Statistical aspects of pharmaceutical subsidy

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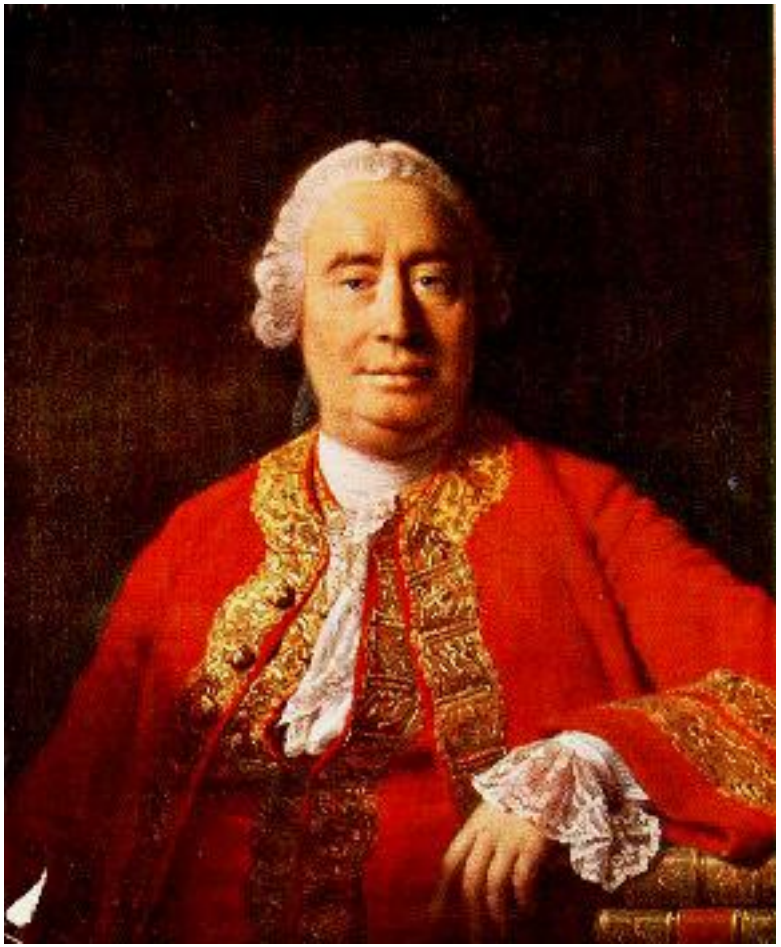
Pharmaceutical

Drug

Biological

Vaccine

- Pharmaceutical subsidy in Australia
- Vignettes
  1. Indirect comparisons
  2. Probabilistic Sensitivity Analysis



"A wise man proportions his belief to the evidence"

1992

World first: Australia

Changed legislation

Set price for government subsidy of pharmaceuticals

Based on evidence

Considered successful public policy

- Australia pays lower prices
- Other countries have copied

- How?
  - No-one wanted the sole credit
  - The policy change was a co-production (timing)
    - Academics
    - Bureaucrats

Assessing evidence for subsidy
1. Quality & 2. Relevance

1. Quality of the comparison internal to the study

Internal validity

Blinding

Concealment of allocation

Withdrawals (informative censoring)

Often high; RCT for marketing approval

2. **Relevance**

External validity; baseline event rate

- Patients younger; fewer co-morbidities

Other aspects of relevance

- Surrogate & switching
- Time horizon
- Comparator
- Post hoc subgroup vs ITT
- Co-dependent technologies: pharmacogenomic markers becoming more common

Often (not always) a trade-off

- High quality evidence is often not relevant
- Relevant evidence is often not of high quality

Guidelines on assessing evidence

- 100 pages on internal validity
  - Was randomisation concealed?
  - Were the patients and investigators blinded?
  - Was intensity of FU the same in both groups?
  - Informative censoring
  - Missing data
  - etc, etc
- One paragraph on external validity
  - Were the patients in the RCT similar to your patients?
- Nothing on other issues for assessing relevance

Relevance

- Baseline event rate (external validity)
  - Are the patients in the RCTs similar to patients who will receive the new pharmaceutical should it be subsidised?
- Comparator
  - Indirect comparison
- Outcome
  - Surrogate/switching
- Time horizon
  - Extrapolation of comparative treatment effect from the RCT to the time horizon relevant for subsidy
- Intention to treat population versus post-hoc subgroup
- Co-dependent diagnostic test
  - Pharmacogenomic markers
  - Prevalence
  - sensitivity/specificity

Process of pharmaceutical subsidy in Australia

1. Marketing approval

   TGA (FDA, EMA)

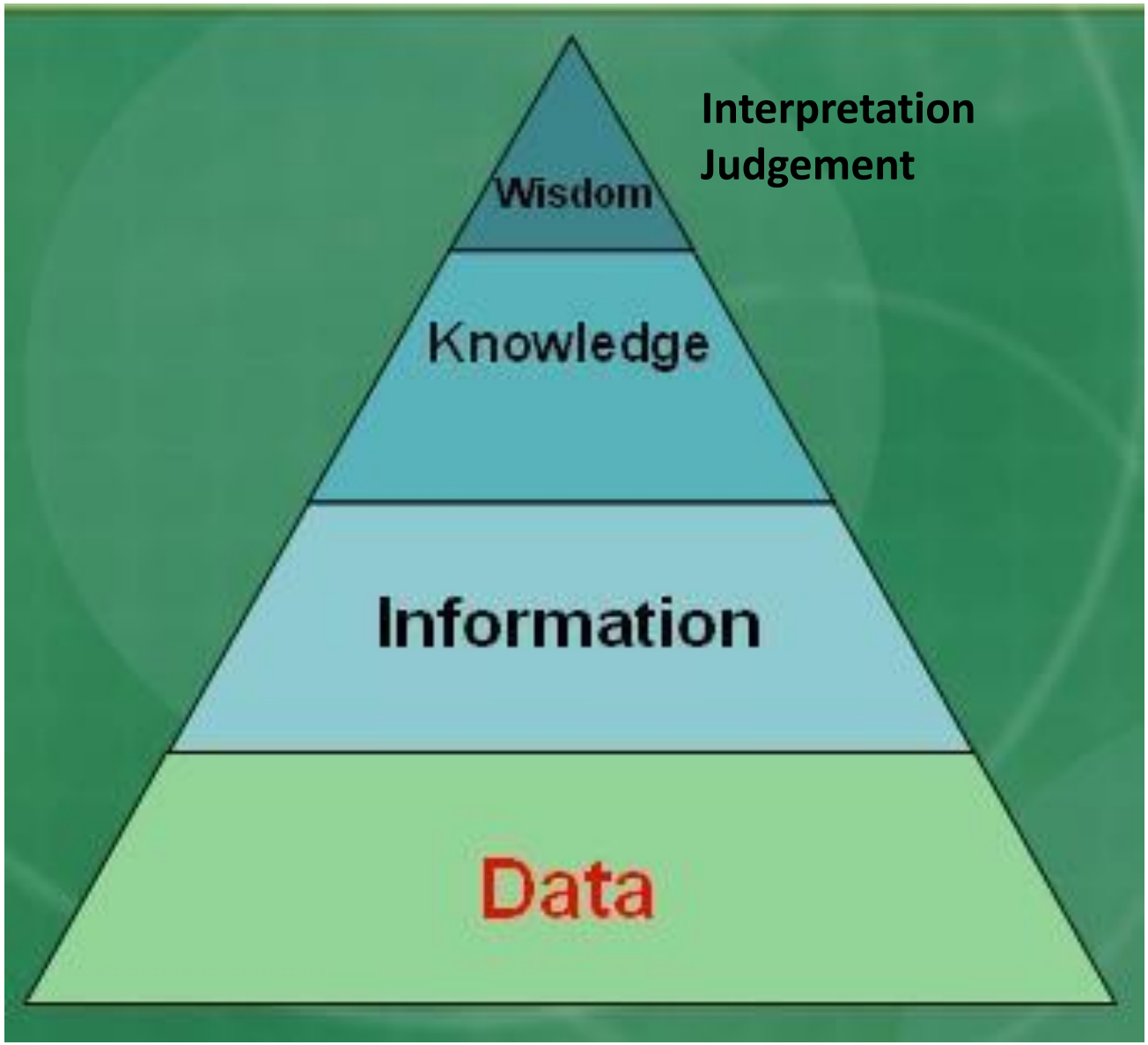
   - Quality (of manufacture)
   - Efficacy
   - Safety

2. Apply for subsidy through the

   Pharmaceutical Benefits Scheme (PBS)

Applications to PBS

- Sponsor (pharmaceutical company)
  - Submission (200-1000 pages)
- 1 of 5 evaluation groups at universities
- Technical subcommittee (peer review)
- Pharmaceutical benefits advisory committee (PBAC)
  - 16 clinicians; health economist; pharmacist



PBAC

Sub-committee review

University evaluation

Sponsor's submission

Legislation (1992)

PBAC should consider

- Comparative clinical effectiveness
- Comparative cost

Comparator:

Treatment most likely to be replaced should the new pharmaceutical be listed for subsidy

Health economic analyses

- Cost minimisation

  Claim: Same health gain as comparator

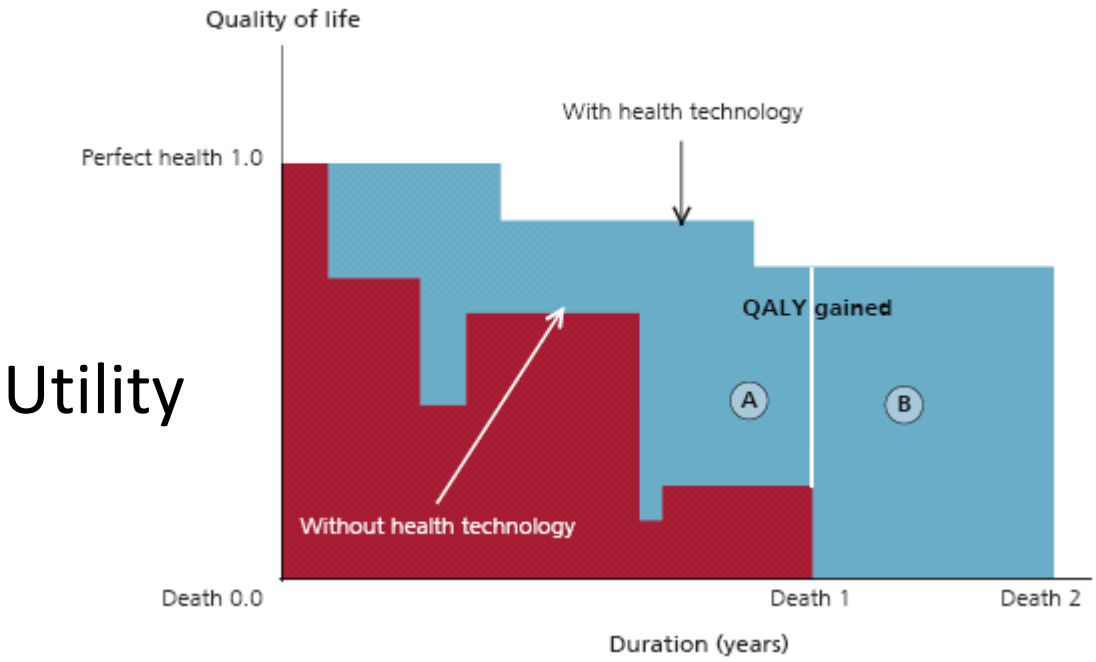
  Non-inferiority
  - Same cost (higher price if cost offsets)
  - Often in the same pharmacological class; me-toos
  - not always cost neutral; can expand market
- Cost utility analysis

  Claim: greater health gain than comparator

  Superiority
  - Incremental cost effectiveness ratio (ICER)
  - ICER=Cost/QALY

QALY
Quality adjusted life year

Figure. Diagram of the concept of QALY (quality-adjusted life years)



QALY is life-years-saved weighted by utilities

Utility:

0: dead

1: perfect health

Advantage of QALY

Common metric across all health care technology

In theory, can compare cancer pharmaceuticals to those for:

heart disease

multiple sclerosis

depression

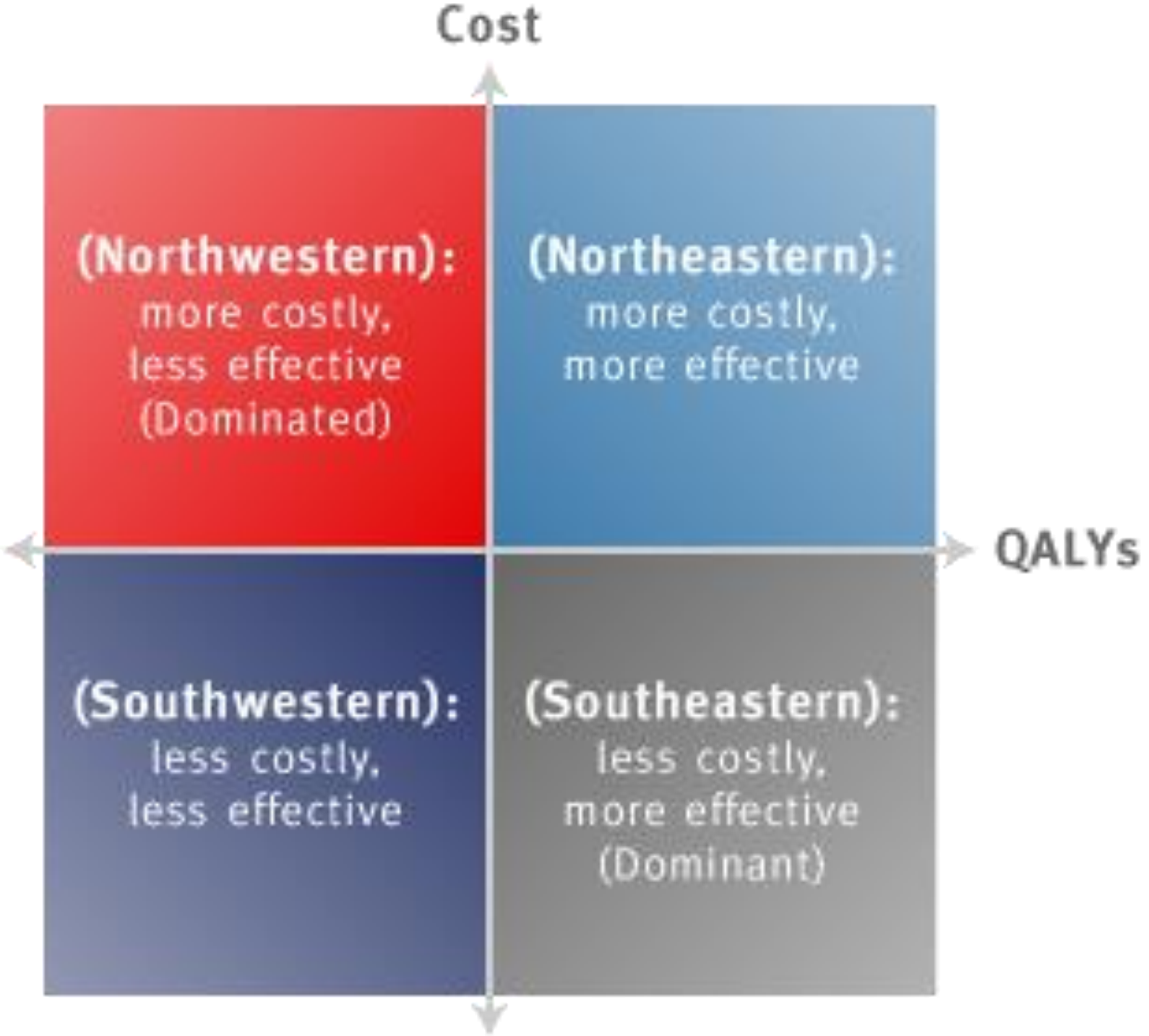
prevention (vaccines)

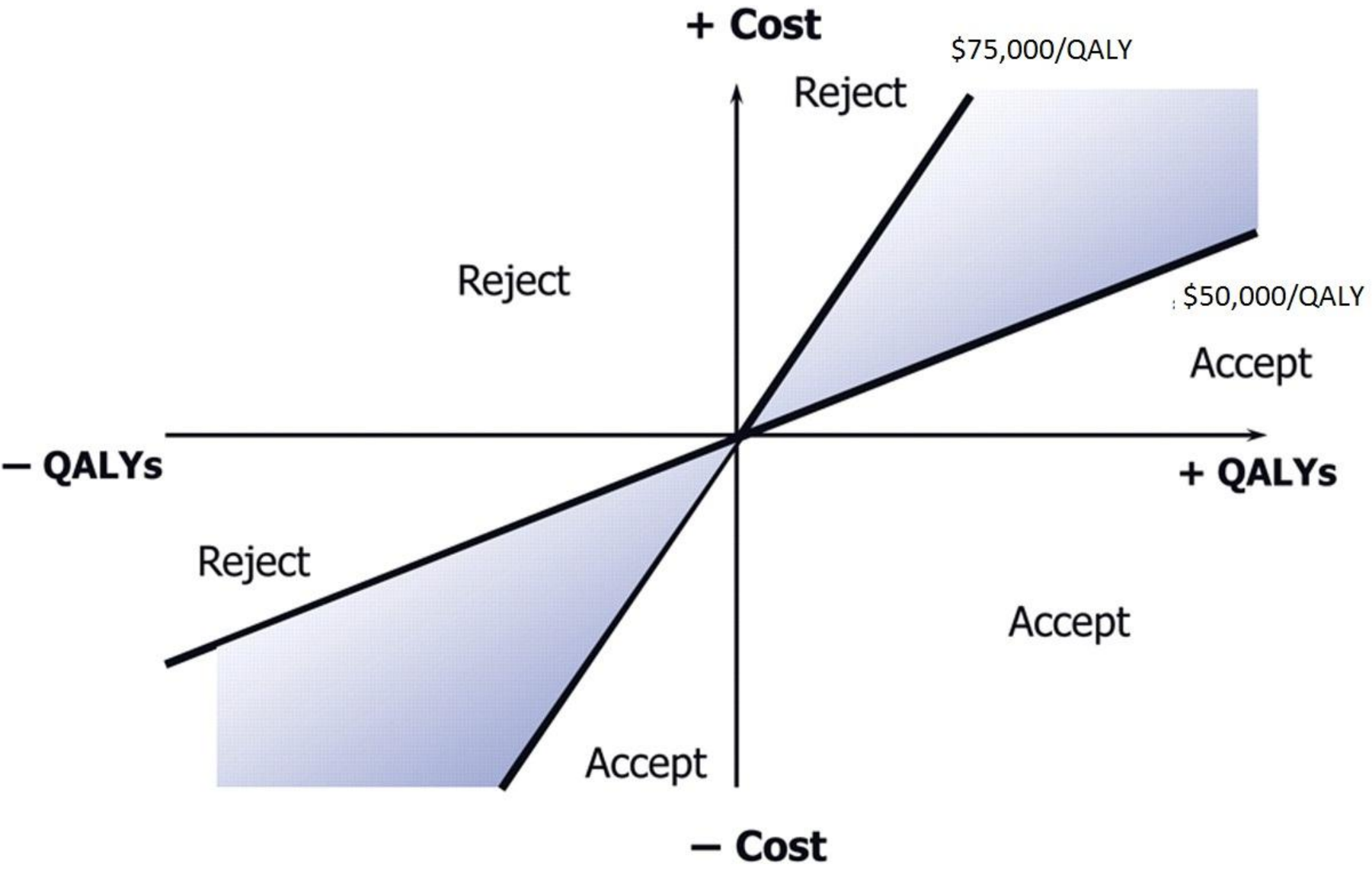
pain relief

etc, etc

Difficulties with QALYs

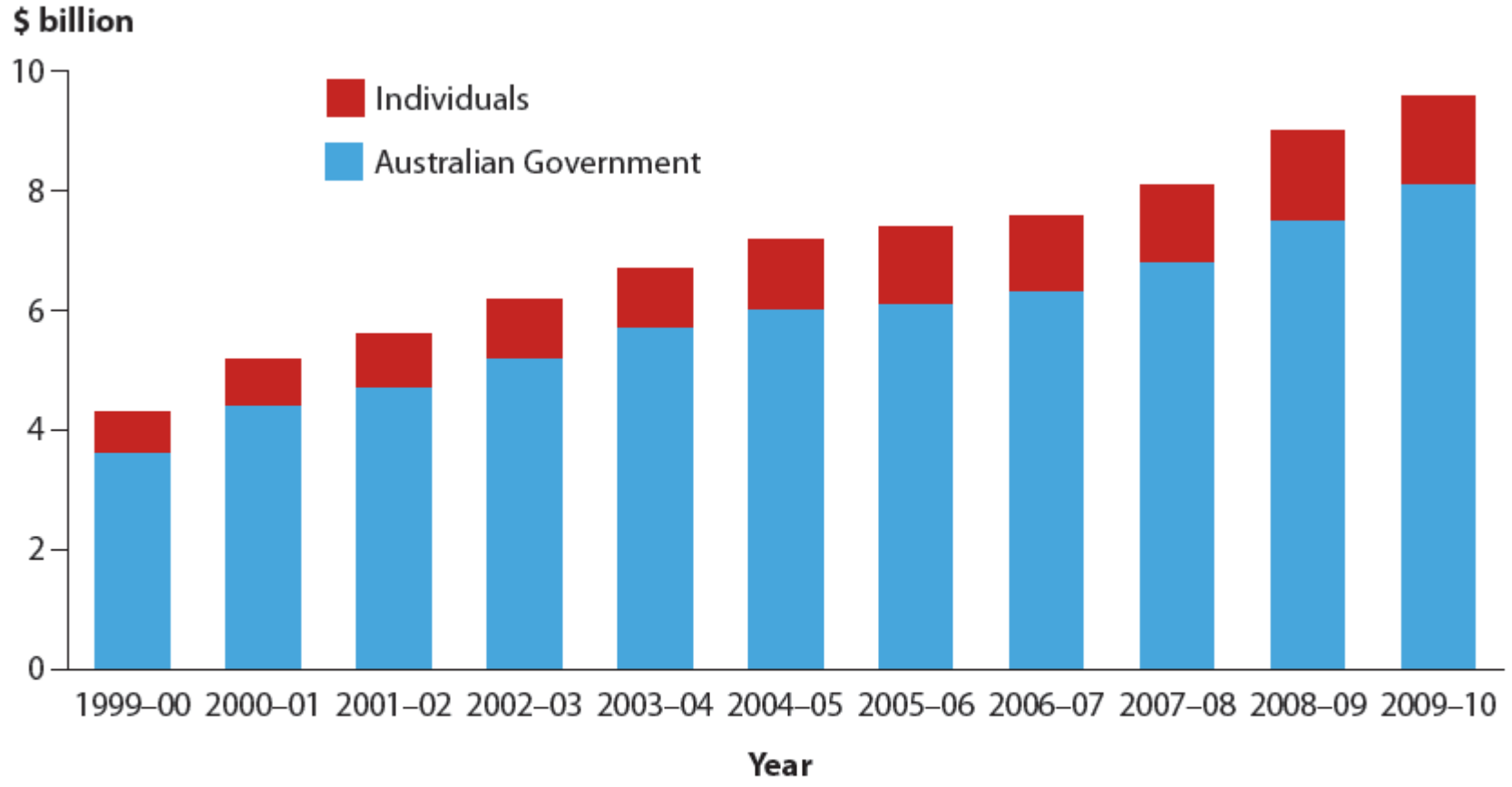
- Calculating/agreeing utility values
- For some pharmaceuticals the outcome in RCT is:
  - Headache-free day
  - Relief from constipation
  - Avoidance of diarrhoeal illness
- Easier for cancer or heart-disease, say
  - Outcome: life years saved or related measure


Cost
(Northwestern):
more costly,
less effective
(Dominated)
(Northeastern):
more costly,
more effective
QALYs
(Southwestern):
less costly,
less effective
(Southeastern):
less costly,
more effective
(Dominant)


+ Cost
$75,000/QALY
Reject
Reject
$50,000/QALY
Accept
– QALYs
+ QALYs
Reject
Accept
Accept
– Cost

How do pharmaceutical companies arrive at a price?

- R&D
  - High risk venture
  - Cervical cancer vaccine: $3B
- Innovation
  - Patent
- High clinical need
  - Early HIV drugs
- Manufacturing costs



Source: AIHW 2011a.

Figure 8.7: Recurrent spending on benefit-paid pharmaceuticals, by source of funds, 1999–00 to 2009–10

Total health expenditure: $122B ~9% GDP

Vignette 1

Indirect comparisons

Why do we need indirect comparisons?

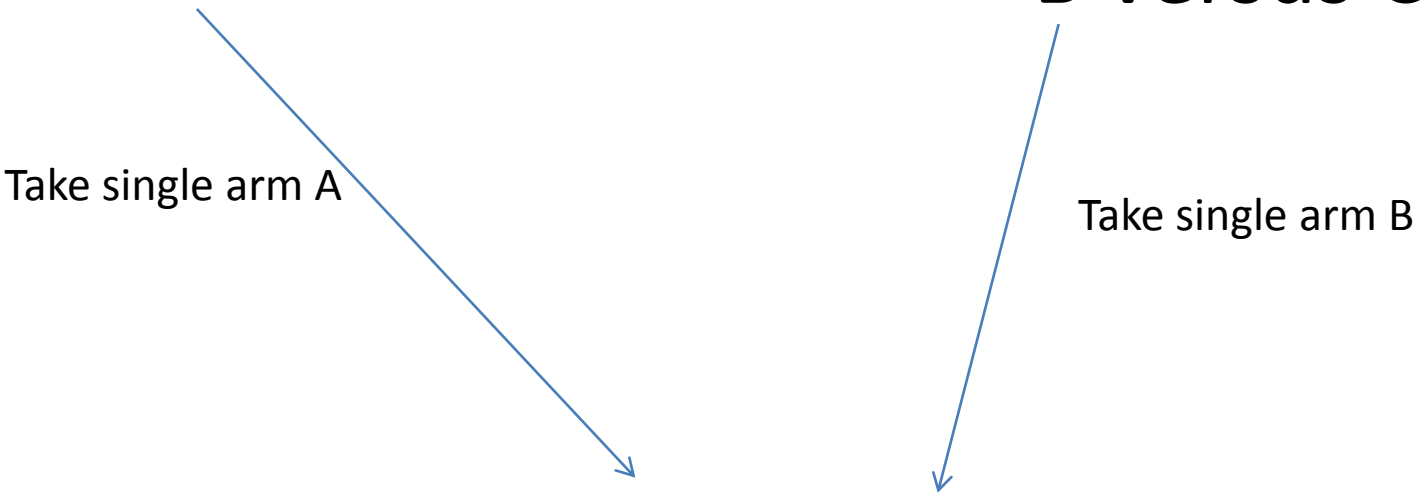
- Comparator used in RCT might not be the relevant comparator for Australia

An incorrect approach

Pool results from the active treatment arms

A versus C

B versus C



Compare the event rate in A with event rate for B

Naive indirect comparison

Loose the benefits of randomisation

The Results of Direct and Indirect Treatment Comparisons in Meta-Analysis of Randomized Controlled Trials

Heiner C. Bucher, Gordon H. Guyatt, Lauren E. Griffith, and Stephen D. Walter*

Department of Clinical Epidemiology and Biostatistics,
McMaster University, Hamilton, Ontario,
Canada, L8N 3Z5

J Clin Epidemiol, 1997

Naive indirect comparison: prone to bias
Direct head-to-head comparisons: whenever possible

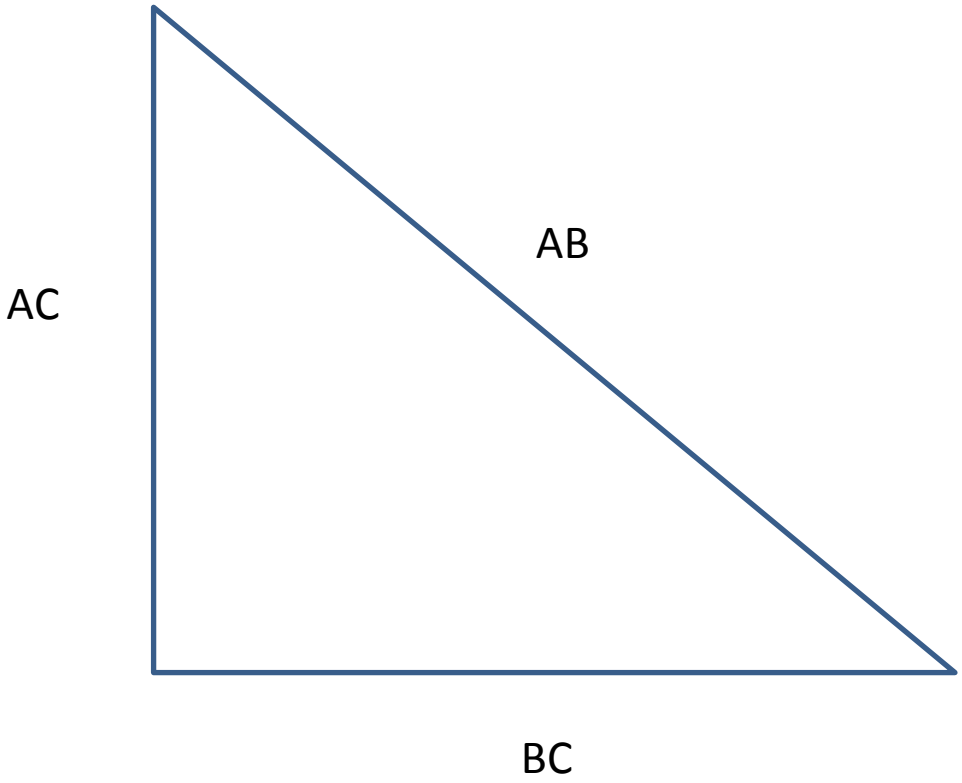
Proposed ***adjusted*** indirect comparison
- But still limited strength of inference
- Exchangeability problem

Appendix

$$\ln(OR_{Ind}) = \ln(OR_{AB}) - \ln(OR_{CB}). \quad (4)$$

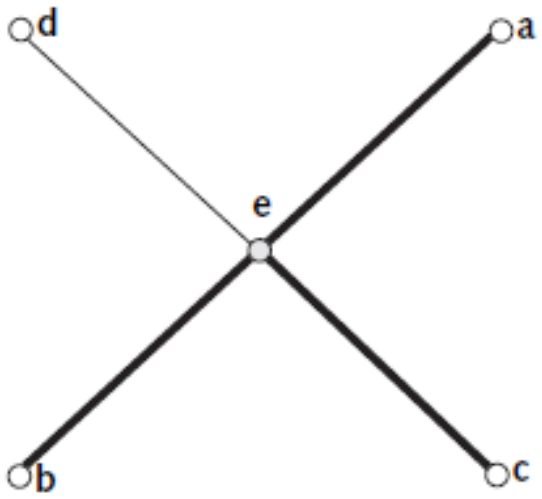
Because OR_{AB} and OR_{CB} are estimated from different studies, they are statistically independent, and hence the variance of OR_{ind} can be obtained from

$$\mathrm{Var}(\ln OR_{Ind}) = \mathrm{Var}(\ln OR_{AB}) + \mathrm{Var}(\ln OR_{CB}) \quad (5)$$


AB
AC
BC

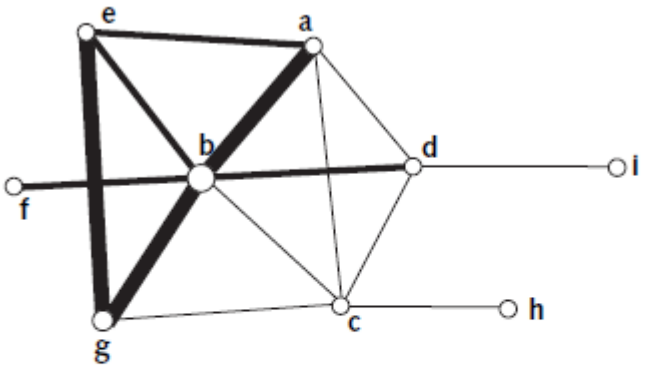
Extensions
Network meta-analysis
WinBugs

Biologic treatments for rheumatoid arthritis



a: adalimumab, b: infliximab,
c: etanercept, d: anakinra, e: placebo

Chemotherapy regimens for ovarian cancer



a: platinum monotherapy, b: platinum-based combination,
c: taxane monotherapy, d: platinum + taxane-based combination,
e: nonplatinum/nontaxane monotherapy,
f: platinum-based combination (ip), g: nonplatinum/nontaxane combination, h: taxane-based combination,
i: platinum/taxane-based combination (ip)

Mixed treatment comparison

STATISTICS IN MEDICINE
Statist. Med. 2004; **23**:3105–3124 (DOI: 10.1002/sim.1875)

Combination of direct and indirect evidence in mixed treatment comparisons

BMJ

Simultaneous comparison of multiple treatments: combining direct and indirect evidence

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Report to the Methods Review Working Party

Key issues arising from workshop on evidence synthesis (indirect and mixed treatment comparisons)

BMJ

BMJ 2011;343:d4909 doi: 10.1136/bmj.d4909

RESEARCH

Inconsistency between direct and indirect comparisons of competing interventions: meta-epidemiological study

2011: "The inconsistency between indirect and direct comparisons might be more prevalent than previously observed."

Apples and oranges problem

Assumption of exchangeability

Synonyms

- Similarity
- Lack of heterogeneity
- Lack of treatment-effect modification

More problematic than “heterogeneity”

in a H2H systematic review

Potential reasons for lack of exchangeability

Patient characteristics

- Co-exiting disease
- Concomitant treatments
- Severity of index condition

Methods

- Length of FU
- Withdrawals
- Measurement of outcome

Treatment

- Common comparison treatment can be different

Most RCTs assess add-ons

Besides the problem of exchangeability, indirect comparisons are subject to ***statistical imprecision***

Not like a H2H meta-analysis where precision increases

- Need 4X as many patients in an indirect as in a direct H2H RCT to get CI of same width

Some examples

Cost-minimisation [non-inferiority]

OR=0.97; 95% CI (0.75, 1.68)

Cannot meet any sensible non-inferiority margin

Cost-utility [superiority]

OR=0.73 (0.49, 1.23)

Hard to interpret

How does PBAC assess indirect comparisons?

(15% of submissions)

- Rarely assumption of exchangeability holds
- Looks at the number crunching as supplementary information

Summary
Vignette 1. Indirect comparisons

- Unhelpful over-enthusiasm
  "bloated optimism"

- Took 15 years to get back to the conclusions/advice in the Bucher/Guyatt/Walter paper

- Number crunching ok, given the assumptions
  But, assumption of exchangeability rarely holds

Vignette 2
Probability Sensitivity Analysis (PSA)

Cost utility model is a forecast

Economic model is typically run until all patients have died

- Cancer
  - RCT: md FU ~12-18 months
  - Economic model ~ 5-10 years
- Statins for secondary prevention heart disease
  - RCT: md FU ~ 5 years
  - Economic model ~ 30 years
- Depression
  - RCT: FU 12 weeks
  - Economic model ~ 30 years

To proceed, might have to make guesses about

- Comparative treatment effect for time frame beyond the RCT
- Calculation of baseline risk for population for subsidy
- Translation of surrogate to life years gained then QALYs
- Effect of subsidy on use other treatments

Also could be uncertainty about

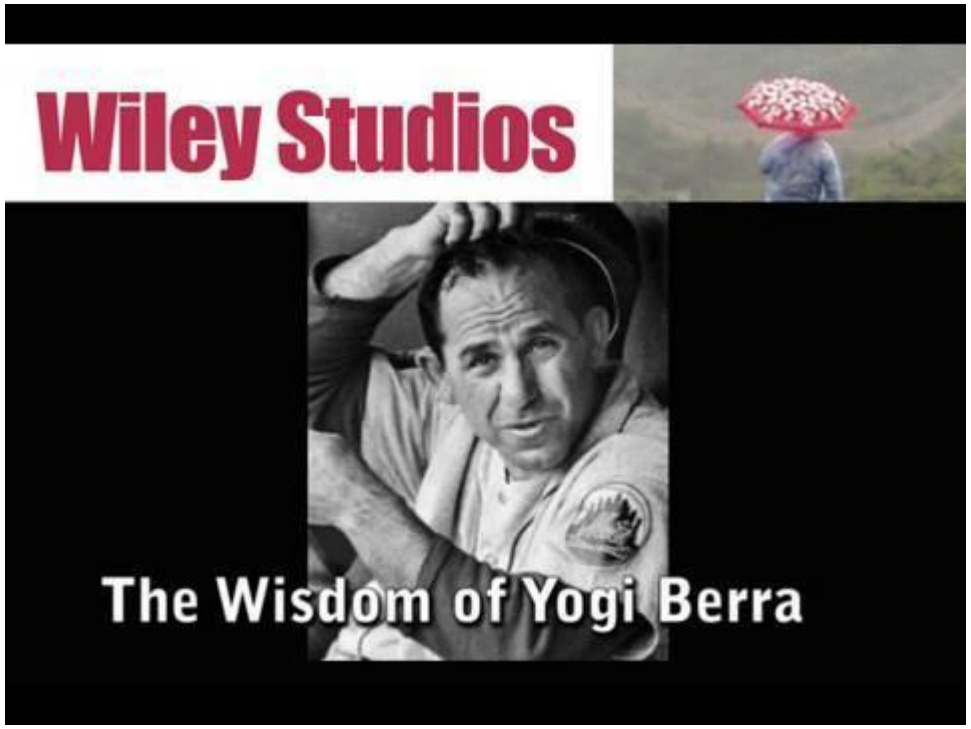
- Size of the comparative treatment effect

  (post-hoc subgroup)
- Utilities
- Costs/cost offsets

Even if cost data is collected as part of the RCT "trial-based economic evaluation"

Still need modelling to:

- Extrapolate the time horizon
- Translate baseline risk to population for subsidy
- Evaluate co-dependent technologies
- Assess the effect of subsidy on use of other treatments

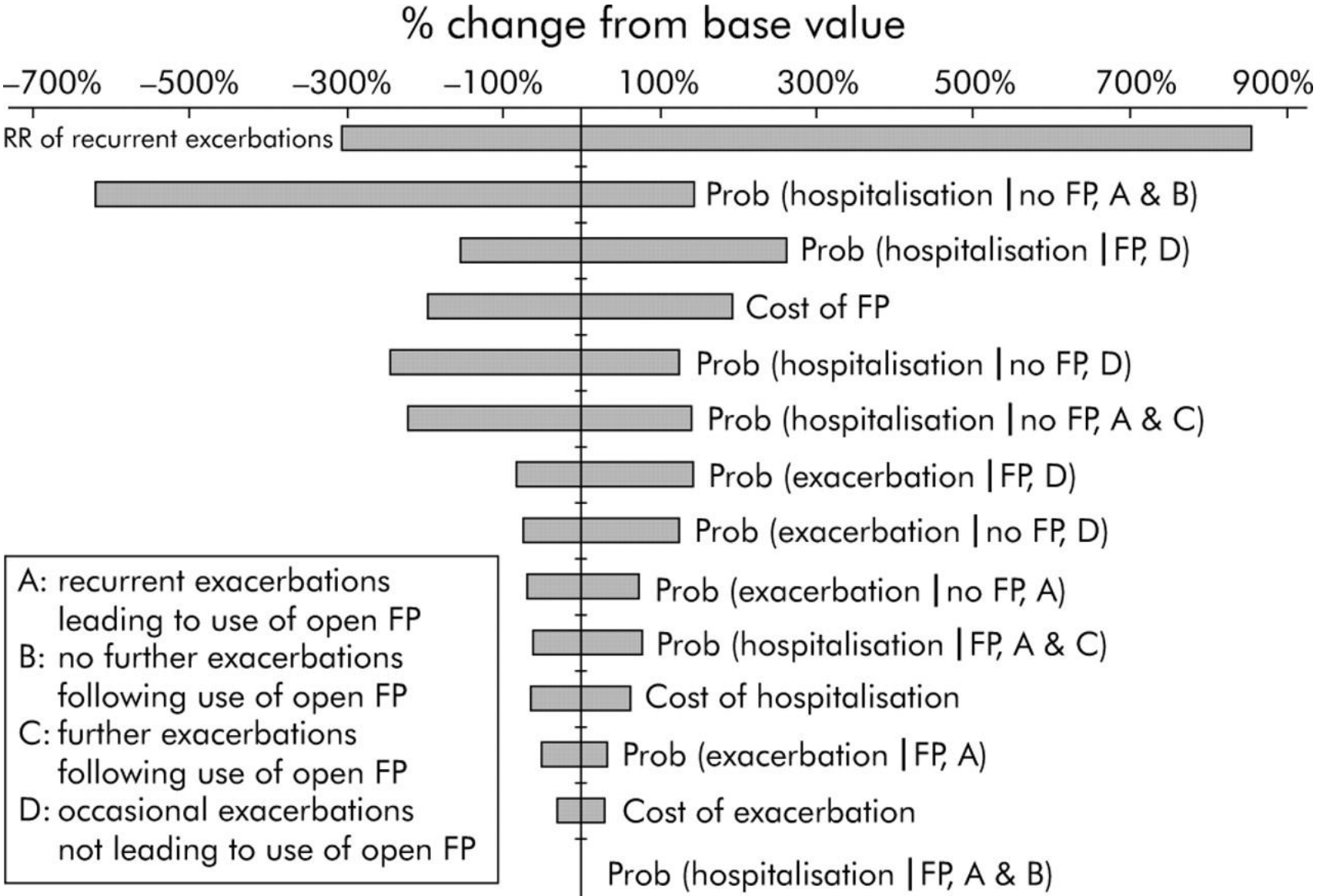


It’s like deja vu all over again

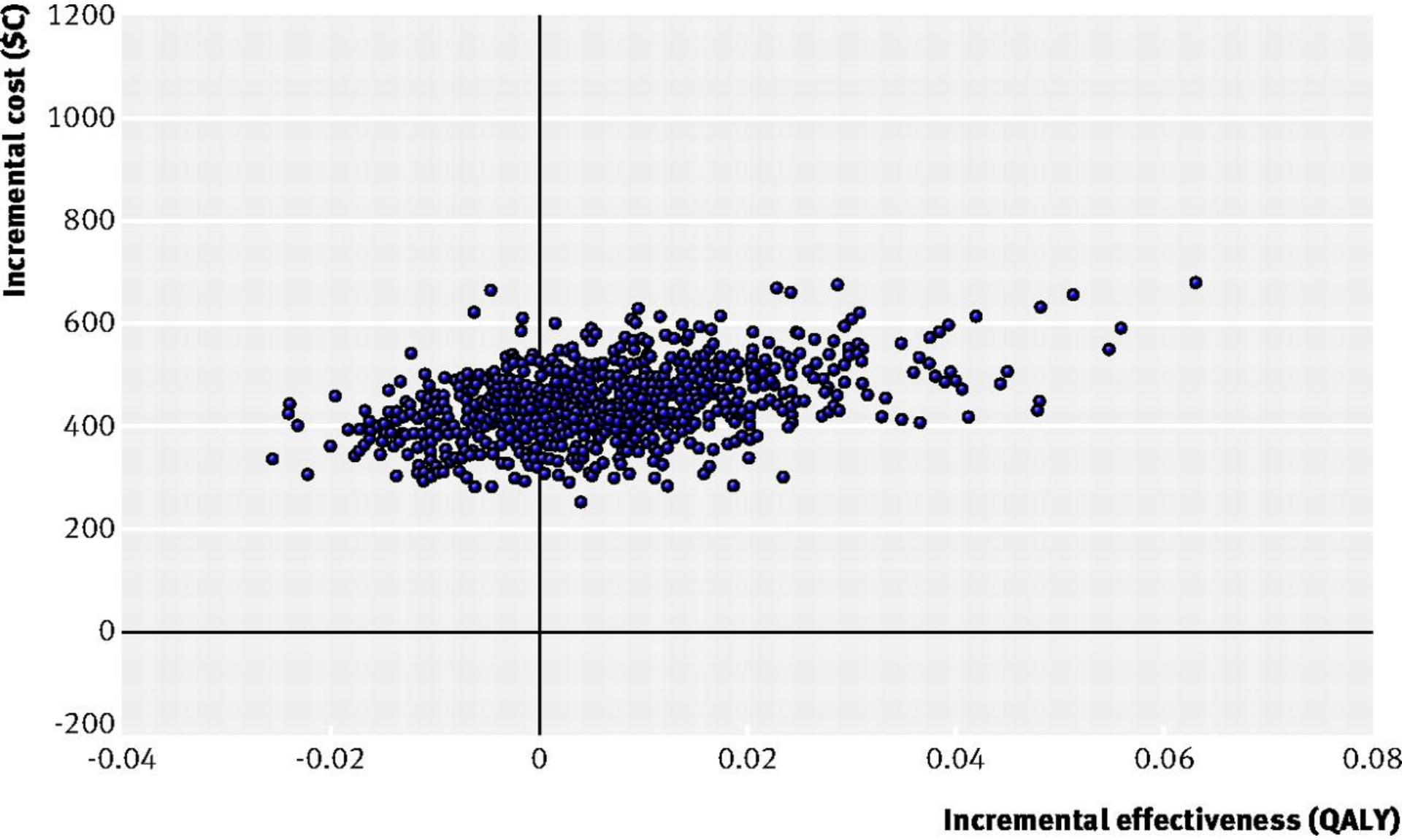
You should always go to other people’s funerals, otherwise they won’t come to yours

It hard to make predictions, especially about the future

One-way sensitivity analysis
Tornado diagram



Probability sensitivity analysis



Mechanics of PSA
Bayesian

- Set up priors for the parameters in the model
- Set up the structure of the model
- Run it through WinBugs [or similar]

PBAC prefers one-way sensitivity analysis over PSA

- PSA: often shows huge range for ICERs
  - Just confirms it's hard to predict the future
- Some uncertainty can be quantified
  - Utilities
  - Costs
- Some uncertainty might not be able to be quantified
  - Comparative treatment effect beyond RCT
  - Changes to the treatment algorithm
  - Treatment effect for patients not included in RCT

- PSA advocates
  - Ask experts about appropriate prior

- PBAC
  - Expert committee of 16 clinicians (content experts)
  - Paid to make expert judgements
  - What's the point of getting other experts to put priors on known unknowns?

  Then there are the unknown unknowns

Summary
Vignette 2

- In an environment where evidence is often contested
  - Bayesian framework is not helpful
- Complex models to capture reality, but
  - No data to populate the model
- One-way sensitivity analyses
  - Simplistic
  - Arguably more useful for decision-making (judgement)

Why statisticians should become more involved in cost-utility modelling

- Statistics is partially about quantifying uncertainty

- Is it worth building a realistically complex model if
  - There is no data to populate it ?
  - Decision-makers won't use it?

  Deliberately (skilfully) simplified models

- Co-dependent technologies
  - Synthesise data on clinical effectiveness & diagnostic accuracy

- Extrapolation of treatment effect