Statistical Challenges within Health Economics and Health Technology Assessment

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Overview

Health Economics and Health Technology Assessment

Definitions and key concepts

Health Economic Models

Statistical Challenges

Examples

Summary

Disclosure statement: Claire Watkins is an employee of AstraZeneca LP. The views and opinions expressed herein are my own and cannot and should not necessarily be construed to represent those of AstraZeneca or its affiliates

What is Health Economics (HE)?

A branch of economics concerned with issues related to efficiency, effectiveness, value and behaviour in the production and consumption of health and health care

What is Health Technology Assessment (HTA)?

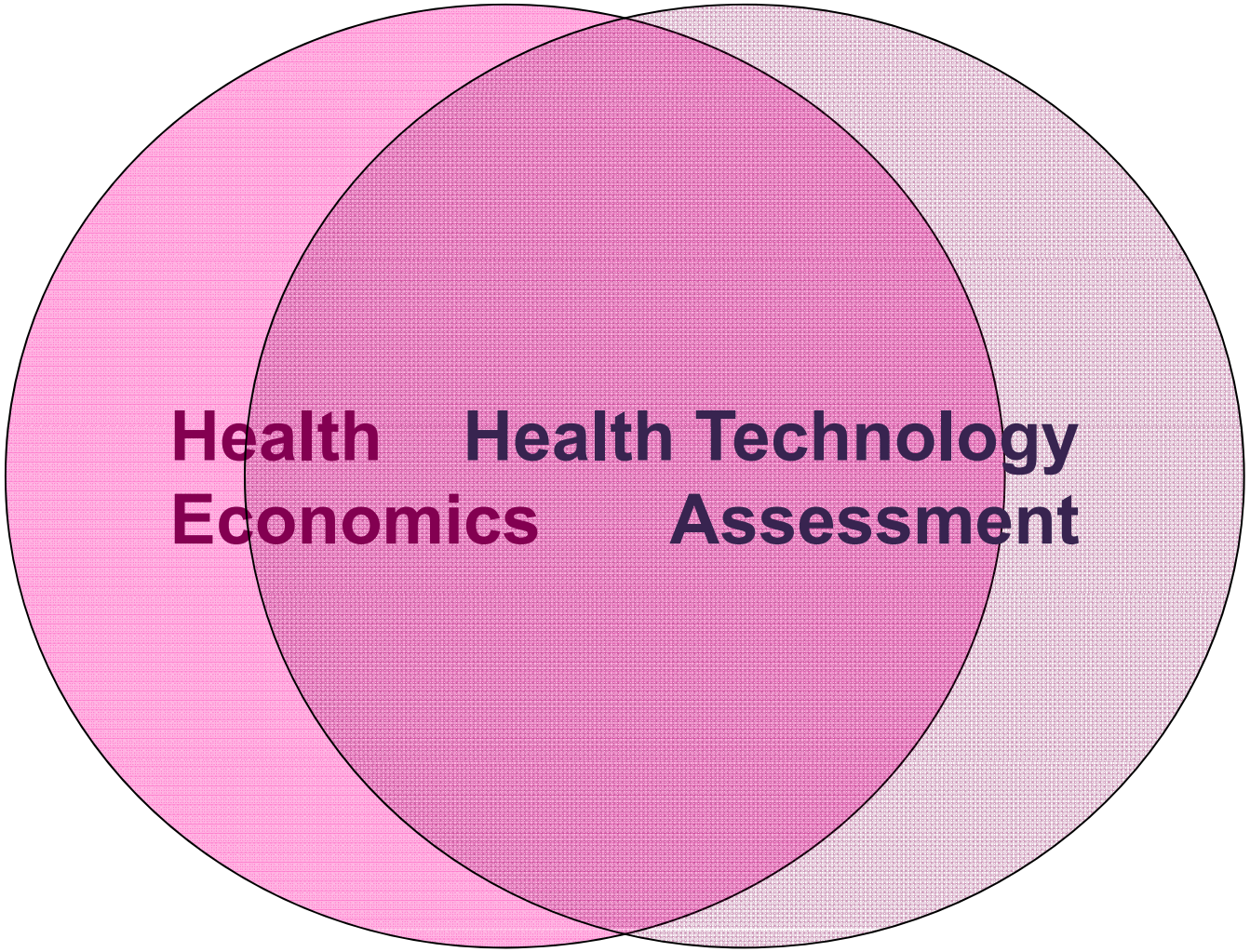
Health technology is an intervention to/for:

- Promote health
- Prevent, diagnose or treat disease
- Rehabilitation
- Long-term care

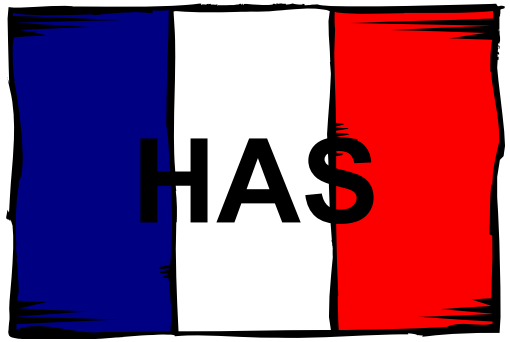
Assessment Process

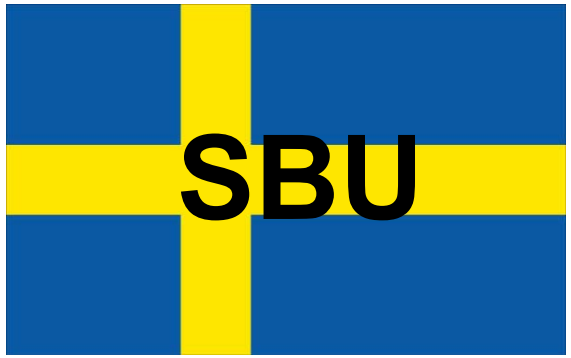
- Evaluate evidence for use of health interventions
- Examine implications and value of medical technology in healthcare

Overlap between HE and HTA

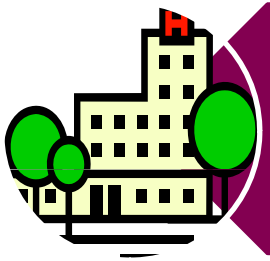


Some National HTA agencies



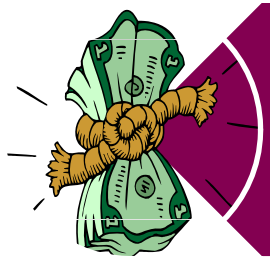


The right question for regulators may not be the right question for payers



Can it work?

Does it work?



Is it worth it?

Standard RCTs may not be able to answer the right question for payers

- Philosophy of most payers: *"Better an approximate answer to the right question than a precise answer to the wrong question"*

- Leads to MODELLING using evidence from many sources
  - RCTs
    - Multiple sponsors, treatments, even other diseases
    - Extrapolation or mapping or simulation common
  - Observational clinical data (trials or databases)
  - Cost data

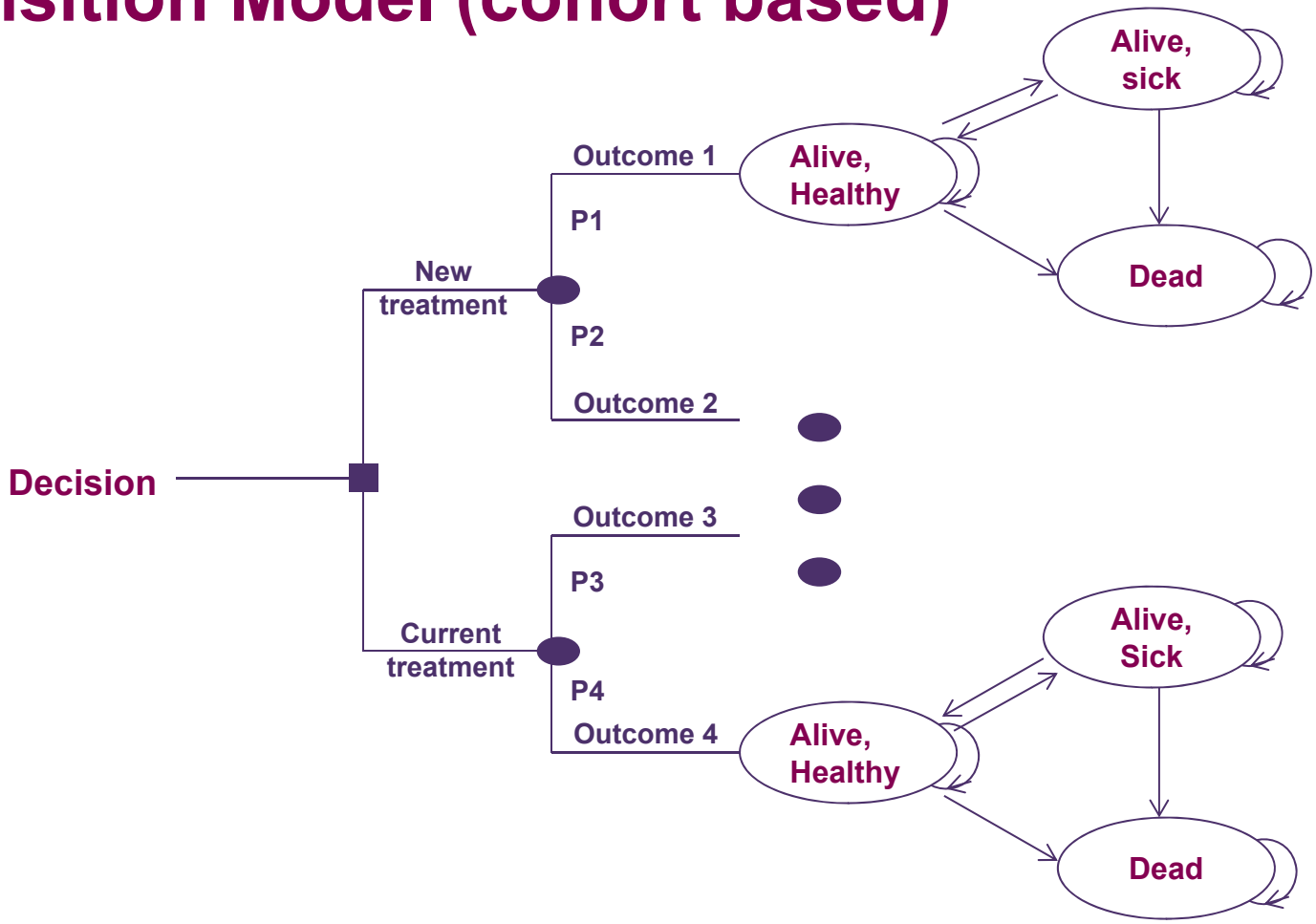
- Submission is still EVIDENCE BASED
  - Just considers a wider net of evidence than a regulatory submission
  - Requirement for robustness remains

Some Types of Economic Analysis

Different payers have different requirements

- Cost effectiveness analysis
- Cost utility analysis
- Cost-benefit analysis
- Cost minimisation analysis
- Budget impact analysis

A typical health economic model: State Transition Model (cohort based)



Arnold, 2010

Input Parameters in a Cost Utility Model

The input parameters for a cost utility model are…….

These parameters can be treated in 2 ways……

1 **Deterministic**

Assumed to be fixed

2 **Probabilistic**

Assumed to be random, with an associated distribution

Incremental Cost-Effectiveness Ratio (ICER)

$$ICER = \frac{Cost_A - Cost_B}{Outcome_A - Outcome_B}$$

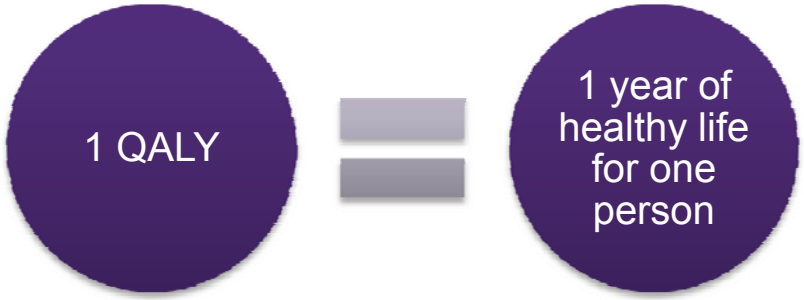
A = new treatment

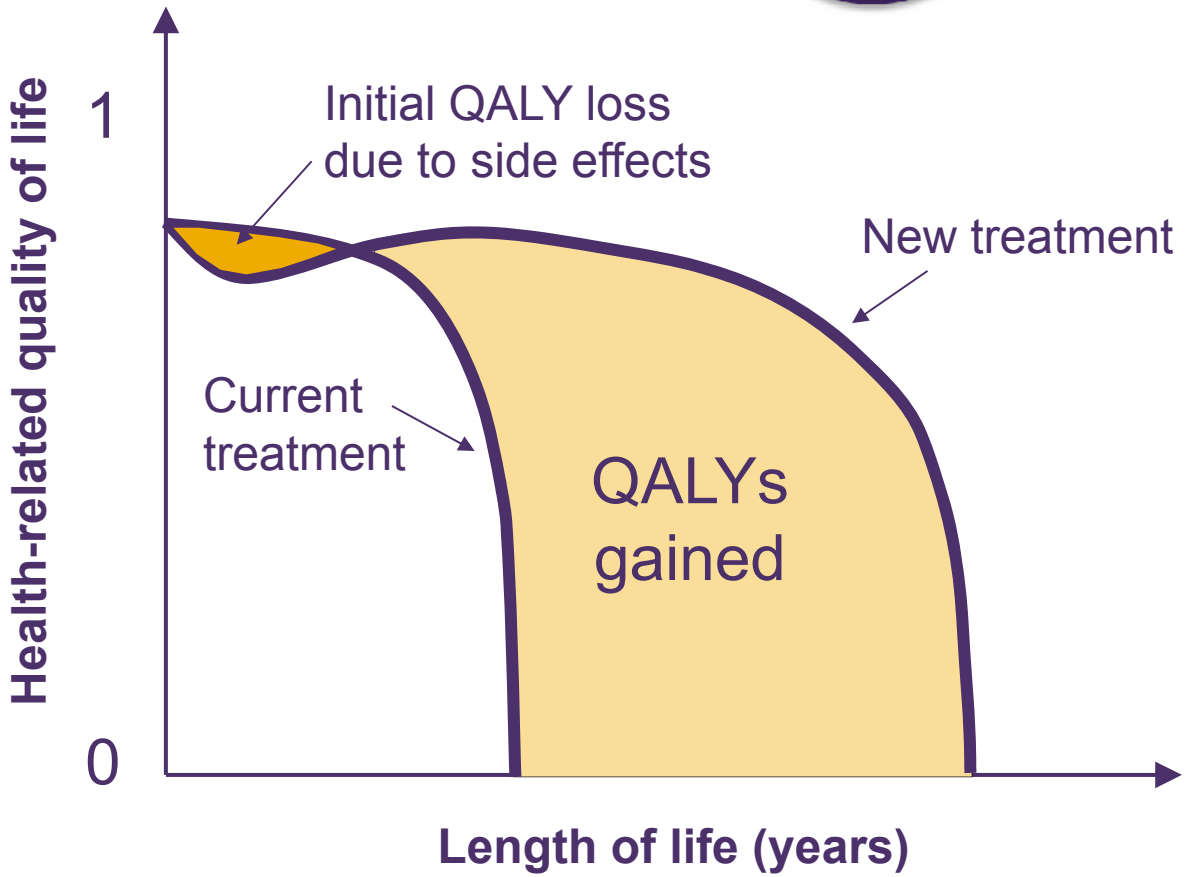
B = current treatment

Measured in QALYs for a Cost-Utility Analysis

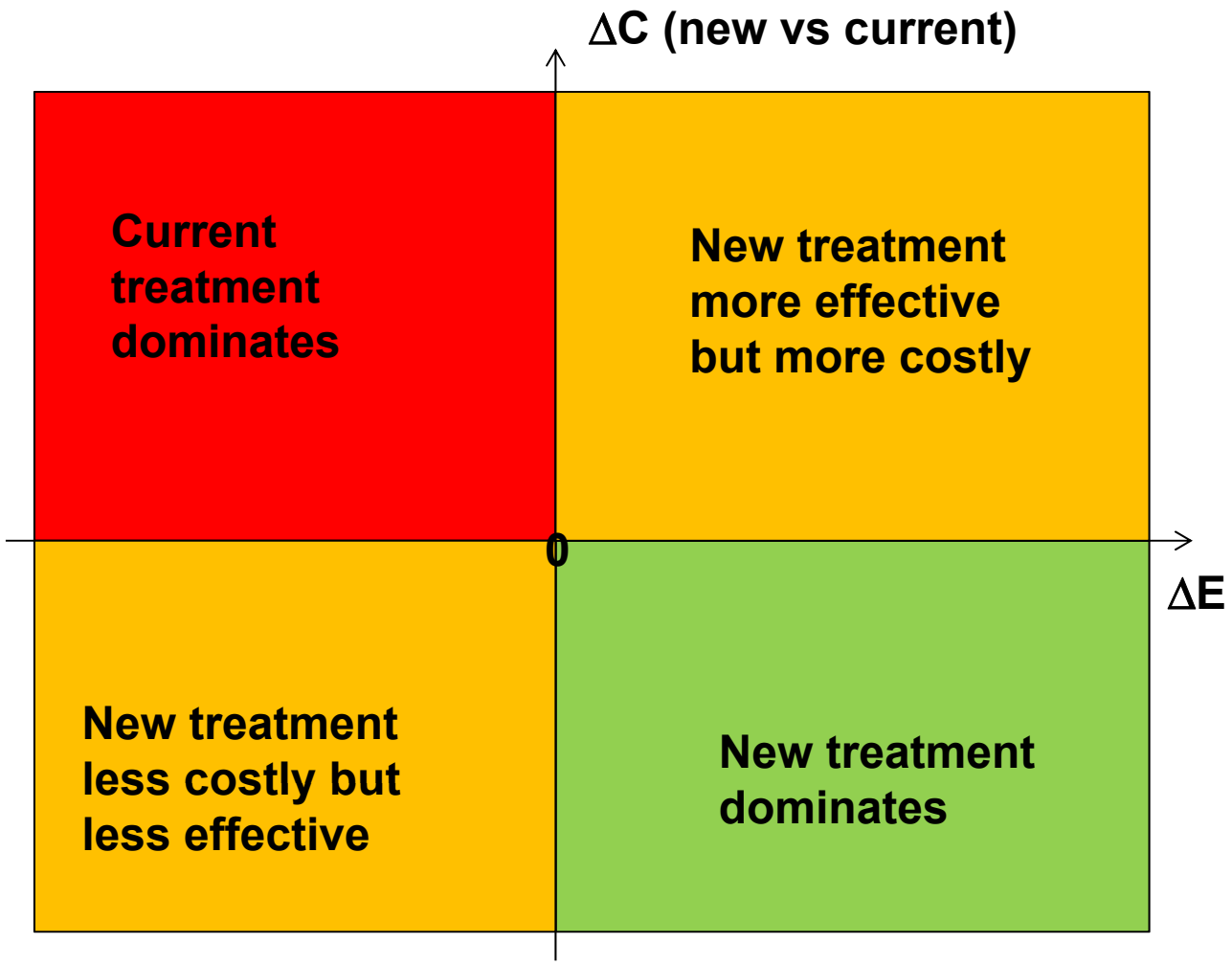
What is a QALY?

Calculating QALYs



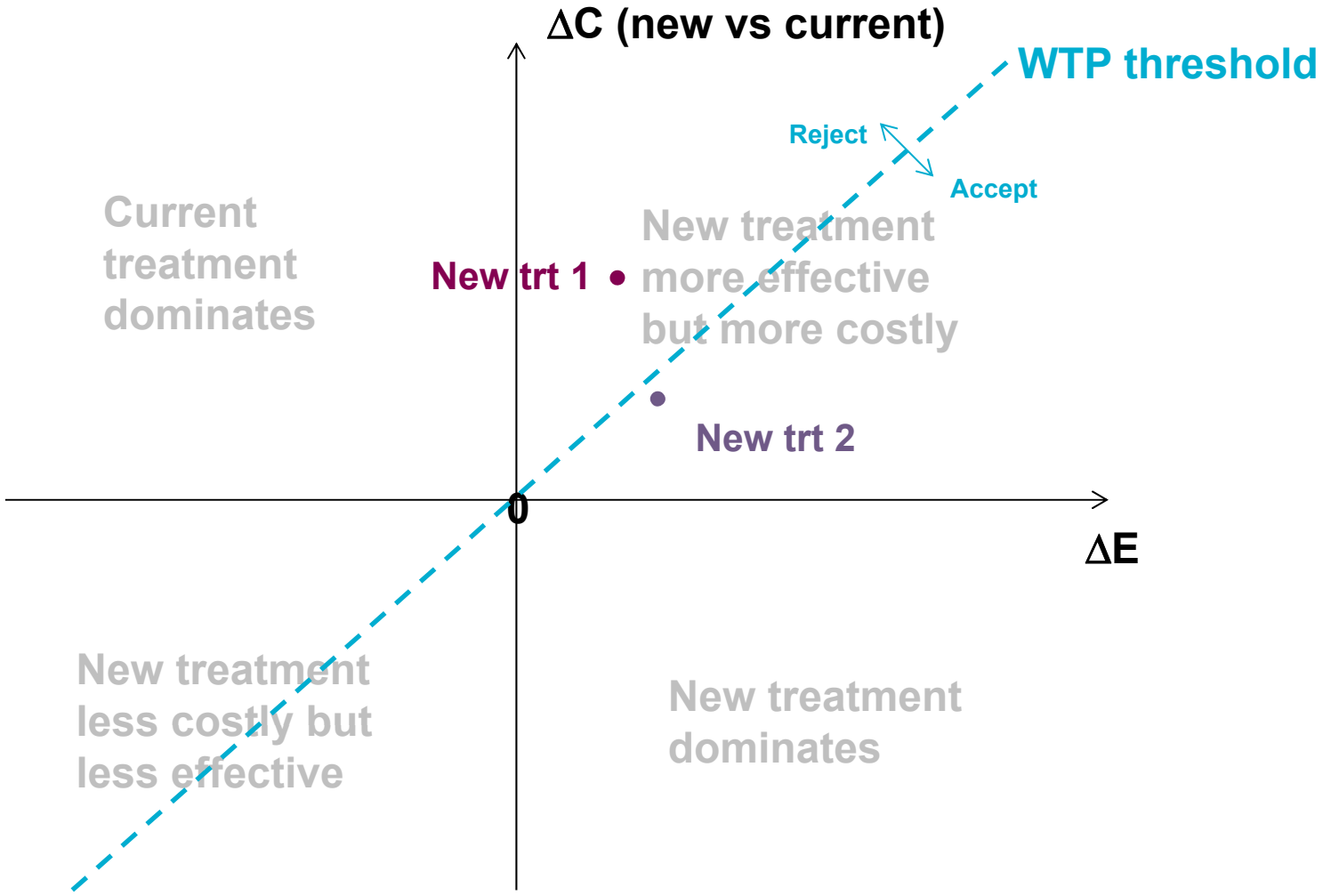


The Cost-Effectiveness Plane



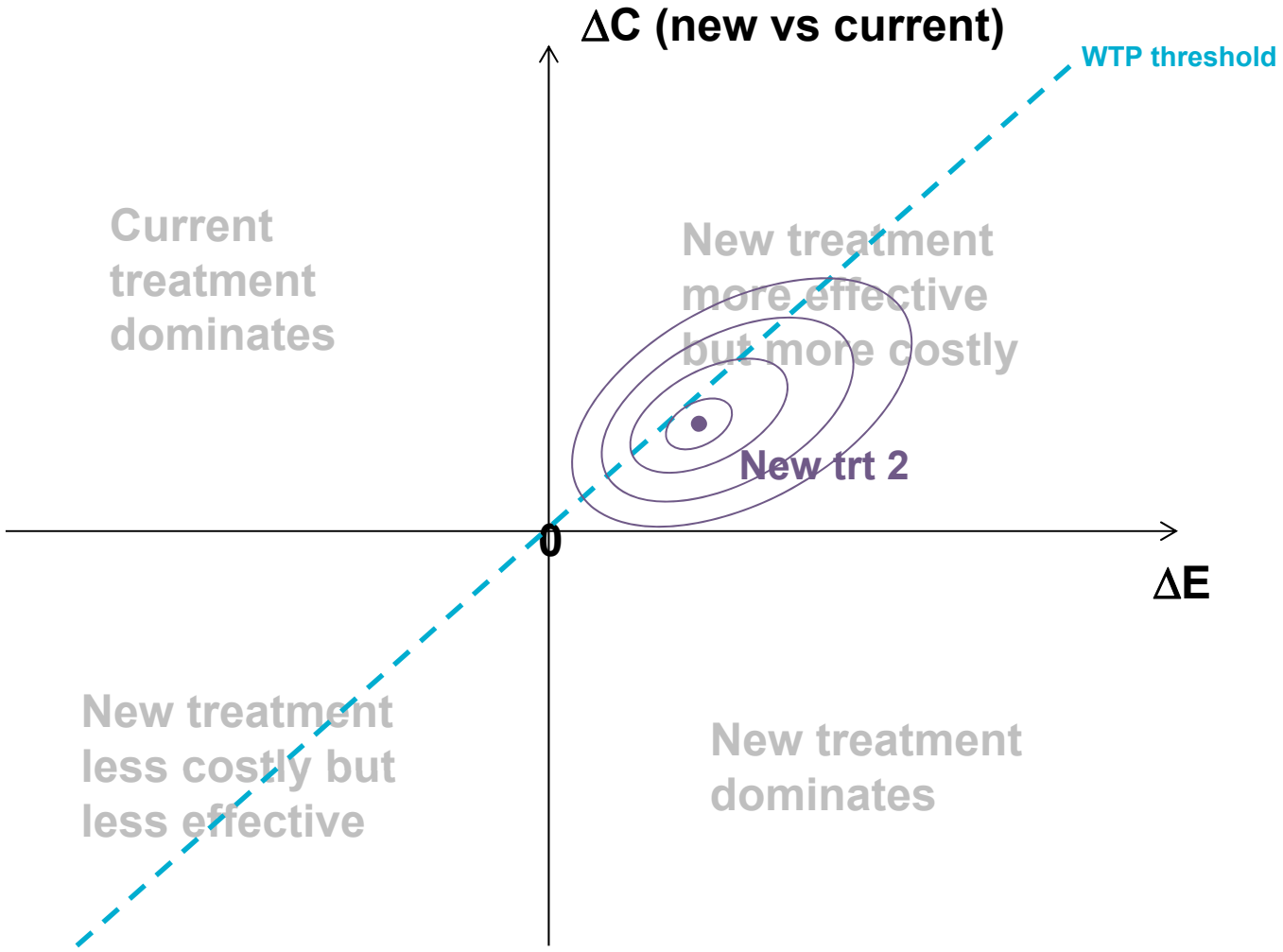
The Cost-Effectiveness Plane

Deterministic

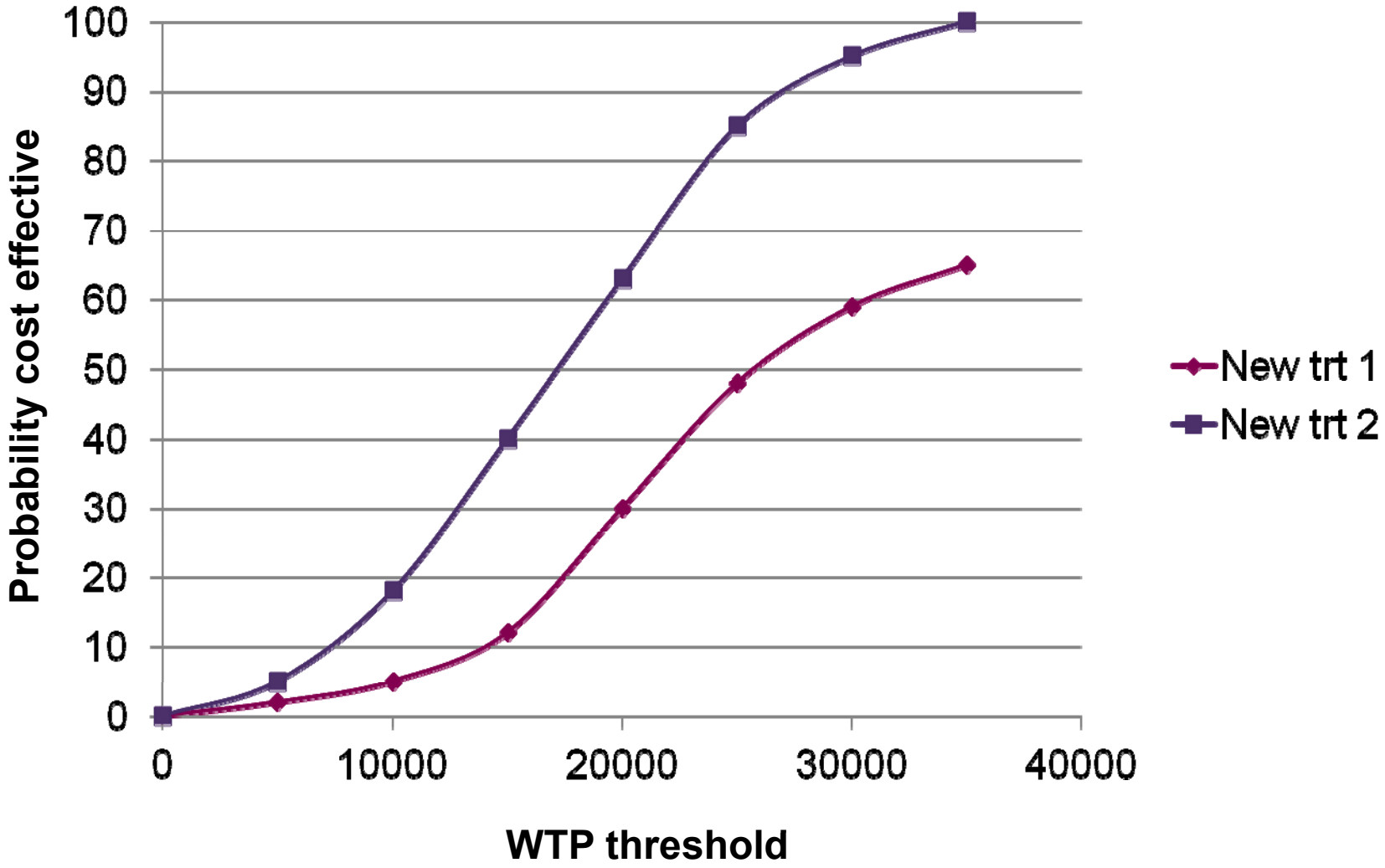


The Cost-Effectiveness Plane

Probabilistic



Cost-Effectiveness Acceptability Curve (CEAC)



Statistical challenges/opportunities in HE & HTA

Lots of room for statistical improvements!

- Methods and models developed by statistical/mathematical experts
- But may be applied formulaically by non-experts
  - Low awareness of assumptions
  - Little appreciation of implications
  - Lack of ability to adapt to new situations

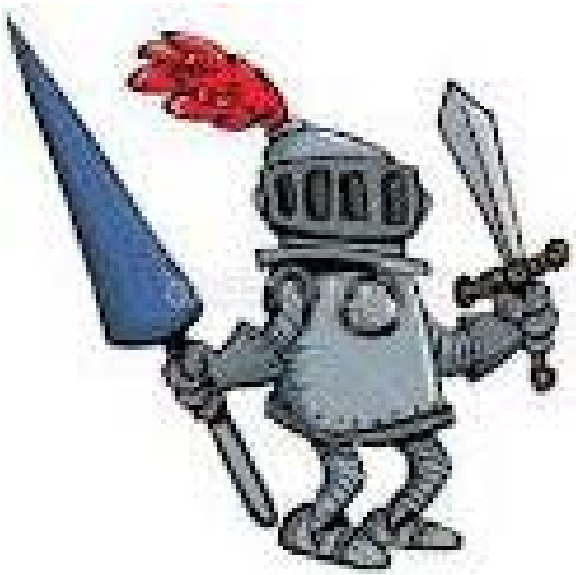
- Combining multiple data sources
  - IPD from sponsor RCTs
  - Summary stats from literature RCTs
  - Observational data
  - Utility data
  - Cost data

- Non-standard data
  - Costs, ICER, extrapolation

- Differing perspectives
  - Health economist asks statistician for analyses to use as model inputs

Differing perspectives?

THE STATISTICIAN



THE HEALTH ECONOMIST

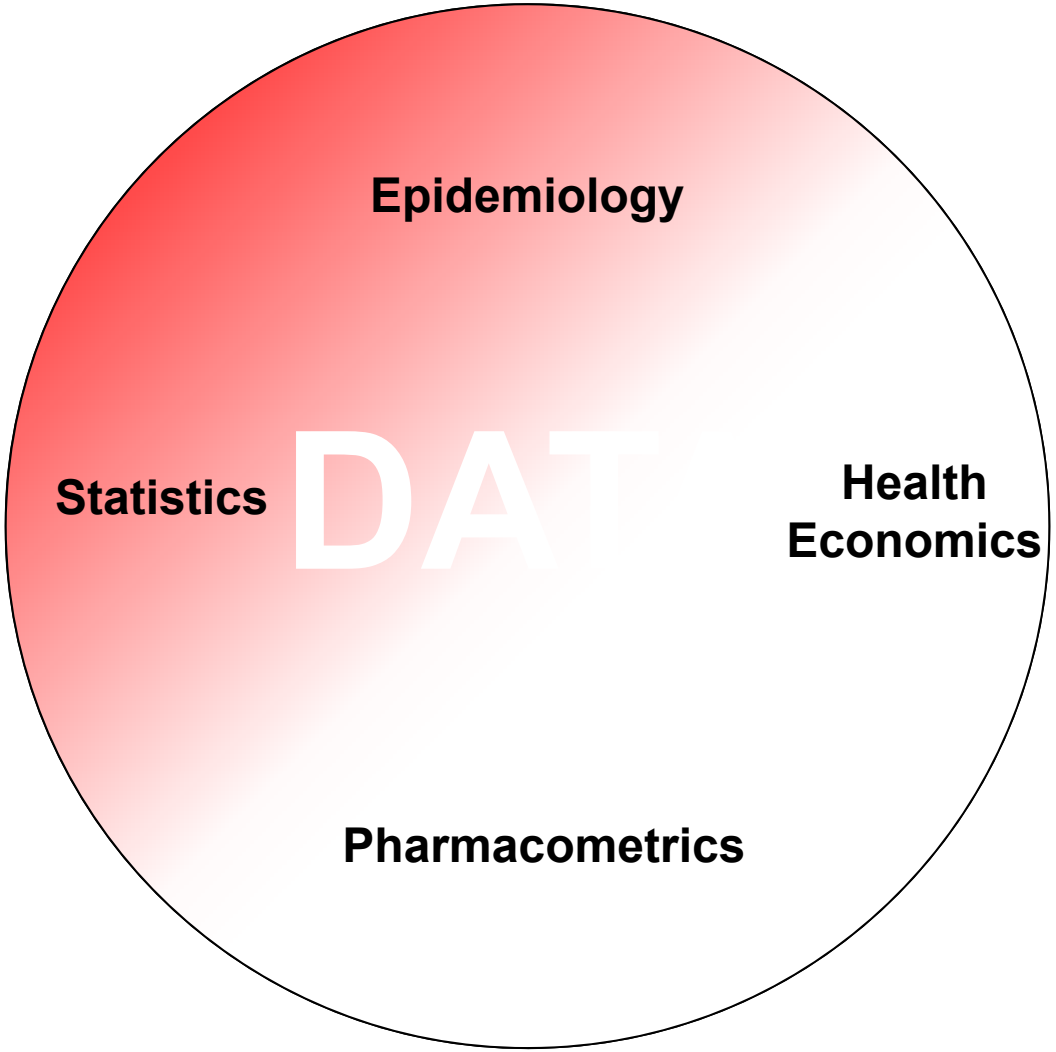
Differing perspectives?

THE STATISTICIAN

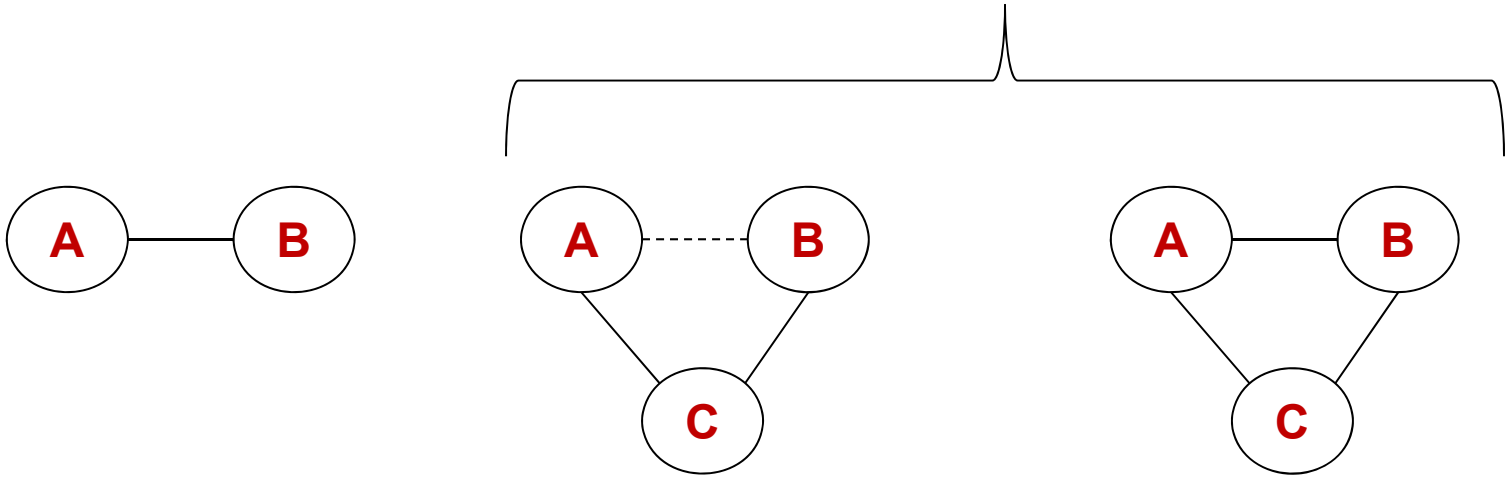
THE HEALTH ECONOMIST

In reality: Overlap of Quantitative disciplines

Common ground: Data analysis for evidence-based decisions



Evidence Synthesis
Meta-Analysis and Network Meta-Analysis



Direct comparison | **Indirect comparison** | **Mixed treatment comparison**

Trt difference d_{AB}^{dir}
Variance V_{AB}^{dir}

$d_{AB}^{indir} = d_{AC}^{dir} - d_{BC}^{dir}$
$V_{AB}^{indir} = V_{AC}^{dir} + V_{BC}^{dir}$

Synthesise direct and indirect

Additional assumptions vs standard MA

Just because multiple trials exist it does not mean that it is appropriate to pool them for analysis! *Sutton 2008*

Further info: Jones, Pharm Stat 2011 (10) 523-531

Example: MTC NMA of doublet chemotherapies in 1st line NSCLC

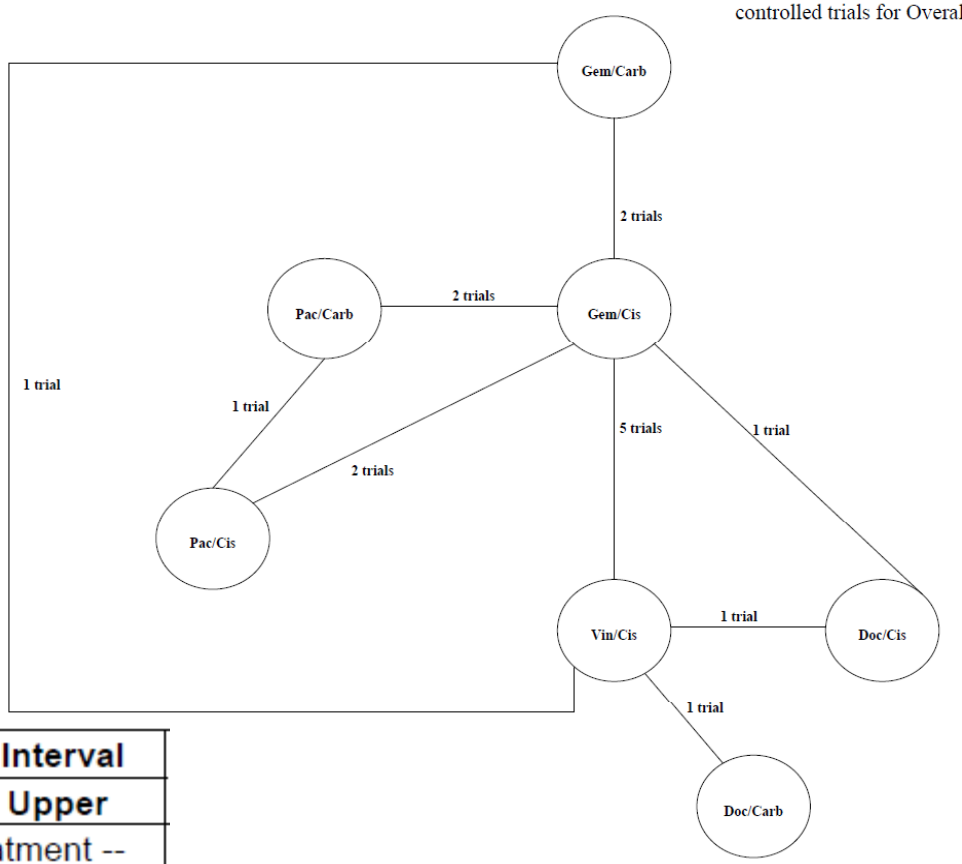


Figure 1. Network of randomised controlled trials for Overall Survival

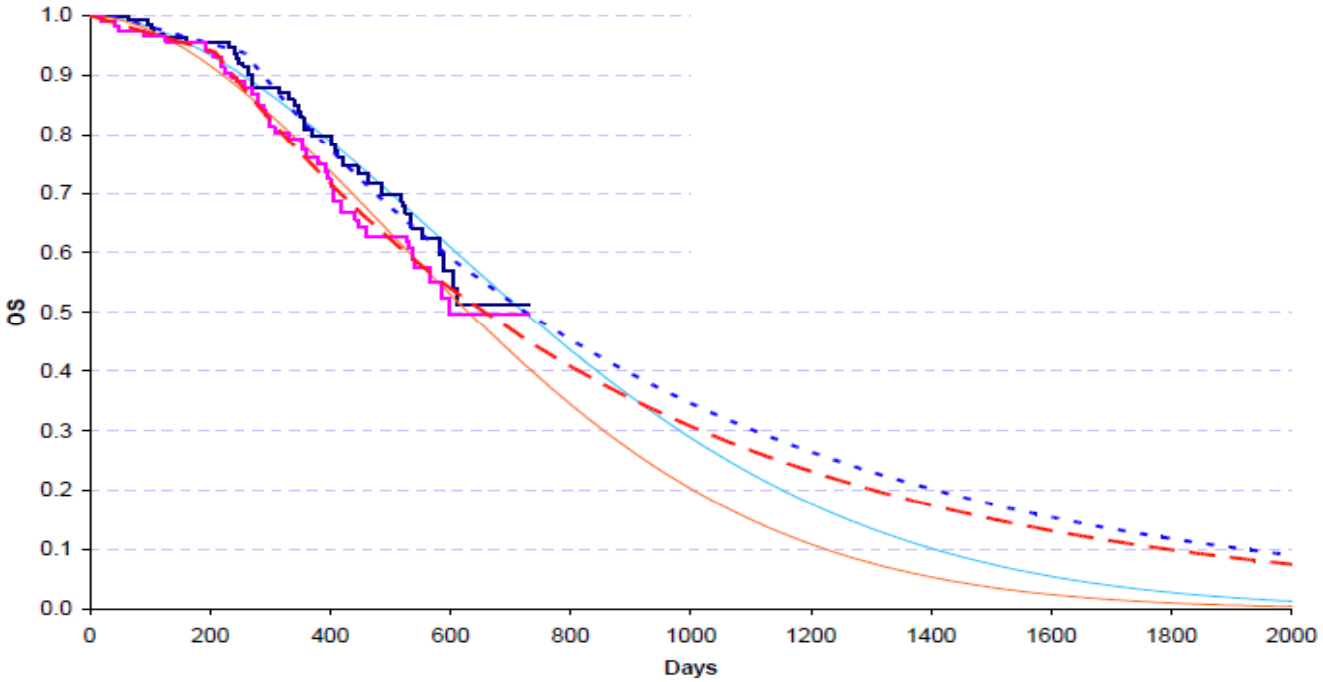
Overall survival hazard ratios from Bayesian MTC

Treatment	Mean	95% Credible Interval	
		Lower	Upper
Paclitaxel/Carboplatin	1.00	-- baseline treatment --	
Paclitaxel/Cisplatin	0.91	0.80	1.04
Docetaxel/Carboplatin	1.03	0.80	1.32
Docetaxel/Cisplatin	0.94	0.78	1.14
Gemcitabine/Carboplatin	0.95	0.73	1.23
Gemcitabine/Cisplatin	0.92	0.81	1.04
Vinorelbine/ Carboplatin	ND	ND	ND
Vinorelbine/Cisplatin	1.08	0.90	1.28

ND = No Data

Source: NICE website, gefitinib appraisal, manufacturer submissions
http://www.nice.org.uk/nicemedia/live/12185/47254/47254.pdf
http://www.nice.org.uk/nicemedia/live/12185/47251/47251.pdf

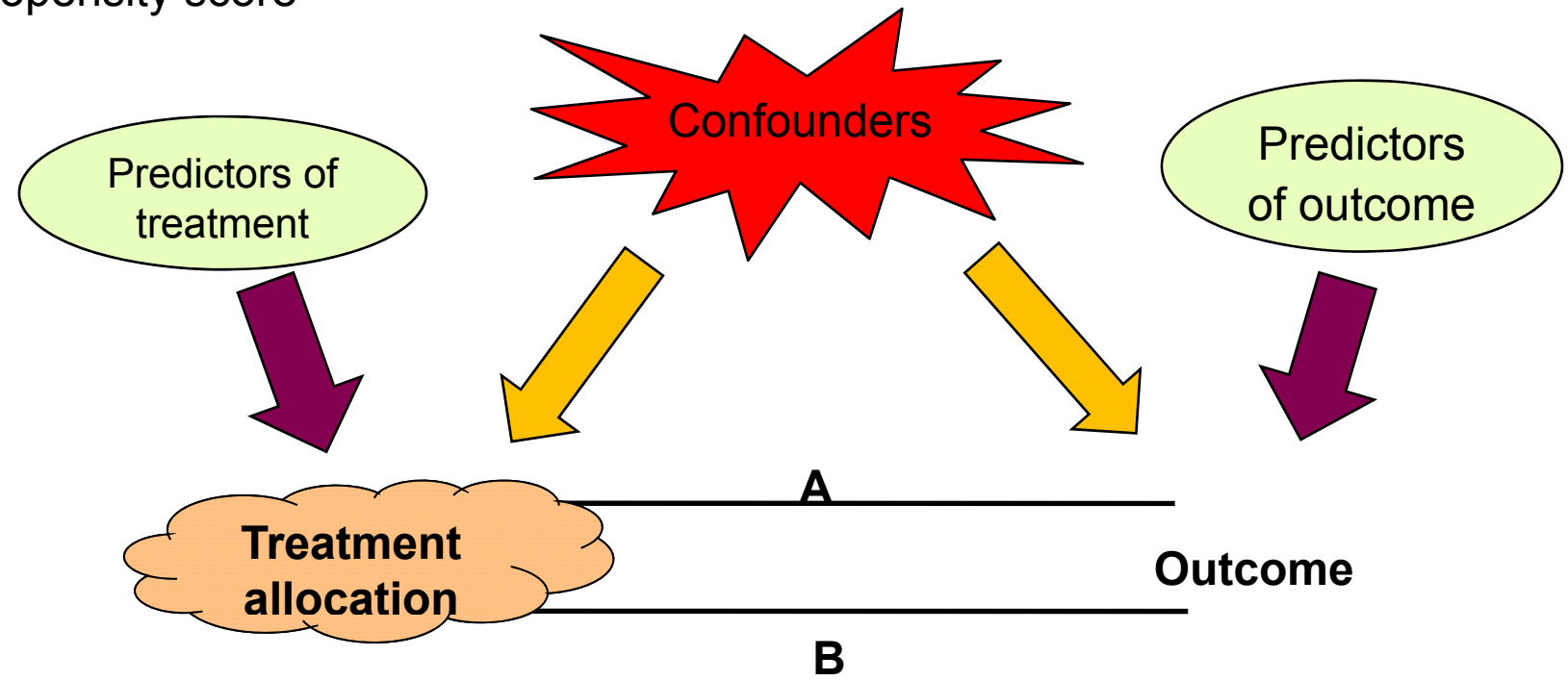
Extrapolating data beyond the trial period



- QALYs use mean survival to reflect a lifetime horizon
- Parametric modelling needed (unless very mature data)
  - Standard distributions (exponential, Weibull, generalised Gamma, Gompertz, log-logistic, log-normal)
  - Piecewise or flexible models
  - Fit to all data with treatment covariate, or each arm separately
- Use a logical and critical approach for model selection (NICE DSU TSD14)

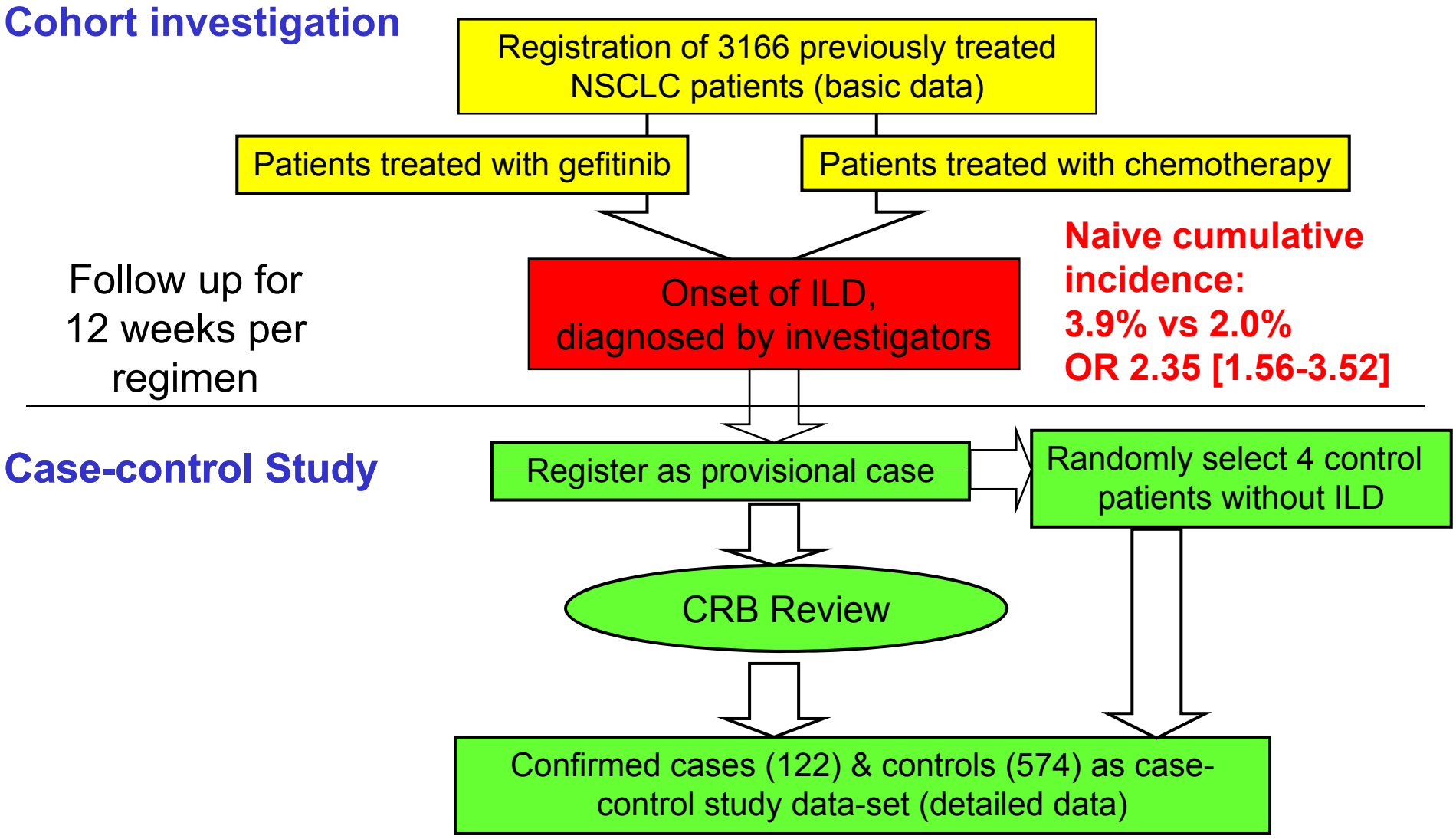
Real World Evidence (Observational data)
Study Design and Analysis

- A big problem:
  Two treatment groups were not comparable **before** the start of treatment.
  due to imbalanced covariates between two treatment groups.
- So, direct treatment comparisons are invalid.
- Adjust for confounding covariates: matching, stratification, regression, propensity score



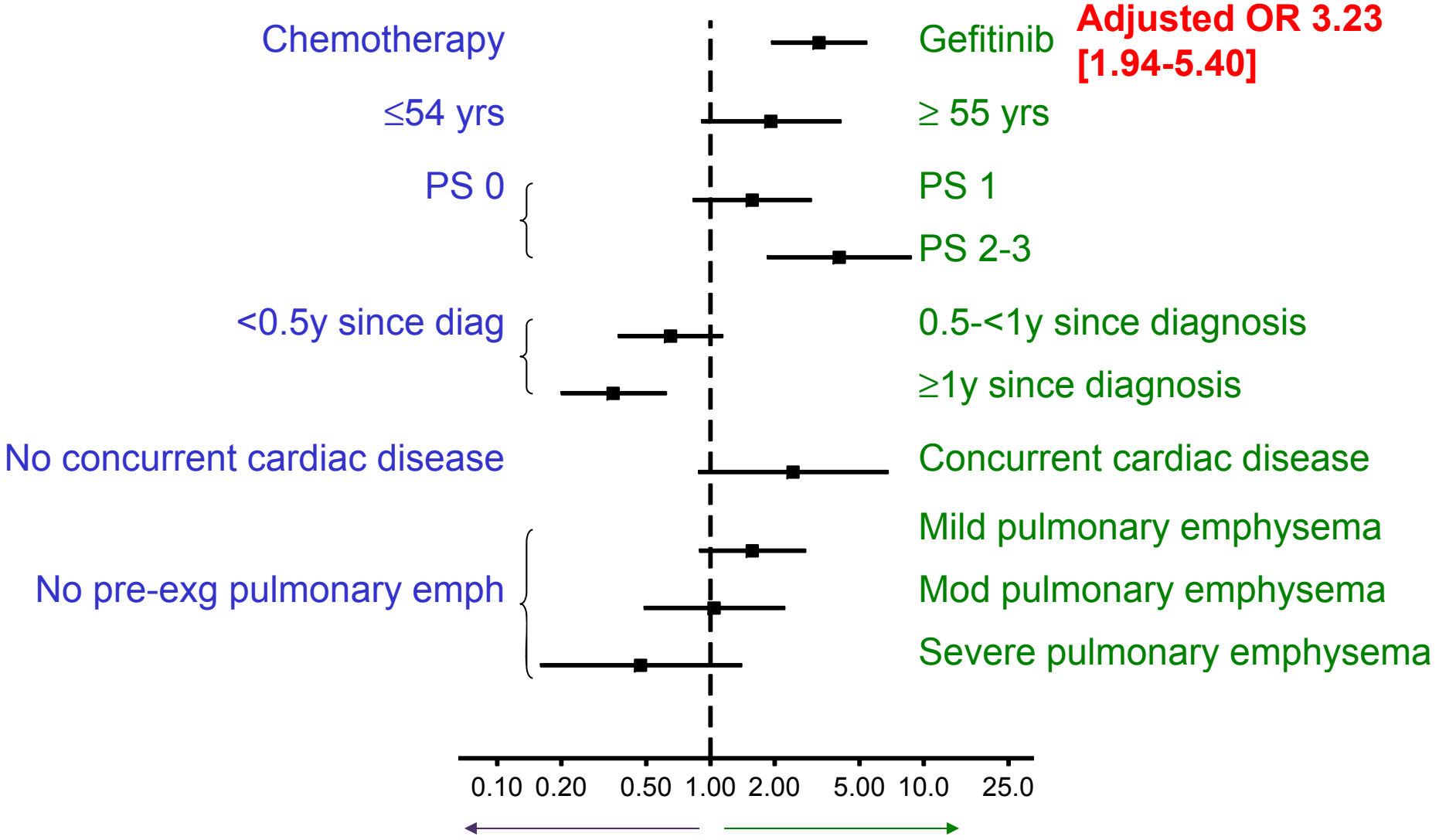
Example: Nested Case-Control Study

Interstitial Lung Disease in Japanese NSCLC patients



Kudoh et al, 2008

Adjusted odds ratios for risk factors for ILD



Conclusions

- Statistics plays a pivotal role in health economics and health technology assessment
- Payers, like regulators, want evidence based submissions
- The type of evidence may differ due to the question
  - Can cast a wider net, but still needs to be robust
- There are many ~~challenges~~ opportunities for statisticians looking to make a positive difference in this rapidly growing area

References

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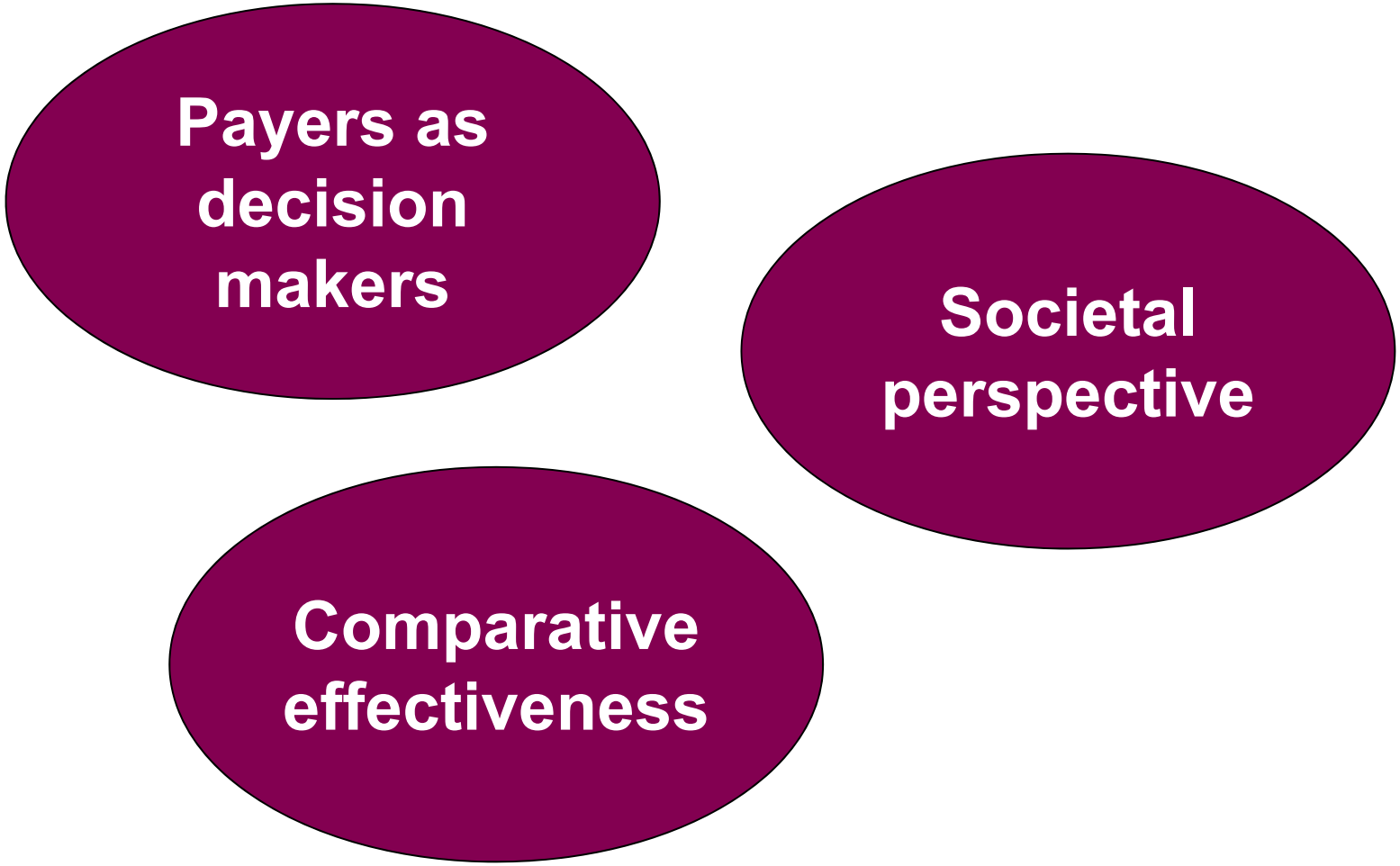
- NICE website: http://www.nice.org.uk/
- NICE Methods Guide 2008 (currently under revision): http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf
- NICE Decision Support Unit Technical Standards Documents: http://www.nicedsu.org.uk/Technical-Support-Documents(1985314).htm
- Sutton A et al. Use of Indirect and Mixed Treatment Comparisons for Technology Assessment. Pharmacoeconomics 2008; 26 (9): 753-767

Backup slides

Some key concepts in HE and HTA
Different priorities to regulatory assessment



The role of the clinical statistician
Providing evidence to support HTA submissions

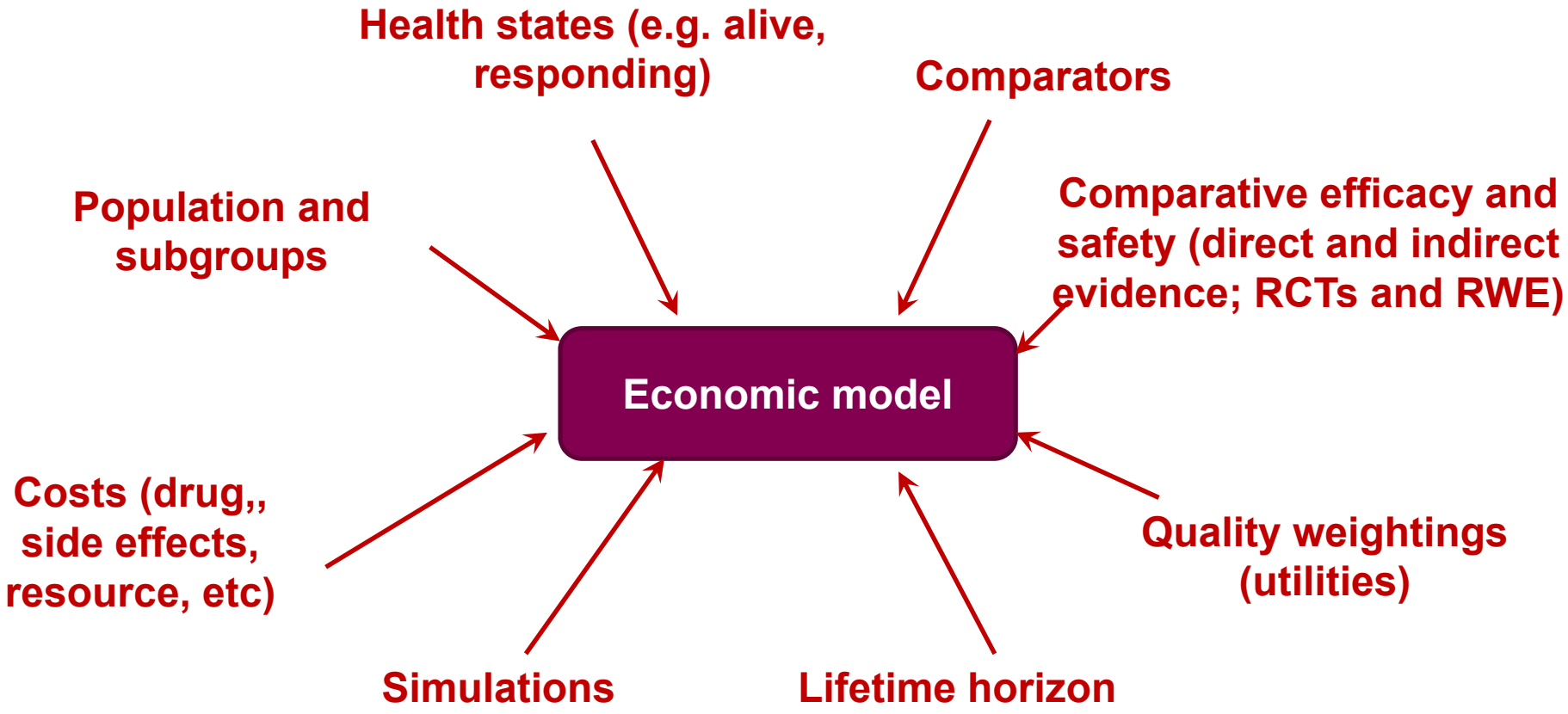
- Economic model inputs are often statistical analyses of clinical data

- As with all models, Garbage In = Garbage Out

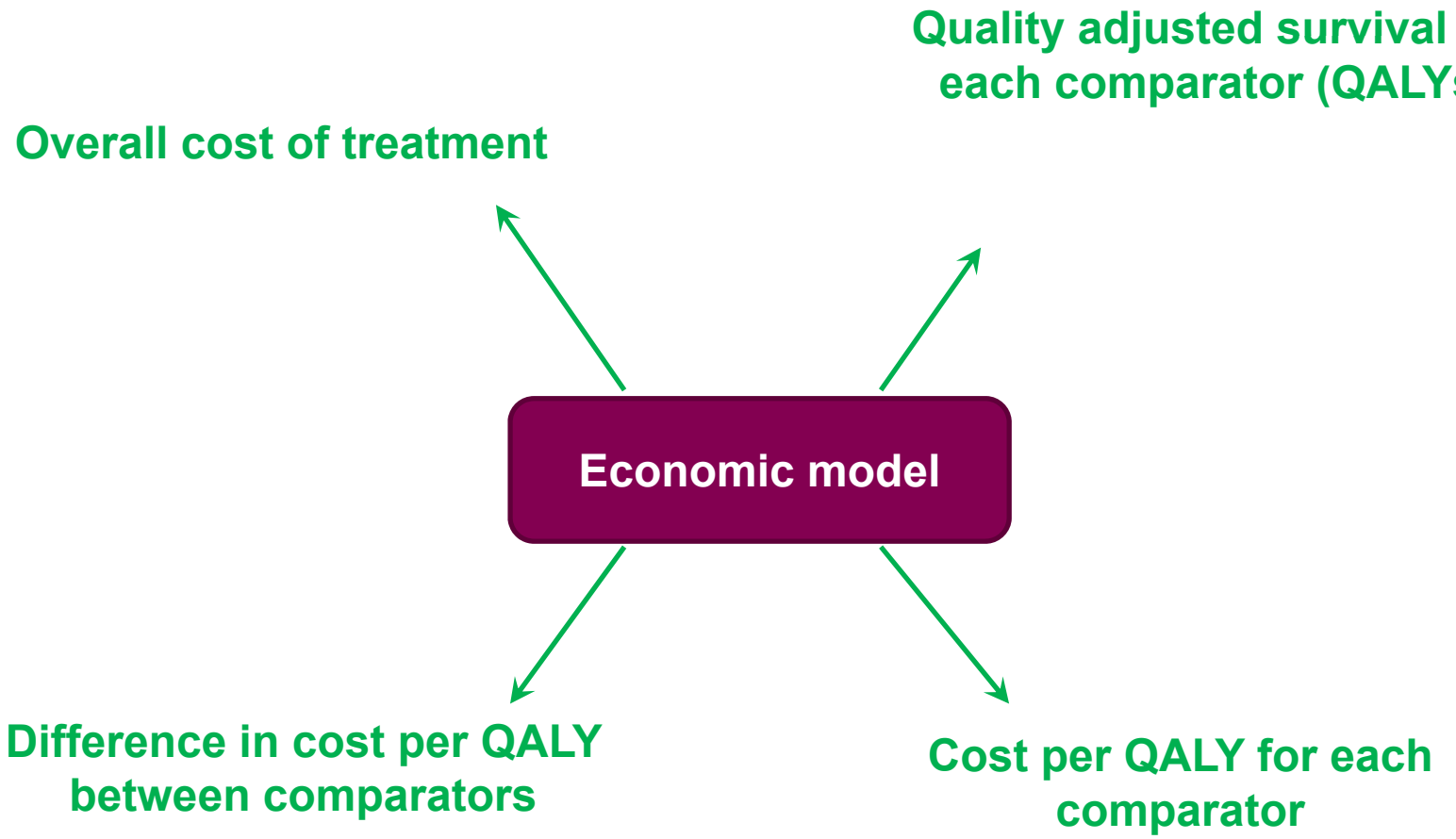
- The statistician needs to understand what the inputs will be used for
  - The analysis people ask for may not be the one they actually need
    - Strive to understand the underlying question (right answer, wrong question?)
    - Then work together to decide the optimal way to answer it
    - Clearly articulate the assumptions and limitations of different approaches
  - Standard regulatory analyses may not be the most appropriate for payers

- Work as a cross functional team
  - Payer agencies often have health economic, statistical and medical expertise

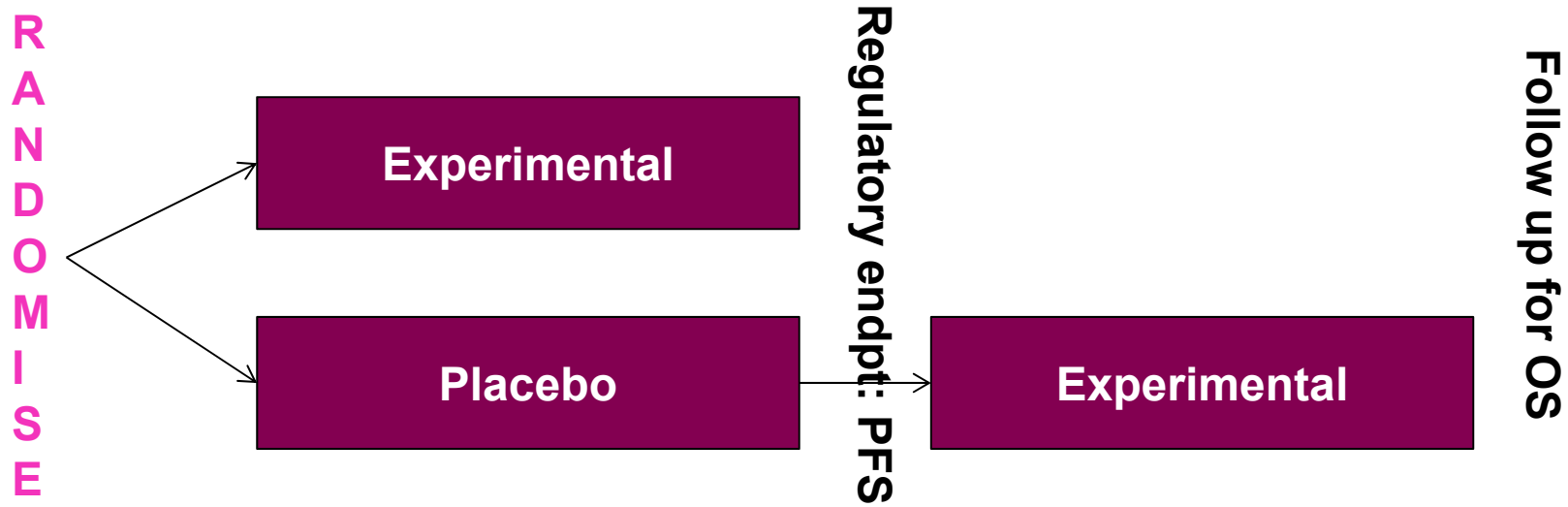
Economic model - inputs



Economic model - outputs



Adjusting OS for treatment switches



- Real life treatment strategies for payers: Experimental first vs never
- **QALY depends on OS**
- ITT placebo arm does not reflect real life
- Censoring at switch or analysing non-switch only is biased
- Alternatives that aim to reduce bias include:
  - Inverse Probability of Censoring Weighting (IPCW) - weight non-switchers by patient characteristics predictive of switch
  - Rank Preserving Structural Failure Time Models (RSPFT) - estimate counterfactual survival in absence of experimental
- Methods make strong, often untestable assumptions
- Area of active research (Morden 2011, etc)
- **Preferable to avoid switching in study design!**

Example: Pazopanib vs Placebo
Renal Cell Carcinoma, NICE submission

Interim overall survival in treatment-naive population (N=233; E=90)
31/78 (40%) placebo patients crossed over to pazopanib

	HR (95% CI) from Cox PH model	
Method	**Without covariates**	**With covariates**
ITT	0.752 (0.491-1.153)	0.524 (0.336-0.817)
Censor at crossover	0.683 (0.426-1.093)	0.508 (0.312-0.825)
Crossover as time dependent covariate	0.684 (0.428-1.095)	0.517 (0.319-0.837)
IPCW	-	0.450 (0.280-0.721)
RPSFT	0.345 (0.086-1.276)	-

Source: NICE website, pazopanib appraisal, manufacturer submission
http://www.nice.org.uk/nicemedia/live/12032/52274/52274.pdf

Derivation of utilities

Quality values or weights that are placed on different health states
The "Q" in QALY

Statistical aspects of:

- Utility values themselves

  - What value to place on the health states
  - Often want perspective of general population in the payer's country
  - Requires a well designed value elicitation study
  - Several value sets already available for existing tools, e.g. EQ-5D

- The health states to which they are applied

  - Often collected in the trial
  - Could use existing tools, e.g. EQ-5D
  - Or mapping relationship from another trial
  - One that collected the health state from your trial and the health state you want to map to
  - E.g. FACT-L and EQ-5D, pre-progression and post-progression and EQ-5D

Trial design and quantification of uncertainty are key

Confidentiality Notice