# Statistical methods for cost-effectiveness analysis: a personal history

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1

The last 25 years have seen a large increase in the contribution that health economic analysis has made in national and international decisions about health care provision. Andy Briggs has been working at the interface between medical statistics and health economics throughout this period. In this talk he gives a personal history of that journey with an emphasis on how statistical thinking has improved the methods of health economic evaluation over that period. Looking to the future, there remains much potential for statistical methods to continue to improve the way in which we evaluate the cost-effectiveness of health care interventions and to improve health care decision making as a result.

2

## Statistical methods for cost-effectiveness analysis: a personal history

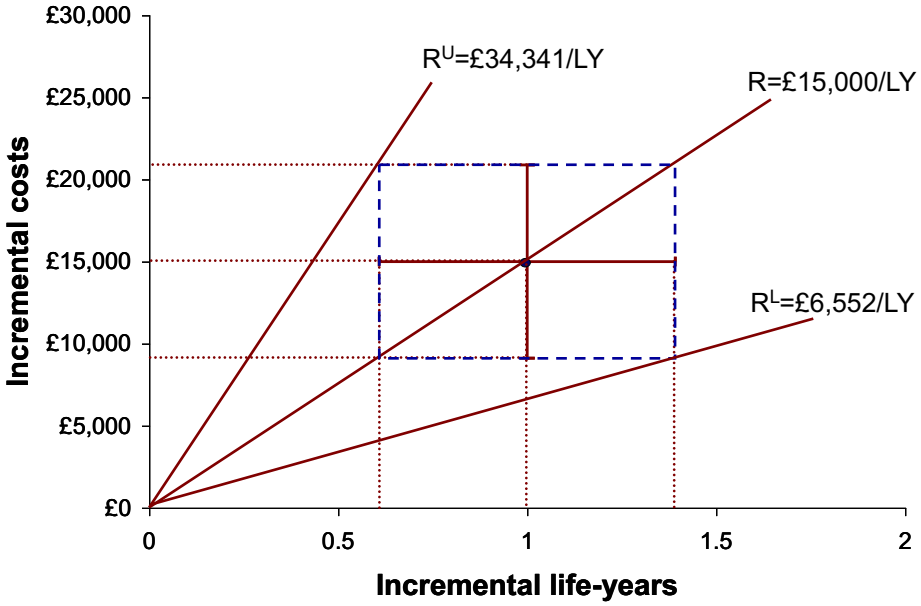
- Representing uncertainty in cost-effectiveness analysis
- Clinical trials versus decision models: a false dichotomy?
- Statistical decision theory
- Survival analysis
- Comparative effectiveness and the rise of Network Meta Analysis

3

## Representing uncertainty in CEA

4

## CIs on the CE plane: the confidence box

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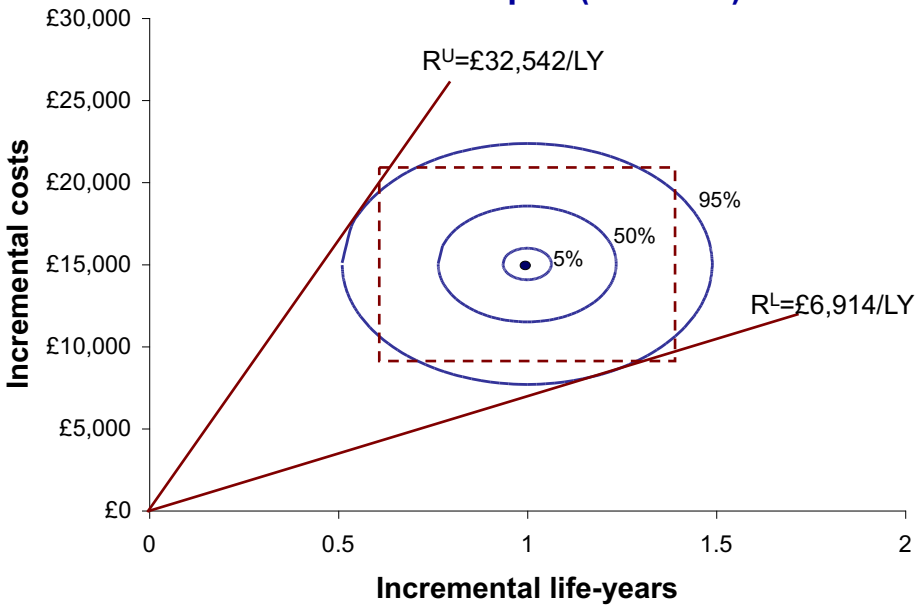
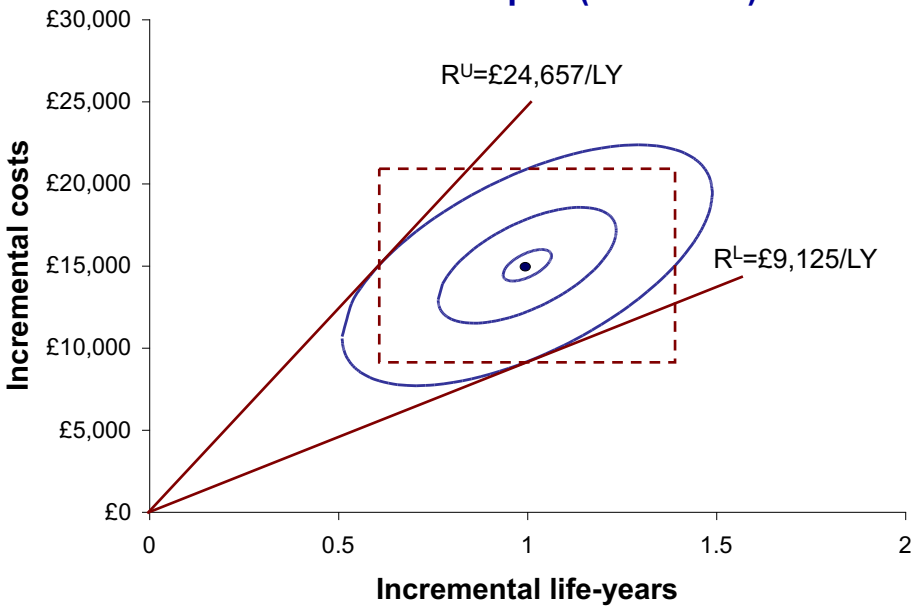
## CIs on the CE plane: the confidence ellipse (zero cov)



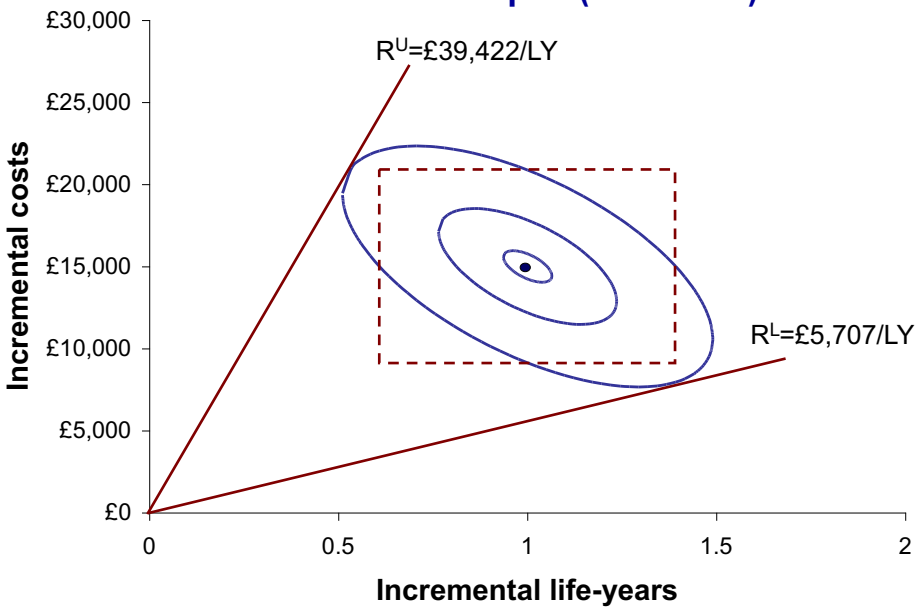

6

## CIs on the CE plane: the confidence ellipse (corr=+0.6)



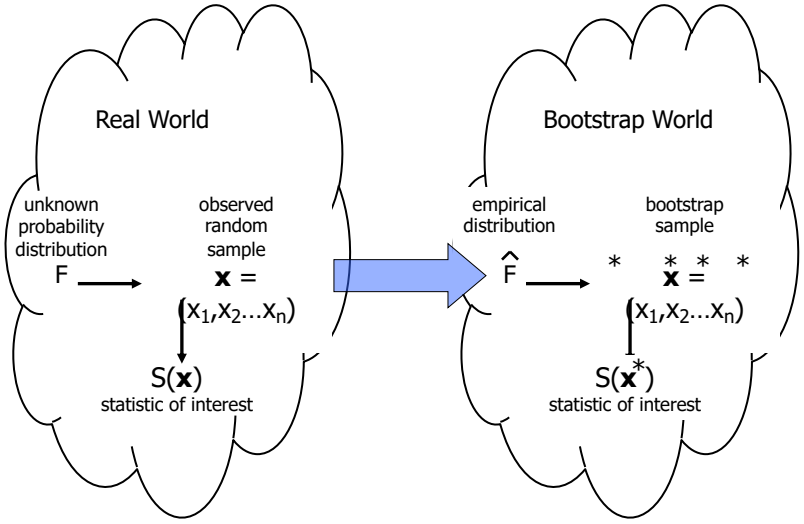

7

## CIs on the CE plane: the confidence ellipse (corr=- 0.6)




8

## Two worlds: the real world and the bootstrap world




9

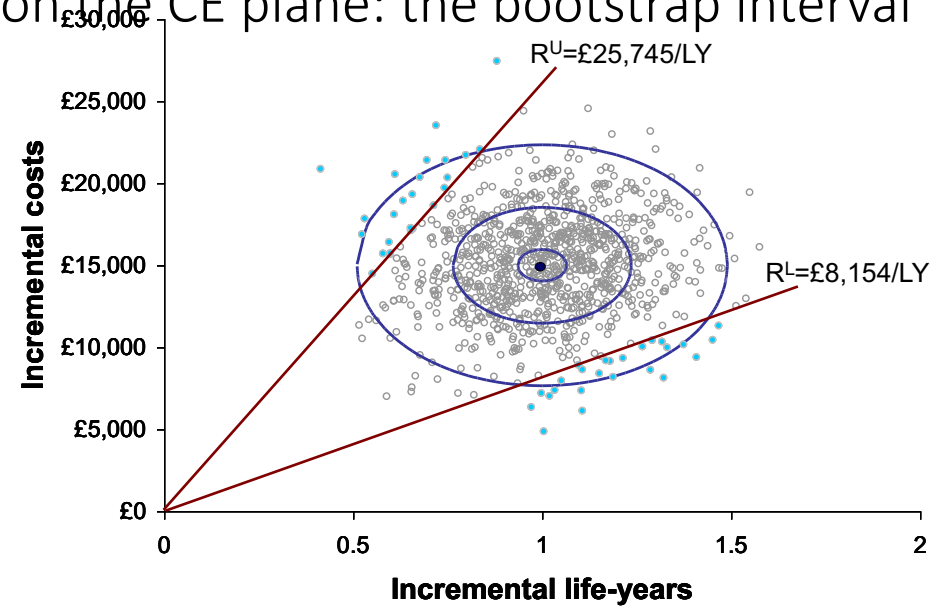
# Bootstrapping the ICER

Four stage process:

1. Bootstrap $n_C$ cost/effect pairs from the control group: calculate means
2. Bootstrap $n_T$ cost/effect pairs from the treatment group: calculate means
3. Calculate the bootstrapped ICER from these bootstrapped means
4. Repeat many times to create the bootstrap estimate of the ICER sampling distribution

10

# CIs on the CE plane: the bootstrap interval




11

# A parametric approach: Fieller's theorem

$$\Delta\bar{C} - R\Delta\bar{E} \sim \text{Normally}$$

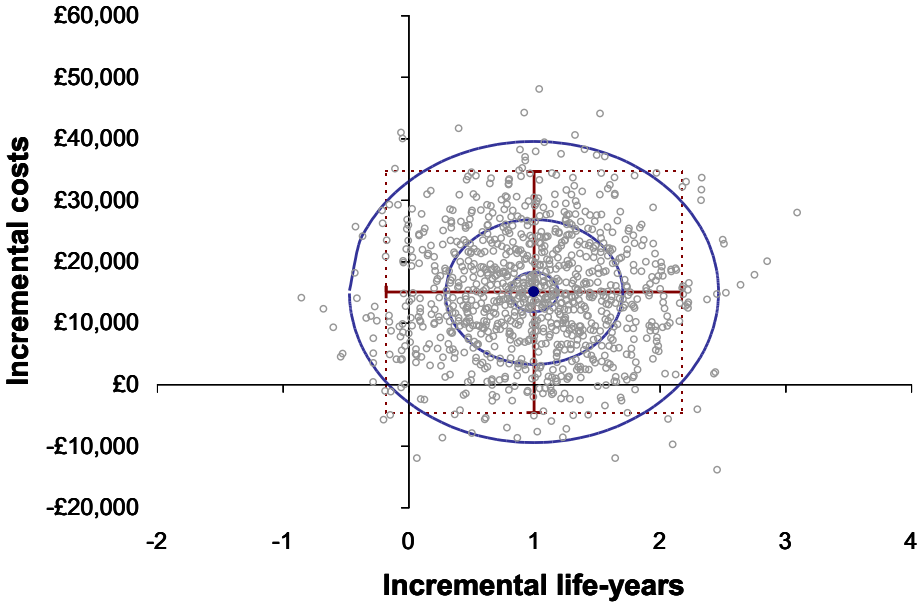
$$\frac{\Delta\bar{C} - R\Delta\bar{E}}{\sqrt{\text{var}(\Delta\bar{C}) + R^2\,\text{var}(\Delta\bar{E}) - 2R\,\text{cov}(\Delta\bar{C},\Delta\bar{E})}} \sim N(0,1)$$

$$\left.\begin{aligned} & R^2\left[\Delta E^2 - z_{\alpha/2}^2\,\text{var}(\Delta E)\right] \\ & -2R\left[\Delta E\cdot\Delta C - z_{\alpha/2}^2\,\text{cov}(\Delta E,\Delta C)\right] \\ & +\left[\Delta C^2 - z_{\alpha/2}^2\,\text{var}(\Delta C)\right] \\ & = 0 \end{aligned}\right\} \text{ Standard quadratic equation in } R \left\{\begin{aligned} & aR^2 \\ & +bR \\ & +c \\ & = 0 \end{aligned}\right.$$

$$\frac{\left[\Delta E\cdot\Delta C - z_{\alpha/2}^2\,\text{cov}(\Delta E,\Delta C)\right]}{\Delta E^2 - z_{\alpha/2}^2\,\text{var}(\Delta E)} \pm \frac{\sqrt{\left[\Delta E\cdot\Delta C - z_{\alpha/2}^2\,\text{cov}(\Delta E,\Delta C)\right]^2 - \left[\Delta E^2 - z_{\alpha/2}^2\,\text{var}(\Delta E)\right]\cdot\left[\Delta C^2 - z_{\alpha/2}^2\,\text{var}(\Delta C)\right]}}{\Delta E^2 - z_{\alpha/2}^2\,\text{var}(\Delta E)}$$

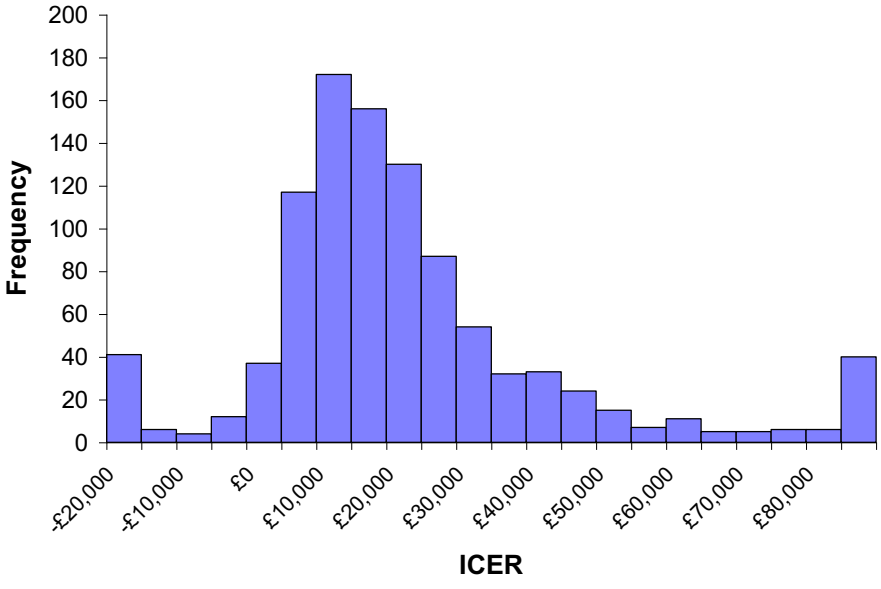
12

# Non-significant differences?



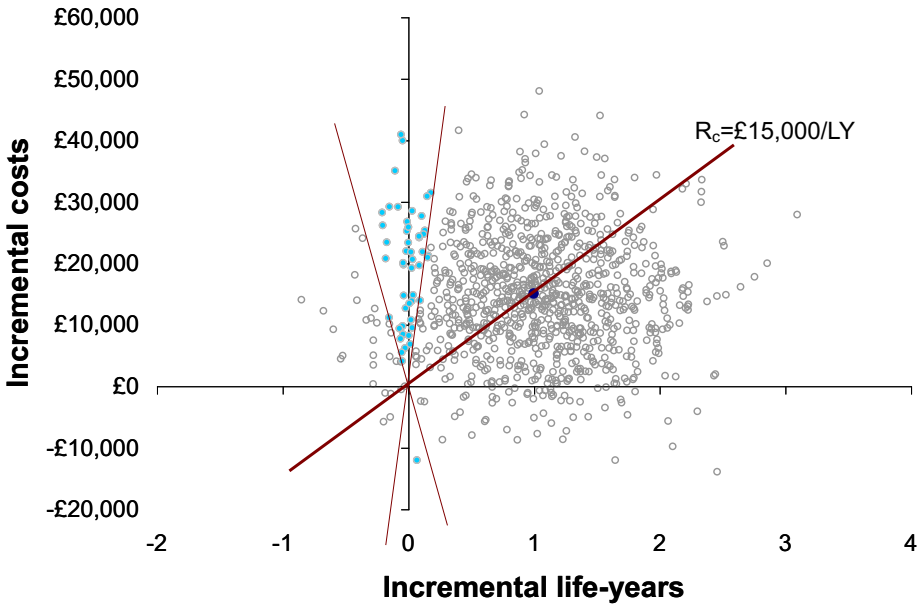

13

# The estimated distribution of the ICER



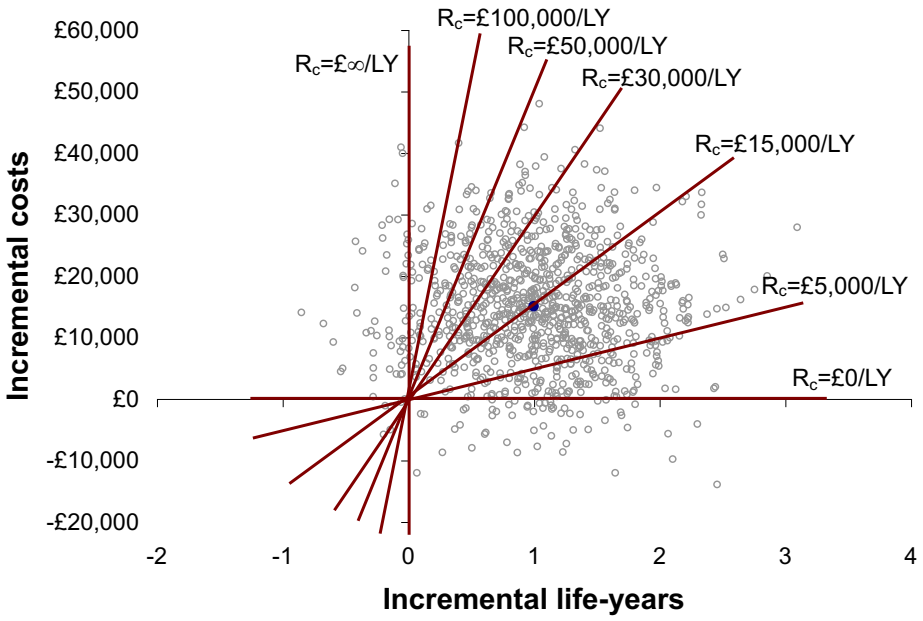

14

# Problems with negative with negative ratios



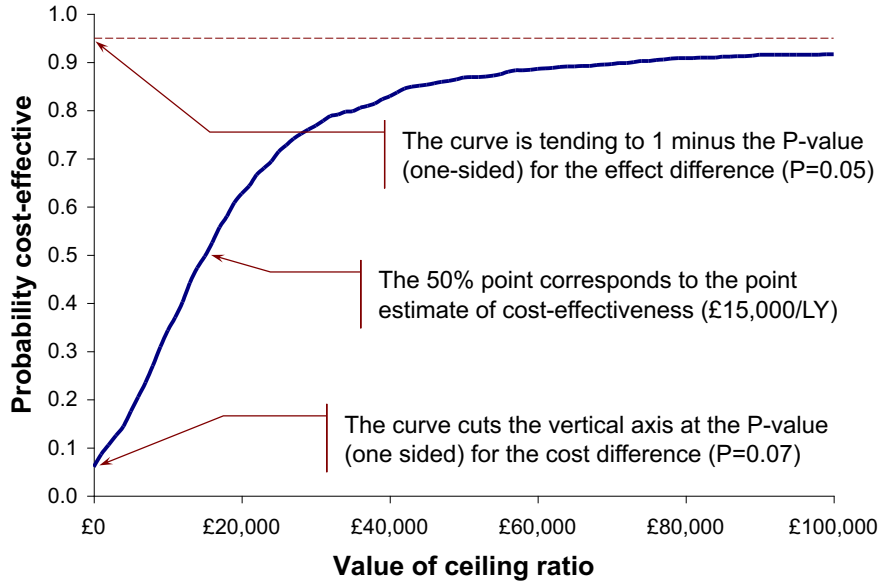

15

# Uncertainty on the CE plane: using the decision rule



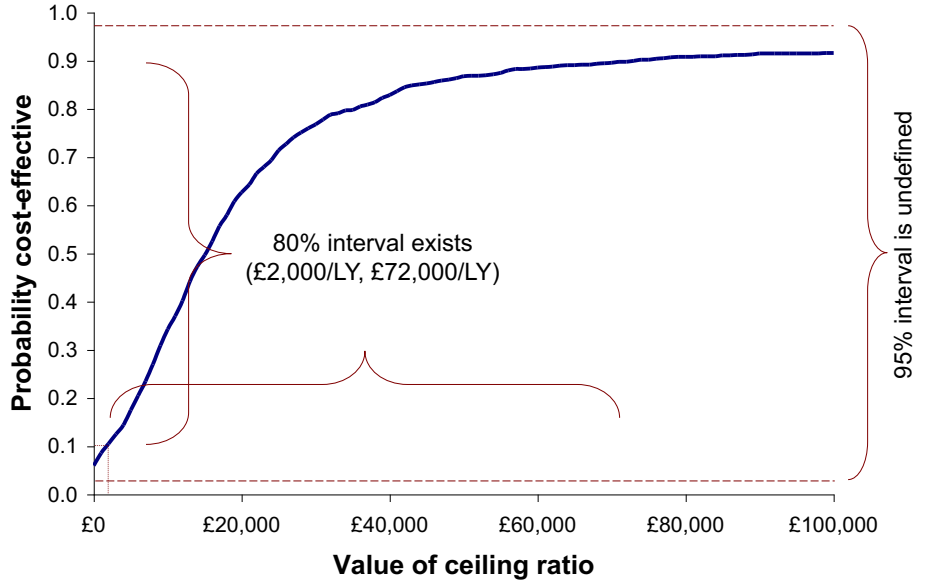

16

# Cost-effectiveness acceptability curves




17

# Cost-effectiveness acceptability curves




18

# Trials versus models: false dichotomy?

19

# Whither 'trial-based' analyses?

- Failure to compare all relevant options
- Truncated time horizon
- Lack of relevance to the decision context
- Failure to incorporate all evidence
- Inadequate quantification of uncertainty

*Source: Sculpher et al, 2006, Health Economics*

20

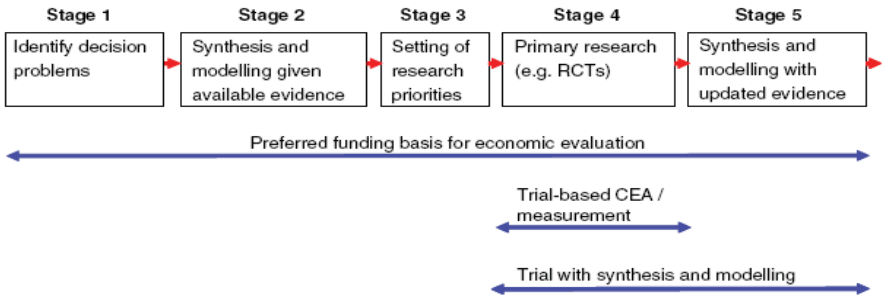
# Requirements of economic evaluation for decision making

- Clear statement and measurement of the objective function
- Consistent perspective
- Appropriate specification of the decision problem
- Appropriate time horizon
- All relevant evidence
- Relevant to the decision context
- Appropriate characterisation of uncertainty

*Source: Sculpher et al, 2006, Health Economics*

21

# An iterative approach to economic appraisal




*Source: Sculpher et al, 2006, Health Economics*

22

# UKPDS Outcomes Model v1

- Series of linked risk equations from UKPDS study
- Capable of predicting (quality adjusted) life expectancy and lifetime cost

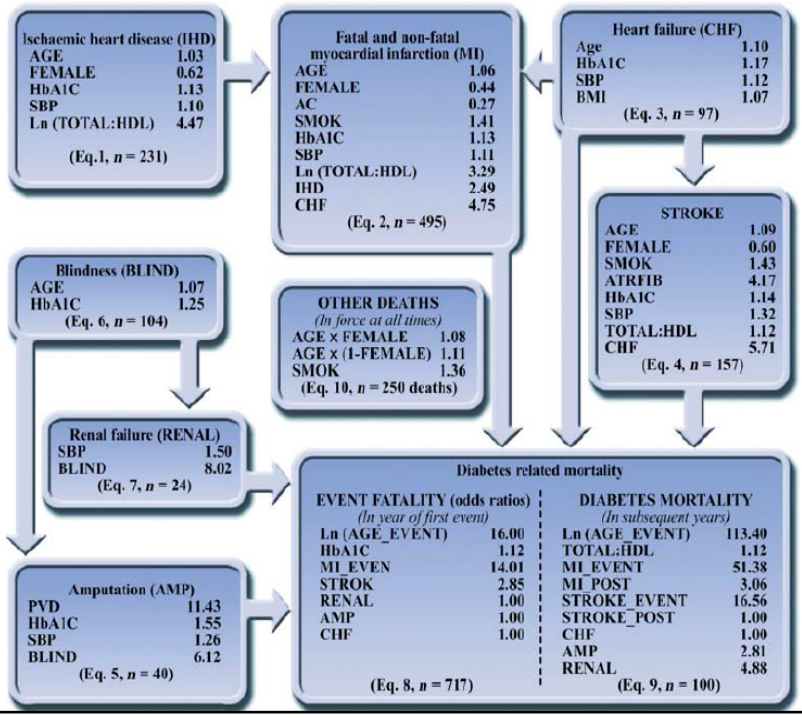
Diabetologia (2004) 47:1747–1759
DOI 10.1007/s00125-004-1527-z

Diabetologia

## A model to estimate the lifetime health outcomes of patients with Type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68)

P. M. Clarke[1,4] · A. M. Gray[1] · A. Briggs[1] · A. J. Farmer[2] · P. Fenn[3] · R. J. Stevens[4] · D. R. Matthews[5]
I. M. Stratton[4] · R. R. Holman[4] · on behalf of the UK Prospective Diabetes Study (UKPDS) Group

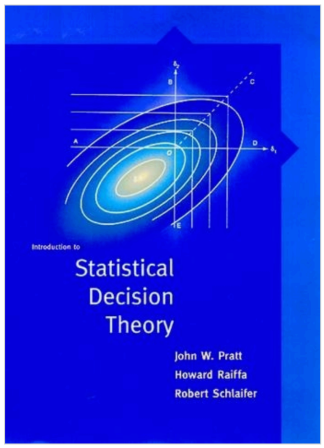
23




24

# Statistical decision theory

25




**Introduction to Statistical Decision Theory**

By John Pratt, Howard Raiffa and Robert Schlaifer

26

Health Econ. 1996 Nov-Dec;5(6):513-24.

**An economic approach to clinical trial design and research priority-setting.**

Claxton K[1], Posnett J.

Author information

**Abstract**

Whilst significant advances have been made in persuading clinical researchers of the value of conducting economic evaluation alongside clinical trials, a number of problems remain. The most fundamental is the fact that economic principles are almost entirely ignored in the traditional approach to trial design. For example, in the selection of an optimal sample size no consideration is given to the marginal costs or benefits of sample information. In the traditional approach this can lead to either unbounded or arbitrary sample sizes. This paper presents a decision-analytic approach to trial design which takes explicit account of the costs of sampling, the benefits of sample information and the decision rules of cost-effectiveness analysis. It also provides a consistent framework for setting priorities in research funding and establishes a set of screens (or hurdles) to evaluate the potential cost-effectiveness of research proposals. The framework permits research priority setting based explicitly on the budget constraint faced by clinical practitioners and on the information available prior to prospective research. It demonstrates the link between the value of clinical research and the budgetary restrictions on service provision, and it provides practical tools to establish the optimal allocation of resources between areas of clinical research or between service provision and research.

PMID: 9003938 DOI: 10.1002/(SICI)1099-1050(199611)5:6<513::AID-HEC237>3.0.CO;2-9

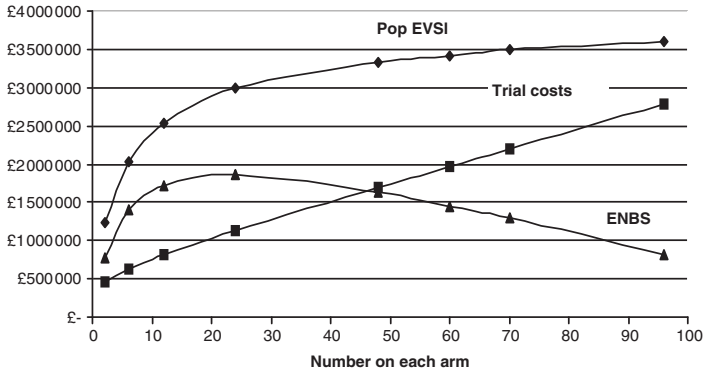
27

## Expected Net Benefit of Sampling (ENBS)

- Is it cost-effective to run a new study? If so, to choose the best design (e.g. sample size per arm).
- Difference between monetarised gain from collecting further data from chosen study design, and the cost of that study
- ENBS (n) = population EVSI (n) – cost (n)

28

FIG. 3. Population EVSI, trial costs and ENBS for the breast cancer screening example. Adapted from Ref. [12].



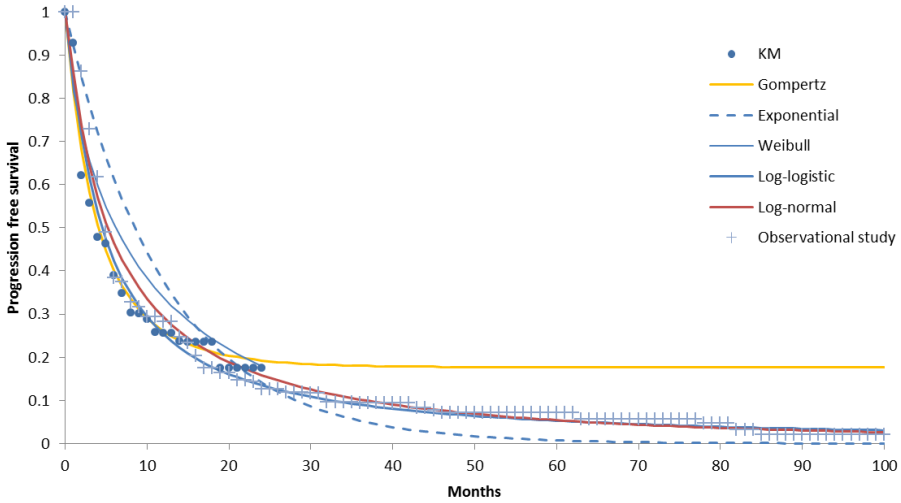

*Welton et al. Rheumatology 2011;50:iv19-iv25*

29

# Survival analysis

30

# Parametric survival - distribution selection




Coiffier (2012); Mak (2013)

31

## Parametric PFS vs Kaplan-Meier - distribution selection (4)

- Latimer (2011) recommends selecting the most appropriate parametric model based on both within-trial fit, and external and clinical validity

| Method | Description |
|---|---|
| ***Within trial period*** | |
| AIC & BIC statistics | Assess the relative fit of parametric models whilst accounting for the number of parameters |
| Cox-Snell residuals | Assess how closely a parametric function follows the Kaplan-Meier function |
| Cumulative hazard plot | Assess the behavior of the hazard function over time and the plausibility of the proportional hazards assumption |
| Log-cumulative hazard plot | Assess the behavior of the hazard function over time and the plausibility of the proportional hazards assumption |
| Quantile-quantile (Q-Q) plot | Assess how closely an accelerated-failure time treatment effect model fits the data |
| Visual inspection | Assess how closely a parametric function follows the Kaplan-Meier function and the clinical plausibility of the prediction in relation to other endpoints |
| ***Extrapolation period*** | |
| Monthly event probabilities | Compare event probabilities based on each parametric function and external longer term observational data |
| Visual inspection | Assess how closely the tail of a parametric function fitted to the active treatment arm(s) concur with external longer term observational Kaplan-Meier data |

32

## Cure modelling

- For some outcomes, a proportion of patients may never experience the event.
  - e.g. patients who are cured of their disease may never experience disease recurrence
- Identified graphically by a plateau in the Kaplan-Meier where the hazard equates to the general population hazard
- Standard parametric models may be incapable of fitting to these hazard functions
- May also be an interest in estimating the proportion of patient who are cured, referred to as the "cure fraction"

33

## Parametric cure models

- Mixture cure models assume that a proportion of patients are cured and the excess (disease) hazard function tends to zero at the cure fraction.

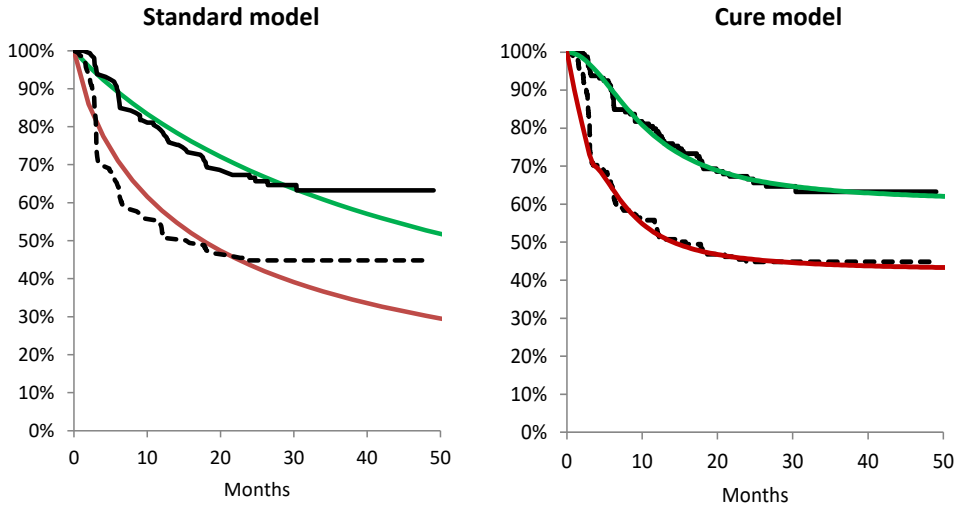
$$S(t) = S^*(t)[\pi + (1-\pi)S(t_u)]$$

  - $t$ is time
  - $S^*(t)$ is the survival for the general population
  - $\pi$ is the cure fraction
  - $S(t_u)$ is the survivor function for uncured patients
- Need to choose a parametric form for $S(t_u)$
  - Weibull, Lognormal, Generalised gamma
- Available using the `strsmix` command in Stata and other packages (SAS, R)

Lambert (2007)

34

# Parametric cure models – application




35

# Treatment switching

- Patients switch from control to treatment arm following primary endpoint
  - Common issue in oncology trials
- As a subset of patients in the control arm receive the benefit of treatment, overall survival times for patients who switched treatment are overestimated.
  - Failure to adjust for treatment crossover can result in an underestimated relative treatment effect.
  - Adjustment for treatment crossover aims to reduce bias in relative treatment effect estimates resulting from such treatment switching.
  - Methods that preserve randomisation are needed to provide unbiased treatment effect estimates in the presence of treatment switching

36

## Methods for adjusting for treatment crossover

- NICE guidelines provide a range of approaches to consider when faced with treatment switching, including:
  - Rank Preserving Structural Failure Time Models (RPSFTM)
  - Iterative parameter estimation (IPE) algorithm
  - Inverse Probability of Censoring Weights (IPCW) method

37

# Comparative effectiveness

38

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# The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials

Heiner C. Bucher*[1], Gordon H. Guyatt, Lauren E. Griffith, Stephen D. Walter[2]
Department of clinical epidemiology and biostatistics, McMaster university, Hamilton, Ontario, Canada, L8N 3Z5

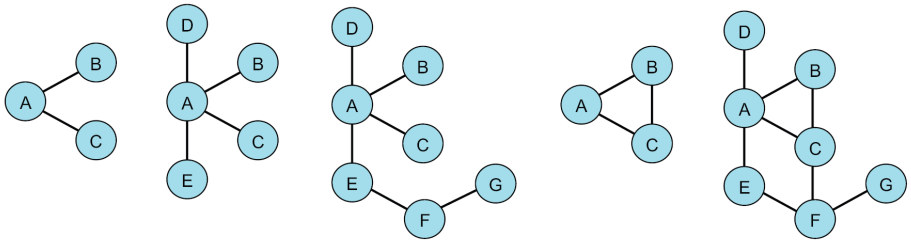


DOI: https://doi.org/10.1016/S0895-4356(97)00049-8

39

# Network Meta-Analysis

Networks of evidence




*Closed loops in network: combination of direct and indirect evidence*

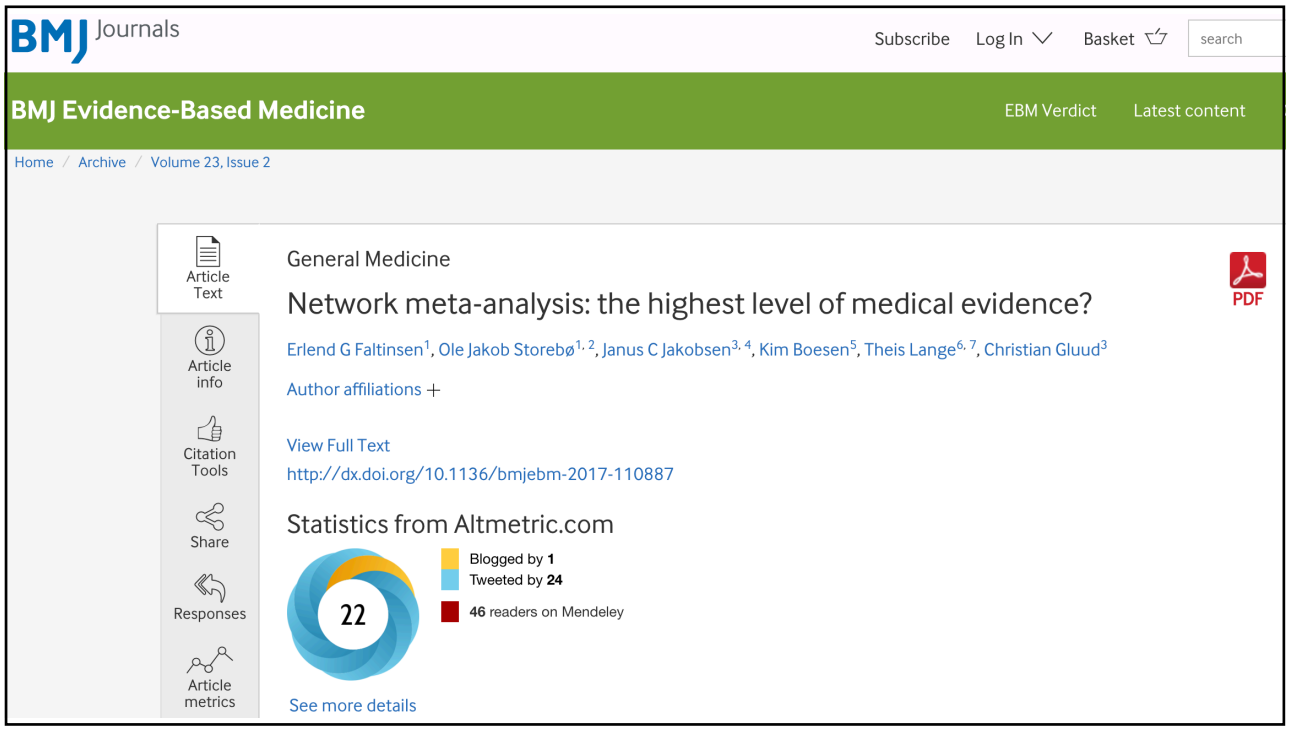
Definitions

**Anchored Indirect Treatment Comparison**
(or 'adjusted' ITC)

**Mixed Treatment Comparison**

**Network meta-analysis**
(>2 studies in network)

40




41

# Comparative effectiveness without a network?

Comparing existing but unconnected data:

- Naïve comparison
- Match adjusted indirect comparisons (MAIC)
- Simulated Trial Comparison (STC)

Single arm studies:

- Historical controls
- Synthetic controls
- Self control

42

# Statistical methods for cost-effectiveness analysis: looking to the future

- Real world data, big data and personalised medicine
  - Application of ML and AI
  - Use of innovative methods for causal inference (MR / other IV approaches)
  - SEM (modelling components of CEA?)
- Refinement of existing methods
  - Methods for statistical estimation of counterfactuals
  - Application of existing VOI methods (under-used)
  - Novel survival analysis approaches (multi-state survival / competing risks)
  - Uncertainty in the face of multiple methods challenges (bootstrapping)

43