interval 15.9–45.4) RVALYs per 1000 patients treated relative to placebo over 52 weeks of treatment. Overall, there was >99% chance that both the incremental benefit and incremental risk associated with alosetron are greater than placebo. As hypothesized, the INB of alosetron was greatest in patients with the worst quality of life experienced at baseline. The mean INB associated with alosetron in patients with mild, moderate, and severe symptoms at baseline was 17.97 (–0.55 to 36.23), 29.98 (17.05–43.37), and 35.98 (23.49–48.77) RVALYs per 1000 patients treated, respectively.

Conclusions: This study demonstrates the potential utility of applying the INB framework to real-life decision-making, and the ability to use simulation modeling incorporating outcomes data from different sources as a benefit–risk decision aid.

Keywords: alosetron, benefit–risk analysis, discrete event simulation, irritable bowel syndrome.

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Net benefit analysis

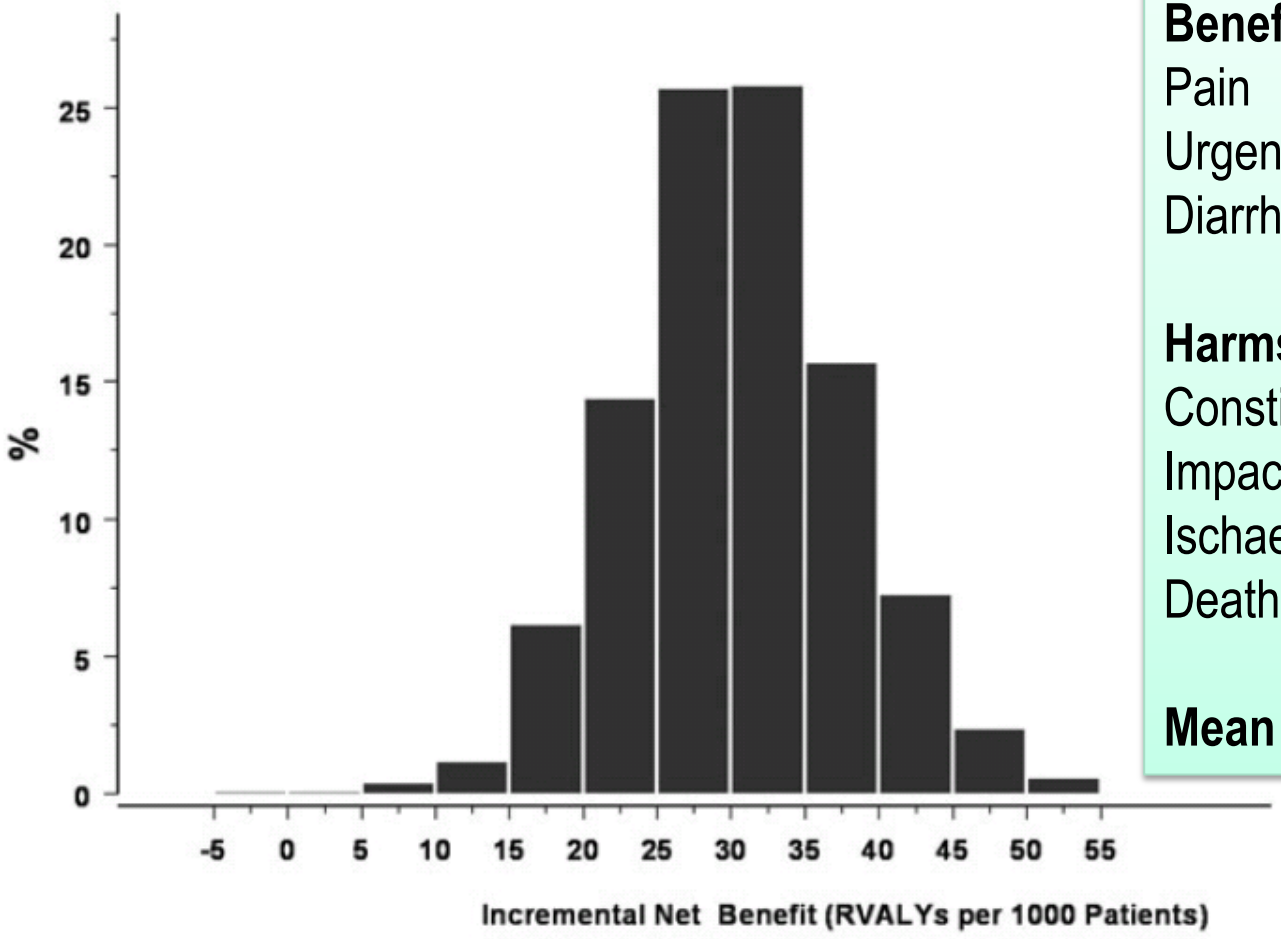
Example in irritable bowel syndrome

Outcome	Frequency	Disutility* (scaled)
Abdominal pain	1–2 days a week	0.0151
	3–5 days a week	0.0378
	6–7 days a week	0.0529
Urgency	1–2 days a week	0.0198
	3–5 days a week	0.0753
	6–7 days a week	0.0817
Diarrhea	1–2 times a day	0.0269
	3–4 times a day	0.0827
	>4 times a day	0.1042
Constipation	1–2 days a week	0.0143
	3–5 days a week	0.0359
	6–7 days a week	0.0502
Moderate colitis		0.0177
Severe colitis		0.1258
Impacted bowel		0.0987
Perforated bowel		0.3072

Lynd *et al.* *Value in Health* 2010, 13 (4): 411-17

Net benefit analysis

Example in irritable bowel syndrome



Benefits
Pain
Urgency
Diarrhoea

Harms
Constipation 4.6%
Impacted bowel 0.11/1000 wks
Ischaemic colitis 0.15 per 1000 wks
Deaths 4/10,000 per year

Mean net benefit 34.1 RVALYs

Lynd *et al.* *Value in Health* 2010, 13 (4): 411-17

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Methods challenge 4

Will some patients benefit more than others?

Personalised net benefit analysis

Example of HRT

Papers

Benefits and harms associated with hormone replacement therapy: clinical decision analysis

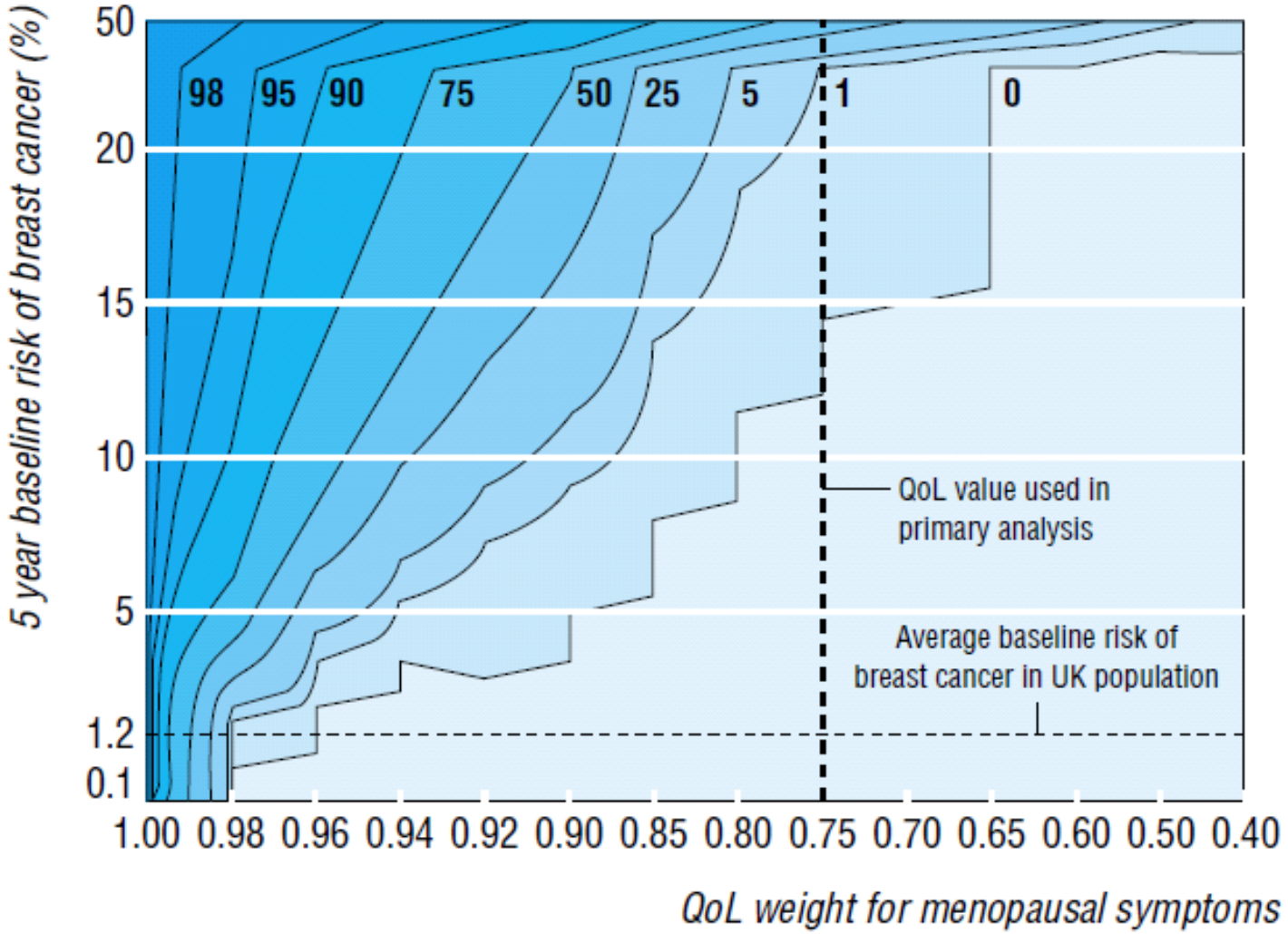
Cosetta Minelli, Keith R Abrams, Alex J Sutton, Nicola J Cooper

Abstract

Objective To evaluate harms and benefits associated with use of combined hormone replacement therapy (HRT) for five years in women with different baseline risks for breast cancer.
Design Probabilistic clinical decision analysis.
Setting Hypothetical population of white UK women aged 50 years with different baseline risks for breast cancer.
Main outcome measure Gain or loss in quality adjusted life years (QALYs).
Results Women free of menopausal symptoms showed a net harm from HRT use, which increased for increasing baseline risk of breast cancer. Those with a baseline risk of 1.2% would expect a loss in QALYs of 0.4 months (−0.03 QALYs, 95% credibility interval −0.05 to −0.01). The main analysis showed HRT to be on average beneficial in women with symptoms, with benefit decreasing with increasing baseline risk of breast cancer. The results were sensitive to the assumed value of quality of life with menopausal symptoms, therefore a contour plot was developed to show the probability of net harm for a range of different values and baseline risks.
Conclusions HRT for primary prevention of chronic diseases in women without menopausal symptoms is unjustified. Perceived quality of life in women with symptoms should be taken into account when deciding on HRT. Thus, a decision analysis tailored to an individual woman is more appropriate in clinical practice than a population based approach.

Personalised net benefit analysis

Example of HRT



Conclusions

- Stated policy contexts in US and Europe markedly different
- HTA and CER need to been seen in these contexts
- Core underlying methods challenges are very similar
- Some important implications for manufacturers
  - Core evidence development similar internationally
  - Presentation will vary by jurisdiction